Pediatric Oncology

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Cancer in Adolescents and Young Adults

Second Edition

Springer

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Foreword

If anything, a 2nd edition of Cancer in Adolescents and Young Adults (AYA) is overdue. An inordinate number of events, organizations, and happenings have occurred since the 1st edition was published in 2007.

In 2000, I launched Planet Cancer, the first online community for young adults with cancer. I had one goal: to keep others from experiencing the same crushing isolation I had felt as a 26-year-old with cancer. There were no support groups, resources, or websites just for AYAs. We were an anomaly in the waiting rooms, and no one quite knew what to do with us when we turned up. On the research side, the extent to which the AYA population was invisible was highlighted by the unexpected challenge of a simple literature review in preparation for the 2005 National Cancer Institute/LIVESTRONG Foundation Progress Review Group (PRG): because the age range was undefined and there were no key AYA search terms. Searches delivered hundreds of thousands of mostly irrelevant results or nothing at all.

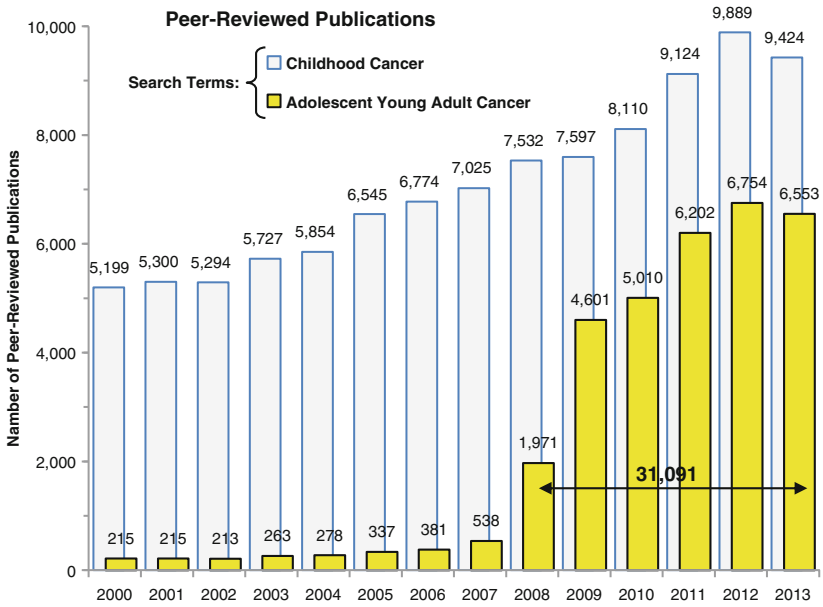
The world has changed dramatically in the years since I was a patient—computers are in everyone's pockets, monthly Facebook users outnumber the population of China, and the human genome has been sequenced. Targeted molecular therapies now save people's lives every day, and there are findings that indicate specific biological distinctions in AYAs with certain cancers compared to their older and younger counterparts facing the same diagnoses. And AYA oncology is, if not completely institutionalized, much more visible. Google delivers nearly 17 million hits to a search request for "young adult oncology." The term "AYA" is solidly ensconced in the cancer literature and lexicon, no longer requiring a follow-up explanation after every use of the acronym. And the number of peer-reviewed publications on AYA has skyrocketed (Figure) although there are still fewer than those reporting results in children with cancer. (The irony here is that, in 2011, there were almost eight times more diagnoses of cancer in AYAs than in children under 15.)

The Progress Review Group established an age range of 15–39 for AYAs, based on Dr. Archie Bleyer's startling "gap," the graphed abyss showing the relative lack of survival rate improvement in this population. However, the age range in the 1st edition was limited to 15–29, resulting in an omission of nearly two-thirds of the AYA patient population. This edition expands the age range according to the broader definition of 15–39, allowing a more thorough exploration of the variety of diagnoses and challenges that occur across the entire AYA spectrum.

But while recognition has increased, the evidence base to support beneficial changes in practice is still growing and will require strong and cohesive calls for change to ensure that such changes are implemented. Thus the new chapter on advocacy in this edition, exploring key components of driving change, the critical participants of successful efforts, and the different paths that progress has been taken internationally.

Thanks to the passion and dedication of many AYA champions around the world, we have come far. And while we still have a long way to go before AYA patients have their own clearly defined, evidence-based care path, I look forward to seeing the progress that will be achieved by the time a 3rd edition hits the press.

Heidi Adams
President and CEO, Critical Mass: The Young Adult Cancer Alliance,
Austin, Texas, USA



Foreword

Despite the remarkable progress made in the treatment of cancer in the pediatric population, cancer remains the leading cause of death from disease in children in the United States. Five-year event free survival exceeds 80 % for many but not all childhood cancers, and late effects are an ongoing challenge for a large number of survivors. Moreover, this progress has not been shared equally across the pediatric-young adult realm, with progress in improving the outcome for adolescents and young adults with cancer too frequently lagging behind advances in other age groups. A number of factors contribute to this, including the lower participation of older adolescents and young adults in clinical trials.

The 1st edition of this textbook highlighted efforts aimed at addressing the scope of the problem of adolescent and young adult under-representation in clinical trials and offered evidence that such a discrepancy may partially explain outcome differences. Chapters presented information about biologic differences between specific cancer subtypes most common in younger children and those exhibited by the same cancers in adolescents and young adults and offered insight into leading factors that contribute to outcome differences as well as potential treatment strategies.

This 2nd edition updates and expands on the work of the original text. Notably, the focus now spans the 15–39 year range, an age group specified by the 2005 Progress Review Group of Adolescent and Young (AYA) Oncology. In these updated chapters, new concepts are presented and data summarized to help bridge our gaps in knowledge. The presenting symptoms and signs, diagnosis, staging, treatment, and late effects are reviewed for each of the common malignancies, together with the epidemiology and risk factors. Principles and practices of care for adolescent and young adult patients with cancer are then discussed, with separate chapters covering specialized units, adherence/compliance, psychological support and related issues, quality of life outcomes, rehabilitation and exercise, late effects, ethical issues, access to care after therapy, future health, resources for survivors, and financial considerations. There are also chapters on access to care before and during therapy, clinical trials, future challenges and opportunities, and international perspectives.

The epidemiology portions use both the International Classification of Childhood Cancer (ICCC) and the International Classification of Diseases-Oncology (ICD-O) because cancers occurring in this age group span the pediatric-to-adult spectrum of diseases. This book will help educate medical

providers and the public about cancer incidence and survival in this age group and provide impetus for further research to improve the survival and the quality of life of these young people.

The Children's Oncology Group (COG), a National Cancer Institute (NCI)-supported clinical trial group, is the world's largest organization devoted exclusively to childhood and adolescent cancer research. The COG unites more than 9,000 experts in childhood cancer at more than 200 leading children's hospitals, universities, and cancer centers around the world. With the advent of the NCI's new National Clinical Trials Network (NCTN), of which COG is the single pediatric focused group alongside four network groups focused on cancers of the adult population, our hope is that, by increasing research studies designed specifically for the AYA population, the current gap in outcome will begin to close. To this end, we look forward to increased enrollment of AYA patients with cancer onto clinical trials, an overarching goal of the current edition of this book.

Peter C. Adamson, MD
Chair, Children's Oncology Group,
Philadelphia, Pennsylvania, USA

Foreword

Adolescents and young adults 15–39 years of age are making the transition from childhood to adulthood, not only physically and psychologically but also financially and educationally. When the burden of cancer is added, it becomes part of this extraordinary and challenging time in their growth and development. They are also unique in the types of cancers that they develop and present problems that neither pediatric nor adult-treating oncologists are fully comfortable in managing. It is no surprise therefore that 15- to 39-year-olds are often lost in a health-care system that concentrates on pediatric and adult cancers, with the resultant limited participation of the intermediate age group in clinical trials.

Until recently, little attention and few resources were devoted to studying the incidence, biology, and treatment outcomes in this age group. With the ability to gather data specific to this age group, the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program allows us to estimate that, in the year 2015, there will be between 86,840 and 87,470 new cases of cancer among 15- to 39-year-olds in the United States, including between 71,030 and 71,540 cases of invasive cancer. Compared to the estimated 11,900 cases of all cancer diagnosed in children younger than 15 years of age, the cancer incidence rate in 15- to 39-year-olds is 7.5-fold greater.

With the establishment of the Adolescent and Young Adult Committee of the NCI-funded Children's Oncology Group (COG) in 2000 and with support from the Aflac Foundation, an organized program in research and education for and about young people with cancer has been initiated. I first heard of this initiative in 1996 when I was Chair of the Cooperative Group Chairs.

In 2005, the NCI conducted an evaluation of the issues facing older adolescents and young adults with cancer. Known as a Progress Review Group, this effort was co-sponsored by the NCI and the LIVESTRONG Foundation, and its impact continues to be implemented by the COG, the Critical Mass Young Adult Cancer Alliance, and other national and international organizations. The mission is to identify and prioritize the scientific, medical, and psychosocial barriers facing adolescent and young adult cancer patients and to develop strategies to improve their outcomes. I have had the privilege to co-Chair, along with Drs. Barry Anderson and Archie Bleyer, the Clinical Trials/Research Subcommittee of the Program Review Group that has partially achieved its goal to increase the participation of young adults and older adolescents in clinical trials.

In 2013, the cooperative groups established the "Intergroup AYA Oncology-NCTN Task Force" and invited representatives from each of the NCTN cooperative groups. This Intergroup effort has now had two face-to-face meetings and will assume responsibility for advancing a collaborative program of research for Adolescents and Young Adults across the NCI NCTN (National Clinical Trials Network).

This comprehensive treatise on cancer in adolescents and young adults, edited by Bleyer, Barr and Colleagues, has helped enable the mission of the Program Review Group. It reviews the presenting symptoms and signs, diagnosis, staging, treatment, and late effects for each of the common malignancies in the age group. It would not have been possible without the support of the cooperative group enterprise in the United States or without the extensive data collection efforts of the NCI's SEER program.

I congratulate the editors and authors on the second edition and look forward to continued successful impact of the book and national initiative.

Robert Comis, MD
Co-chair, ECOG-ACRIN Cancer Research Group, and President and Chairman, Coalition of Cancer Cooperative Groups (CCCG), Philadelphia, Pennsylvania, USA

Foreword

For the past 25 years, the Teenage Cancer Trust has shown the spotlight on the additional disadvantages experienced by teenage and young adult cancer patients.

As a Founder of the Charity, I have been proud to work both within the United Kingdom and worldwide to redress the dearth of focus experienced by young cancer patients in regard to clinical trials and other research, resources, specialist psychological services, rehabilitation, and particular cancers among other issues. Within the United Kingdom, this formerly neglected cohort of cancer patients has now been recognized not only at the clinical level but also by government. We now see this recognition repeated elsewhere in the world, and the publication of the second edition of Cancer in Adolescents and Young Adults is an example of the enhanced awareness of the problems of the co-incidence of youth and cancer.

Many of those contributing to the first edition and also to this edition have been the flag bearers to put young people with cancer on the map—not the least of which are Archie Bleyer and Ronnie Barr who have proved to be motivating voices in the field and originated the 1st edition.

This edition not only updates the original but extends the scope, bringing in new and respected voices from those dedicated practitioners in many fields who have embraced the message promoted by Teenage Cancer Trust many years ago. It will make a valuable contribution to the pool of knowledge and experience put forward by Teenage Cancer Trust's International Conferences and prove to be an essential tool in the fight to improve outcomes in this very sensitive and complex group of cancer patients.

The issues addressed are wide ranging and will be of great assistance to those working in the field seeking to increase clinical trial involvement and improvement in outcomes currently experienced by other cancer groups but not correspondingly by young people. This edition embraces a wider field, in regard to age, topics, authors, and editors, and so offers increased expertise to its readers.

The contributors, their work, and their research lend respect to the quality and usefulness of "Cancer in Adolescents and Young Adults," and I commend them and the editors and co-editors for this informative, inspirational, and valuable book.

Myrna Whiteson, MBE
Life President—Teenage Cancer Trust,
London, UK

Preface

The Evolution of Adolescent Oncology in the United States

Background

Although the history of adolescent and young adult (AYA) oncology is relatively recent, there is evidence that cancer in AYAs precedes and transcends written human history [1–3]. One of the earliest cases of cancer in an AYA was found by Louis Leakey in 1932 in the remains of either a *Homo erectus* or an *Australopithecus* and was suggestive of a Burkitt lymphoma. Osteosarcoma, which has its peak occurrence in the second decade of life, has been found in Egyptian mummies estimated to be AYAs. A case of possible osteosarcoma was also discovered in the mummified skeletal remains of a Peruvian Inca. Centuries, if not millennia later, and late in the history of modern medicine, AYA oncology was born. This review of the recent history, after decades to millennia of omission, describes the major events and rationale that led to the AYA oncology discipline beginning with adolescent oncology.

From time immemorial, adolescents have been criticized for their behavior. Socrates complained that "children today are tyrants; they contradict their parents, gobble their food, and tyrannize their teachers." Homer declared "thou knowst the over-eager vehemence of youth, how quick in temper, and in judgment weak." Shakespeare suggested that teenagers be put into suspended animation until of age [4]. Ambivalence, rebellion, desire for freedom from family, conflicts with parents, reaction with intensity, identification with their peers, and sexual activities are archetypal of this age group. An imbalanced rate of demands for privileges and acceptance of responsibility, coupled with the desire to be autonomous and different, has led to antipathy and dislike of adolescent behaviors. Yet these characteristics may be appropriate for this age group and likely constitute one of the pillars of human advancements over the ages.

For adolescents, the transition from childhood to adult status is both difficult and stressful. As such, many experience ambivalence and physical and emotional turmoil, which threaten their ability to become healthy and productive adults. Cancer, a catastrophic, life-threatening disease, has major physical, functional, psychological, and social implications, which are amplified in the AYA age group. While cancer in AYAs is not rare, it poses a

sufficiently distinctive challenge to require specialized services [5]. In the 1970s, when cancer was becoming a more "chronic" disease and promising reports of successful treatment in several types of cancer, which heretofore were deemed incurable, appeared in the literature, physicians began treating their patients with curative rather than palliative intent [6]. At that point, it became apparent that a catastrophic disease with uncertain outcome requiring intensive therapy is difficult to face without a major social support system [7]. It had been recognized for some time that care for AYA patients demands an understanding of the process of physical, mental, psychological, and social growth and development [8]. Adolescent services had been in existence in the United States since 1951, when Dr. J. Roswell Gallagher established a unit for adolescent medicine at Boston Children's Hospital [9].

A Decade of Experience: 1978–1989

Against this background, the first adolescent oncology unit, where one of the authors (CKT) was the director, was established in 1978. This was enabled by a grant from the National Cancer Institute (NCI). The unit was founded through the efforts and support of Dr. James Wallace, the then director of the Division of Cancer Control and Rehabilitation, and the endorsement of Dr. Gerald Murphy, the then Institute Director at Roswell Park Memorial Institute. While adolescent medicine as an entity was not new, the idea of a separate unit for adolescent cancer patients was unique. Establishment of a unit dedicated specifically to cancer was received enthusiastically by patients and their families alike. The reception by medical and surgical subspecialists was far less enthusiastic. There was considerable opposition, expressed and implied, by various medical and surgical services. The ten-bed unit, which was located in a separate building and connected to the main hospital, was resented by most departments on several principles. Most medical and surgical staff physicians preferred their patients to be hospitalized on their own floors. Some were unwilling to lose the adolescent population from their services. Our much more modern facility for adolescents and young adults than the then older hospital floors was also resented. Only with the strong support of Dr. Gerald Murphy, the devotion and resilience of the unit staff, and the demand of patients and their families did the unit survive and flourish. Dr. Murphy had personal experience with adolescence in his own biological and adopted children and had considerable knowledge of adolescents' desires and behavior.

The physical structure of the unit, which was designed with the patients' input, proved to be a major draw [10]. The unit was painted with bright colors and geometric designs appealing to AYA patients. It included a sizable patient lounge with bright furniture, a large aquarium, and decorations. An arcade-like recreation room with the latest in electronic games then available, football, air hockey, bumper pool table, jukebox, stereo system, large TV, and musical instruments, drew the patients' friends to visit them in the hospital. An extensive exercise and arts and crafts room, a classroom, and a library with books and magazines appealing to the age group were provided.

A well-stocked and equipped kitchen with dining room allowed patients and their parents to cook and dine together. There was no dress code. A laundry room was available to patients so that they could wear their own, not the hospital's, clothes. A room designated as a quiet room was furnished for patients and their families who wanted to take some time off and not be disturbed by anyone, including medical personnel. A separate parents' lounge and room to stay when their child was critically ill allowed parents to be involved, but not intrusively. Selection of the staff for the unit was based largely on their desire and ability to work with AYA patients. Primary nursing care proved to be essential for the operation of the unit. Various programs were designed to promote communication and support emotional stability in crisis situations. A teacher visited patients on a daily basis and, through an agreement with a local college, post-secondary education was available. In retrospect, the educational opportunities offered, especially for those less engaged in school prior to the diagnosis of cancer, were an important function of the unit [10]. Among other programs offered were music therapy, group sessions, and career planning. The unit, in those early days, offered a computer for patients' use, which was then unique. With a grant from Poets and Writers Inc., a creative writing program was established. The unit's monthly newsletter, entitled "Now and Then News," often contained excellent articles or poems expressing patients' and staff's feelings and experiences.

Offices of the staff, including the medical director, patient care coordinator, family counselor, and occupational therapist, were in the unit and open to patients and their families and friends. Patients' records were computerized, allowing access, using a series of codes, to the patients' prior admissions and discharge notes. This was probably one of the earliest attempts at computerized medical record keeping. The unit shared a research laboratory and accepted pre- and postdoctoral trainees.

The rules governing the unit, including visiting hours and visitors' age limit and number, were liberal [4]. A monthly family night was hosted for the patients and their families to attend. In-patient field trips decreased the monotony of staying in the hospital. A home and terminal-care program was designed for patients who opted to stay at home at the end of life. An evaluation program periodically examined satisfaction with the various aspects of the unit's operation by the patients, their families, and staff [10, 11].

Shortly after the establishment of the unit, it became apparent that information regarding care of the adolescent cancer patients was scanty, if not nonexistent. In a series of investigations, the medical and psychological effects of the diagnosis and treatment of cancer in adolescents were probed. Since nowhere are these effects more exaggerated than with loss of a limb and its effect on body image, physical, psychological, and social functioning of the patient, a major effort was placed on these areas of study. These studies described various aspects of the bone tumors [12–14] and the short- and long-term effects of the amputation on the patients' lives [15–17]. The research found that, in general, despite all adversities, in the long-term most amputee patients had adjusted to their circumstances and were leading full and productive lives [15, 17]. Other investigations probed the role of social support systems [7, 18]. Evaluation of the pattern of religiosity and locus of control

revealed that adolescent cancer patients were not significantly more religious than established norms [19]. However, among younger adolescents, the diagnosis and treatment of cancer may have accelerated the development of internality, which is expected to be associated with increased age [19].

Early during the experience of the unit, significant noncompliance with self-administered cancer therapy was noted. This led to a series of studies of patients and parents and a means to improve compliance [20–25]. Since the psychological aspects of the disease play an important role in the care of patients, great emphasis was placed on this aspect of care [11, 26, 27]. Depression had been observed and studied extensively in adult cancer patients, but no systematic evaluation was available for adolescent cancer patients. In a series of studies, the rate of self-reported depression in cancer patients was examined [28]. Issues pertaining to long-term survivors were other venues for early research. With improved survival, the short- and long-term sequelae of cancer and its treatment, the effects on the vocational achievements of the patients, and their function in the workplace were investigated [29, 30]. This disclosed a greater degree of functional deficits in unemployed than in employed cancer survivors and in health, life, and disability insurance issues [29]. Nevertheless, there was no significant relationship between health status and employment. As a whole, former cancer patients had a higher average income compared to a control group and were competitive members in the workplace [29]. The experiences in establishment of a specialized unit, together with the care and nutrition of these patients, were published [8, 30]. Along with annual adolescent oncology conferences, these reports attracted a large number of interested individuals to work and train in the unit. Publication of the first book solely devoted to adolescent oncology [31] increased the awareness of cancer in adolescents and young adults, albeit to a limited extent.

In 1989, when Dr. Gerald Murphy left Roswell Park, the unit, which was then by far the most modern and progressive floor of the hospital, was viewed as an “extravagance” by the new administration. For cost-cutting purposes, it was decided that its resources should be shared with pediatrics. Consequently, in October of 1989, despite the pleas of dedicated staff and patients, the unit was merged with pediatrics and the AYA cancer program was effectively closed.

Scaling Up: 1992—The Present

A new chapter in AYA oncology commenced when, in October 1992, the American Cancer Society (ACS) sponsored a workshop on Adolescents and Young Adults with Cancer [32]. The conference served as a watershed for recognition of the special needs of this group of patients. It was attended by, and had the support of, Dr. Gerald P. Murphy who, after leaving Roswell Park Cancer Institute and State University of New York, had accepted a position as the chief medical officer of the ACS. To organize this conference was a departure from prior attitudes toward the importance of specialized care for AYA cancer patients. Before the leadership of Dr. Murphy, when an earlier confer-

ence, entitled "Advances in Care of the Child with Cancer," was being planned by the ACS in 1985, the first author (CKT) suggested that the subject of adolescent oncology be included in the agenda. The organizer of that conference indicated that nothing was new or important enough in adolescent oncology to merit a session, and the subject was declined. The 1992 "Adolescent and Young Adult Conference" was attended by many leaders in pediatrics, adolescent medicine, and medical and surgical oncology, including the chairs of the major pediatric cancer groups. The workshops included sessions on long-term care and lifetime follow-up [33], insurance and employability [34], psychological and emotional issues, specialized support groups and compliance [35], and clinical research implications [36]. The published proceedings of the conference had an important conclusion, which recognized cancer as a significant health problem in the AYA population [32]. It observed that the incidence rate of cancer in patients 15–19 years of age is equal to that of 0–4-year-olds and 1.6 times that in patients between 5 and 14 years of age [37, 38]. The report also brought attention to the relatively infrequent participation of AYAs in clinical trials and ignited initiatives to include AYAs in these endeavors [38–41]. The 1992 conference also emphasized the necessity for long-term follow-up and psychosocial support and called attention to discrimination in insurance and employment [37]. The concluding remarks included recommendations to remedy these concerns [37].

In 1996, the first report on the relative lack of progress in improving survival in adolescents with cancer was published [42]. In 1997, the relative lack of adolescents with cancer on clinical trials compared with children was reported [43]. These observations led the then Chair of the Children's Cancer Group (author AB) to form a task force within the group to research the problem, which led to the appointment, in 1998, of the first AYA Committee in the national cooperative group program of the US NCI. The concept was included for the first time in an NCI Cooperative Group Chair's Competitive Renewal Application, presented at a Site Visit in 1998, and funded with an *Outstanding to Excellent* score rating.

In 1999, the first NCI Workshop was convened by Malcolm Smith, MD, PhD, and author AB to assess how to increase clinical trial participation by AYA cancer patients. Twenty-eight attendees included chairs and other leaders of the NCI cooperative groups, surgeons, radiation oncologists, medical oncologists, and other specialists in the common cancers in AYAs, as well as ten NCI leaders and a health insurance industry representative.

The genesis of the Children's Cancer Group AYA Committee and the NCI Workshop were harbingers of the fact that there are currently approximately 37 million individuals between the ages of 10 and 19 years living in the United States and, based on SEER and other data, the incidence of cancer in 15- to 19-year-olds was on the rise [39, 43–47]. In the United States, this increased an average of 0.7 % per year from 1975 to 1997 [40], yet no age-defined health-care system or providers were generally available to the majority of adolescents [48]. On the other hand, in the United States, the mortality from cancer in the age group decreased at the rate of 3.3 % per year for the period 1965–1974 and 2.6 % per year for the period 1975–1984. Thus, the health care of this group of patients was considered fragmented, in the United

States and elsewhere, between medical, pediatric, and general practitioners and others [49].

In 2000, the four major national pediatric cancer cooperative group organizations (Children's Cancer Group, Pediatric Oncology Group, National Wilms' Tumor Study Group, and Intergroup Rhabdomyosarcoma Study Group) merged into a single national group called the Children's Oncology Group (COG). With this coalescence, an expanded AYA Committee was established to intensify AYA oncology research.

In 2004, the first national philanthropic contribution to AYA oncology research occurred with a grant from the Aflac Foundation to the COG for research by its AYA Committee. The total contribution since then by the Aflac Foundation exceeds US$1.5M. In 2005–2006, the NCI and Livestrong Foundation sponsored the Progress Review Group (PRG) on AYA Oncology [50] that was attended by 97 representatives of the scientific, health care, advocacy, and health insurance organizations. A strategic plan based on the PRG was developed by the Livestrong Young Adult Alliance [51].

The PRG was a sentinel event in the evolution of AYA oncology, subsequent to which much of what has occurred nationally and internationally has been derived. It has been described as the most (albeit the last) productive of the series of PRGs held by the NCI.

The COG AYA Committee took steps to organize a comprehensive program including subcommittees for all major categories of oncological disorders common among AYA patients. The committee now consists of more than 120 members who represent nearly 20 disciplines and is sustained by funding from the NCI and the health insurance industry. It is organized into five Strategy Groups (disease-specific clinical trials, behavioral oncology, health services research, epidemiology, and awareness) and a sentinel task force on survivorship transition. In addition, the committee has established task forces on access to clinical trials and care, cancer control and community oncology programs, adolescent treatment adherence, exercise and adventure therapy, and development of an informative website.

Unfortunately, years after the demonstration of the benefits of treatment of adolescent patients in a unit of their own [10, 52], only a handful of specialized adolescent oncology services in the United States are operational. In the United Kingdom, the Teenage Cancer Trust (TCT) is an advocate of these units [53]. There are currently 27 operational units, and there are plans for the establishment of a TCT unit in every regional cancer center. Adolescent oncology units can provide an environment where the age-appropriate atmosphere and facilities, coupled with medical, technological, and psychosocial expertise, can provide specialized care while reducing dropouts from the treatment as well as short- and long-term side effects of cancer and its therapy. In an inquiry sent to 238 COG institutions in the United States, of the 196 that responded, only one hospital had a formal designated adolescent oncology unit (unpublished observation, CKT 2004). In the same inquiry, ten admitted their patients to a general adolescent unit, and only seven had staff who identified specifically with the care of these patients. While adolescents are generally resilient [54, 55], in adult units these patients are frightened by

the generation gap, adults disfigured by cancer, and rigid rules imposed upon them while they are hospitalized. Medical oncologists tend to regard 16- to 21-year-olds as adults and do not make a distinction between them and older patients [56]. Furthermore, diagnoses common in older adults are rare in adolescents and young adults [56]. While disputed, at least for some oncological diseases, the treatment of adolescents according to a pediatric protocol has yielded better results than medical oncology protocols [5, 57–59]. In a pediatric setting, however, AYAs are often demeaned by an atmosphere created for very young children and the childlike manner with which they are often dealt, not considering their age and accomplishments. The patients are often bypassed by the pediatric staff, who habitually communicate with their parents rather than interact directly with the patient.

The history of the development of adolescent oncology would be incomplete if one were remiss in failing to mention the developments in psychosocial and long-term care of the patients [60]. With increased survival, the problems concerning quality of life have gained prominence. Subjects such as "psychological aspects of cancer survivors," "late effects," "long-term survivors clinics," "second cancer," and "transition to adult care," which did not exist before, found their way into the lexicon of oncologists in the United States and elsewhere [61–66]. Likewise, with significant societal changes in the 1970s and 1980s, the subject of death and dying, which once was "taboo," is discussed openly and has become a new area for research and open discussion. Hospice care, introduced initially by physician Dame Cicely Saunders in the United Kingdom in the early 1960s and culminating with the opening of the first hospice in 1967, has found its way to the United States and has become a part of end- of-life patient care. The American Academy of Hospice and Palliative Medicine, originally chartered as the Academy of Hospice Physicians, was established in 1988 [67]. Publication of 500 interviews with dying patients entitled "On Death and Dying" and analysis by Dr. Elisabeth Kubler-Ross [68] catalyzed a more open discussion with dying individuals, including AYA patients. The trend continues with most major adult and pediatric cancer study groups having established committees on end-of-life care.

Important recent developments in the United States include the publication of guidelines on AYA oncology by the National Comprehensive Cancer Network [69] and the formation of an AYA working group within the National Clinical Trials Network. Corresponding initiatives have been undertaken elsewhere in the world, as in the United Kingdom [70].

The evolution of AYA oncology in the United States and other parts of the world formed the stimulus to prepare a second edition of Cancer in Adolescents and Young Adults. Assembling a large group of authors from many disciplines has enabled the editors to take advantage of international expertise and experience and address a comprehensive compendium of topics across the spectrum of AYA oncology.

Tampa, FL, USA — Cameron K. Tebbi
Portland, OR, USA — Archie Bleyer

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Contents

1 Adolescent and Young Adult Oncology: Historical and Global Perspectives

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Since the first edition of *Cancer in Adolescents and Young Adults* was published in 2007, there have been numerous milestones in the journey of adolescent and young adult (AYA) oncology. These include an expansion of the age range from 15–29 to 15–39 years and a commensurate increase in the number and scope of the constituent chapters.

The evidence that AYA oncology (AYAO) has "arrived" includes the establishment of a society [1] and journals [2, 3] devoted to the subject. The first topic addressed in the first issue of the *Journal of Adolescent and Young Adult Oncology* was "what should the age range be for AYA oncology." A case was made for flexibility and context specificity [4]. From a health-care delivery perspective, most countries have adopted a mid-teens to mid-20s range. Formerly, the USA [5] and Canada [6] have taken 15–29 years for epidemiologic reasons. In the context of clinical trial accrual, the Children's Oncology Group (COG) has extended its upper age limit to 50 in some instances [7], while no limit has been suggested for long-term follow-up; some participants in the Childhood Cancer Survivor Study have now passed 50 years of age [8]. For this second edition, we have taken a middle ground by adhering to the 15- to 39-year age range proposed by the US National Cancer Institute (NCI) Progress Review Group on AYA Oncology in 2006 [9].

The wider age range has major implications, beginning with a dramatic effect on disease distribution, now influenced markedly by the epithelial tumors so prevalent among older adults. Consequently, attention has to be paid to carcinomas of the bladder, lung, head and neck, and even prostate, among others. But it means

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also that the disease-specific chapters that deal with disorders more common in those under 30 now have to incorporate consideration of patients approaching middle age. Meanwhile, greater focus has fallen on sexuality and oncofertility, as well as palliative and end-of-life care, reflecting the inclusion of more AYAs in the reproductive age group and a lower survival rate from cancer overall in the fourth decade of life [10] than in younger AYAs.

But this second edition is only one of the accomplishments of the expanding AYA cancer discipline and community. There are many others to celebrate as illustrated by a review of historical events in North America, the United Kingdom, and Australia (Figs. 1.1, 1.2, and 1.3).

In retrospect, the first publication that identified an AYA cancer gap per se appeared in 1996 [11], following which a series of national programs emanated in North America (Fig. 1.1). The Children's Cancer Group (CCG) created a committee devoted to AYAO research that in 1998 was supported via a Cooperative Group grant from the NCI. In 2000, the first NCI workshop on AYAO was held that stimulated other cooperative groups to include AYAO in their research plans.

Formed in 2005 by a unique partnership between the NCI and the LIVESTRONG Foundation, the *Progress Review Group on Adolescent and Young Adult Oncology* remains active and in September 2013 hosted a workshop on *Next Steps in Adolescent and Young Adult Oncology*: *An Update on Progress and Recommendations for the Future* [12]. Various products of that meeting are under development and being published. The NCI also restructured its cooperative group program with the formation of the National Clinical Trials Network in 2014 [13]. In 2013, COG joined ranks with the NCI adult cooperative group AYA committees to

Fig. 1.1 Landmark events in the development of AYA oncology in North America. *CCG* Children's Cancer Group, *NCI* National Cancer Institute, *PRG* Progress Review Group, *JAYAO* Journal of Adolescent and Young Adult Oncology, *IOM* Institute of Medicine, *NCCN* National Comprehensive Cancer Network, *Aflac* Aflac Foundation, *LSYAA* LIVESTRONG Young Adult Alliance, *CMYACA* Critical Mass Young Adult Cancer Alliance

coordinate intergroup efforts to conduct AYAO research, both at the translational and clinical trial levels.

A parallel development in North America was the formation of a *Critical Mass Young Adult Cancer Alliance* [14], an entity that began life as the LIVESTRONG Young Adult Alliance (LSYAA) under the auspices of the LIVESTRONG Foundation in 2006 [15]. *Critical Mass* and LSYAA aggregated AYAO-focused nonprofit organizations, medical institutions, patient advocacy groups, government agencies, clinicians, researchers, and dedicated individuals. One of their outcomes was a position statement on the preferred training of health-care professionals for AYAO [16]. That same year, the National Comprehensive Cancer Network issued its supportive care guidelines in AYAO [17], and in 2013 the Institute of Medicine in the USA convened a workshop devoted to this subject [18].

North of the border momentum in AYAO received a major boost in 2008 when funds from the federal government were provided, through the agency of the Canadian Partnership Against Cancer, to establish and operate a national Task Force on Adolescent and Young Adult Cancer. The Task Force has held two international workshops, in 2010 [19] and 2012, that have led to a series of recommendations [20], akin to those of the Progress Review Group, and a Framework for Action [21] to advance the discipline. A parallel activity has resulted in the approval of a 1-year, postgraduate diploma program in AYAO (a designated "Area of Focused Competence") by the Royal College of Physicians and Surgeons of Canada.

Across "the pond," there has been a continuing surge of activity (Fig. 1.2) building on the foundation of the Teenage Cancer Trust that has built more than 20 centers for teenagers and

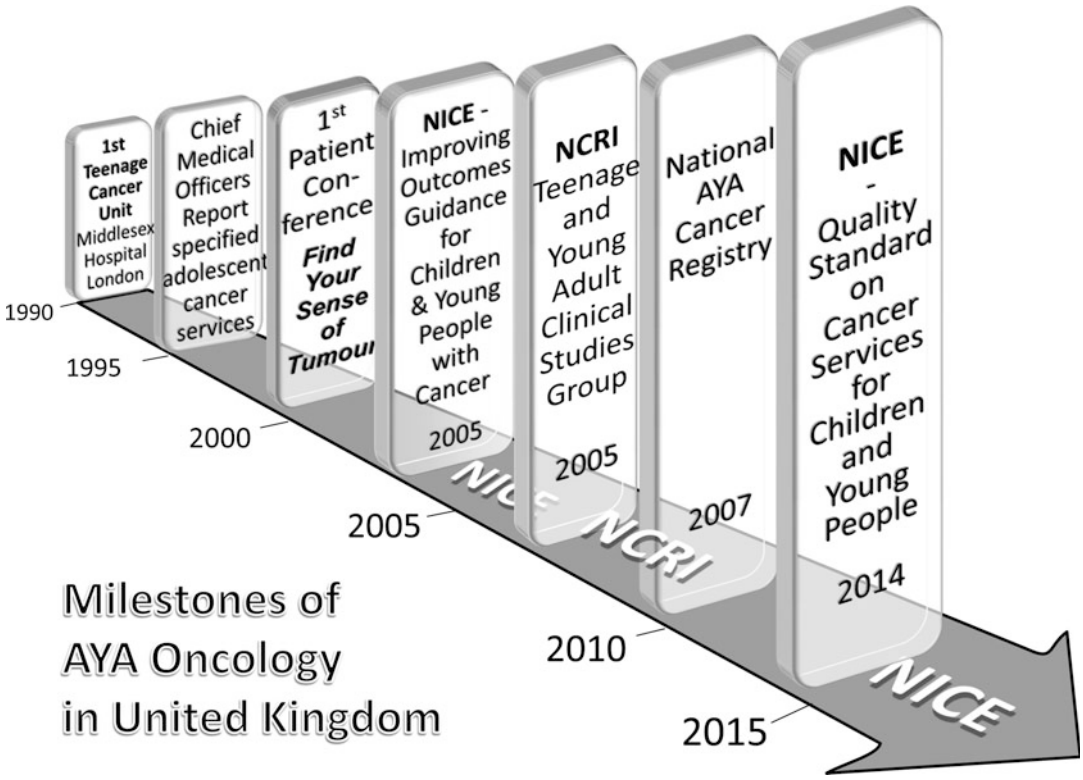

Fig. 1.2 Landmark events in the development of AYA oncology in the United Kingdom. *NICE* National Institute for Health and Care Excellence, *NCRI* National Cancer Research Institute

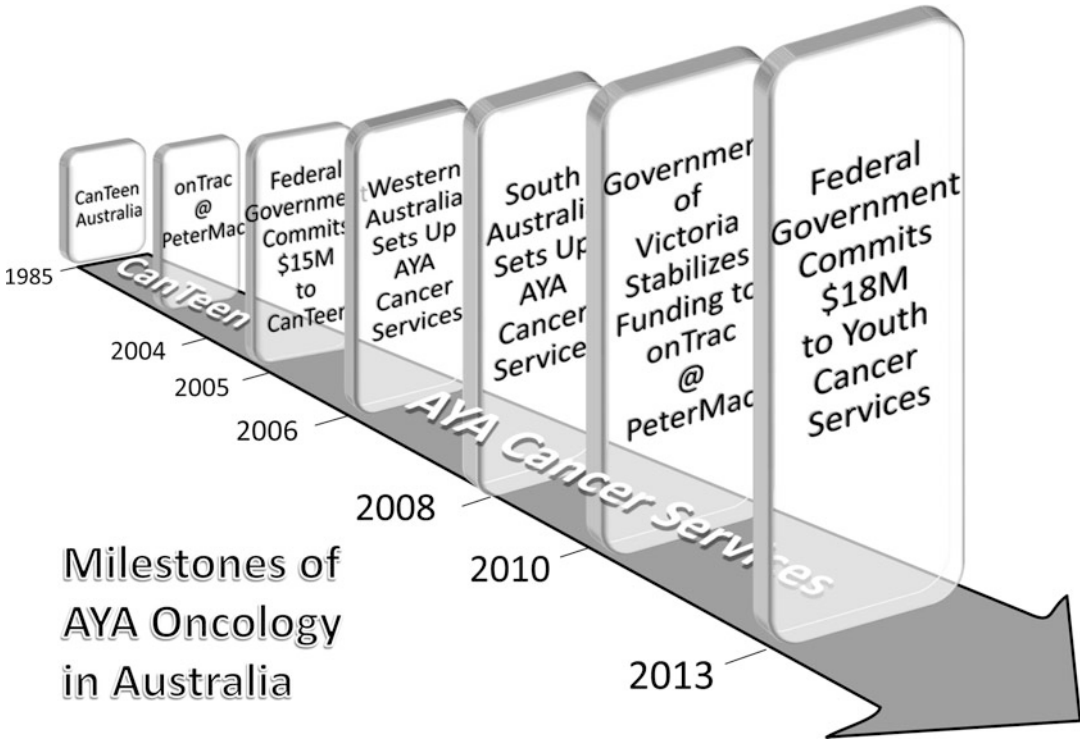

Fig. 1.3 Landmark events in the development of AYA oncology in Australia. *PeterMac* Peter MacCallum Cancer Centre

young adults, ages 13–24, in the United Kingdom since 1990 and continues to host a biennial international symposium. In 2005 the National Institute for Health and Care Excellence (NICE) in the United Kingdom issued a document entitled "Improving outcomes: Guidance in children and young people with cancer" that recommended, in particular, appropriate referral paths in England [22]. At about the same time, the National Cancer Research Institute formed a Teenage and Young Adult Clinical Studies Group (CSG), and the National Cancer Research Network (NCRN) was established. The NCRN set out to double the accrual to cancer clinical trials within 3 years for patients of all ages, from 3.5 % in 2001. This goal was surpassed easily, with a rate of 14 % achieved, and the United Kingdom was labeled "the cancer clinical trials recruitment capital of the world" [23].

The CSG reported in 2008 that accrual to cancer trials of young adults, ages 20–24 years, had declined and that no AYAs with brain tumors who were older than 16 years had been recruited to available trials [24]. In a report 6 years later [25], the CSG noted that accrual rates 15–19-year-olds had improved considerably. The work of the CSG will be a useful guide for the AYA intergroup of the NCTN.

In continental Europe there was limited activity in AYAO at the national level until 2010. An important boost was the provision of funding for 4 years (2011–2015) from the European Commission to build the European Network for Cancer Research in Children and Adolescents (ENCCA) [26]. This organization spans 11 countries and has 34 partners – health-care institutions, advocacy groups, pharmaceutical companies, regulatory bodies involved in drug development, and the health policy community. Although it will sunset in 2015, ENCCA will continue its work in AYAO as the European Network for Teenagers and Young Adults with Cancer. The success of ENCCA reflects its broad composition of stakeholders, especially the productive interaction

between pediatric and medical oncologists, a pattern that has been mirrored in some national projects, as exemplified in Italy where the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) that coordinates the care of children with cancer in all 49 children's hospitals in the country formed a committee on adolescents in 2010. A particular challenge encountered was the considerable variability in the upper age limit for admission to children's hospitals, some as low as 14 years. The AIEOP committee expanded to form SIAMO (Società Italiana Adolescenti con Malattie Oncoematologiche) that includes oncologists who provide care to adults, among other partners [27].

Meanwhile, across the other (bigger) "pond" from North America, Youth Cancer Services (YCS) in Australia received a further commitment of funding from the federal government in 2013, after an initial funding flow in 2007. There are five YCS centers in Australia that cover the entire country which has a large land mass and widely dispersed population. YCS was the product of the AYA Cancer Reference Group formed by Cancer Australia in 2007 and operates in partnership with *CanTeen*, a highly experienced and long-standing consumer support organization through which the federal funds flow (Fig. 1.3). CanTeen has also negotiated successfully with state governments and a large corporate charity, the Sony Foundation, for additional support. The need to develop different models of care, to accommodate the highly varied demography, has been well described [28]. It is exemplified by the functional partnership between the YCS in Adelaide, South Australia, and the Royal Darwin Hospital in Northern Territory – 3,000 km distant! Many of the lessons learned in tackling such challenges should prove to be of value in other parts of the world.

A parallel development over the years since the late 1990s has been the proliferation of AYA cancer websites and awareness generation via social media, starting with Teens Living with Cancer and Planet Cancer in 1999–2000 [29, 30], and rapidly expanded by *I'm Too Young For This* [31] and other progenitors. Today there are innumerable supportive care and informational websites.

So much for the advancement of AYAO in high-income countries (HICs), the great majority of young people live in less privileged societies where they constitute a higher proportion of the population [32]. It has been estimated that there are more than one million incident cases of cancer in AYAs and nearly 400,000 deaths globally each year [33, 34]. Who will provide appropriate care to them? As has been the pattern in HICs, the practitioners of pediatric oncology took up the gauntlet; a symposium on AYAO was held during the meeting of the International Society of Paediatric Oncology (SIOP) in Geneva [35]. But that was almost a decade ago (2006) and there had been no repetition on the SIOP agenda until 2014. Perhaps the leadership will come from our partners in the advocacy community who have been so successful to date. The LIVESTRONG, Teenage Cancer Trust, and CanTeen have all made their mark. Together with CanTeen New Zealand, and Seventy K, these organizations drafted the *International Charter of Rights for Young People with Cancer* in 2010 [36]. Could they form the basis of a truly global initiative, similar to Childhood Cancer International? If so we should all put our collective shoulders to that wheel.

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Cancer Incidence, Survival, and Mortality Among Adolescents and Young Adults

2

Lynn Ries, Annalisa Trama, Kayo Nakata, Gemma Gatta, Laura Botta, and Archie Bleyer

Abstract

While the epidemiology of cancer has been studied in children and older adults for more than a half century, little attention had been paid to the cancers in between those that occur in the older adolescents and young adult (AYA) between 15 and 40 years of age. Yet as recently ascertained, more than a million new cases of invasive cancer are diagnosed in AYAs annually worldwide. Not only are the array of cancers that are diagnosed in AYAs unique, accumulating evidence suggests that many are biologically distinct from what appears to be the same neoplasm in younger and older persons. AYA cancers may thereby have different etiologies and require different therapeutic strategies. Many cancers peak in incidence in AYAs, and there is an intermediate peak between the well-known childhood cancer peak and the predominant one that occurs in the elderly. If the cancers that account for the childhood peak are embryonal/fetal cancers and those that account for the peak late in life as the

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cancers of aging, the AYA peak may be considered as due to cancers of intermediate growth and maturation. For most of the past quarter century, the incidence of the AYA cancers has been increasing for reasons that have not been ascertained. In Europe, the United States, and Japan, the 5-year survival rates of the vast majority of cancers in AYA have been remarkably similar. In the United States, the overall rate of survival improvement had been less in AYAs than in either younger or older patients. The trends and patterns of incidence do offer certain clues as to cancer causation in AYAs and potential methods of prevention. Detailed analyses of incidence patterns by geographic region and demographic factors together with determination of variations in incidence in time and space should provide additional insights into etiology and separate lines of investigation and therapeutic opportunities.

2.1 Introduction

Since the first edition of this textbook was published, we have learned that more than one million new cases of invasive cancers have been diagnosed annually worldwide in adolescent and young adult (AYA) persons (Table 2.1). In most socioeconomically advantaged countries, cancer is a leading cause of death due to disease among AYAs. In the United States, cancer is the second most common cause of death due to disease, after suicide, and the most common cause of death in AYA females.

This chapter expands the age range used in the first edition of 15–29 years of age to a higher upper age limit, 39 years, as defined by the National Cancer Institute Progress Review Group of 2004–2005 [1] and explained in the introductory chapter. Thus, most of the data in this chapter are new, and previously unreported observations are identified as such. The overview in this chapter emphasizes general epidemiologic and survival comparisons of the different cancers by sites and organ systems and how they vary over age, sex, and time. To the extent possible, global, continental, and national data, including those of regional areas in Europe, of Japan, and of the United States, are included. Detailed results for specific sites can be found in the site-specific chapters.

2.2 Sources of Information and Modes of Analysis: Incidence, Survival, and Mortality

2.2.1 Age

The age range for AYAs in this edition of the textbook is 15–39 years, inclusively. It had been 15–29 years in an initial United States (US) National Cancer Institute (NCI) treatise [2], but during the second NCI Workshop on AYA oncology, the upper age limit was raised to 39 years [1]. The Progress Review Group (PRG) on AYA Oncology in 2004–2005 affirmed this age range with full cognizance of the increased heterogeneity and diversity that the additional years encompassed [3].

2.3 Data Sources and Analyses

The data from Europe were obtained from EUROCARE-5 for survival analyses (Fig. 2.1). The data from Japan are taken from six prefectures (J-CANSIS) (Fig. 2.1) representing 14 % of the country's population and in more detail from the Osaka Cancer Registry. Data from the United States were obtained from the NCI Surveillance, Epidemiology, and End Results (SEER) Program

Table 2.1 Worldwide cancer incidence and death: frequencies and rates for ages 15–39 in 2012 based on GLOBOCAN, 2012

Age 15–39	**Estimated cases**[a]	**Incidence rate**	**Estimated deaths**	**Death rate**
All cancers	1,048,821	37.5	390,579	14.0
Males	383,209	26.8	183,116	12.8
Females	665,612	48.7	207,463	15.2
LDR[b]	807,768	33.8	349,529	14.6
MDR[c]	241,053	58.4	41,050	9.9
Age group	**Estimated cases**	**Incidence rate**	**Estimated deaths**	**Death rate**
All ages[d]	14,067,894	182.0	8,201,575	102.4
0–14	163,284	8.8	79,956	4.3
15–39	1,048,821	37.5	390,579	14.0
40–44	655,050	138.8	264,542	56.1
45–49	933,844	220.9	409,105	96.8
50–54	1,239,316	338.2	577,123	157.5
55–59	1,577,831	489.1	784,558	243.2
60–64	1,765,236	683.9	929,790	360.2
65–69	1,671,710	895.8	939,692	503.6
70–74	1,609,588	1114.4	1,023,544	708.7
75+	3,403,214	1544.0	2,802,686	1271.6

Source: GLOBOCAN 2012, IARC – 14.9.2015: http://globocan.iarc.fr, IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France

[a]All invasive cancers except basal and squamous skin cancer

[b]*LDR* less developed regions, all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia, and Polynesia

[c]*MDR* more developed regions, all regions of Europe plus Northern America, Australia/New Zealand, and Japan

[d]All ages, rates are ASR. Other rates are crude

(Fig. 2.1). GLOBOCAN data were used to assess incidence by continent and in Europe by region.

2.3.1 Incidence

GLOBOCAN estimates for 2012 were used for the worldwide projections of cancer incidence counts and rates by sex and cancer site [4]. For the presentation of the incidence data by population, we identified first two large geographic regions: a more developed region (MDR) including all regions of Europe plus Northern America, Australia/New Zealand, and Japan versus less developed regions (LDR), including all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia, and Polynesia. Furthermore, for a more detailed description, we also identified six geographic regions: North America (N America) (United States and Canada) and Northern, Western, and Southern Europe (N, W, S Europe), Central and Eastern Europe (C & E Europe), South America (S America), Asia, and Africa. A listing of the countries in each group can be found in the reference for GLOBOCAN [5].

The SEER Program collected cancer incidence and survival data on approximately 10 % of the US population between 1973 and 1992 (SEER9), 14 % of the US population between 1992 and 2000 (SEER13), and 26 % thereafter (SEER18) (Fig. 2.1), the last of which has 28–29 % of the country's 15- to 39-year-olds. The SEER Program, described in detail elsewhere [6], collects information on primary site and detailed histology according to the International Classification of Diseases for Oncology third edition (ICD-O-3) [7] since 2001. Prior to 2001, site and histology were collected based on International Classification of Diseases

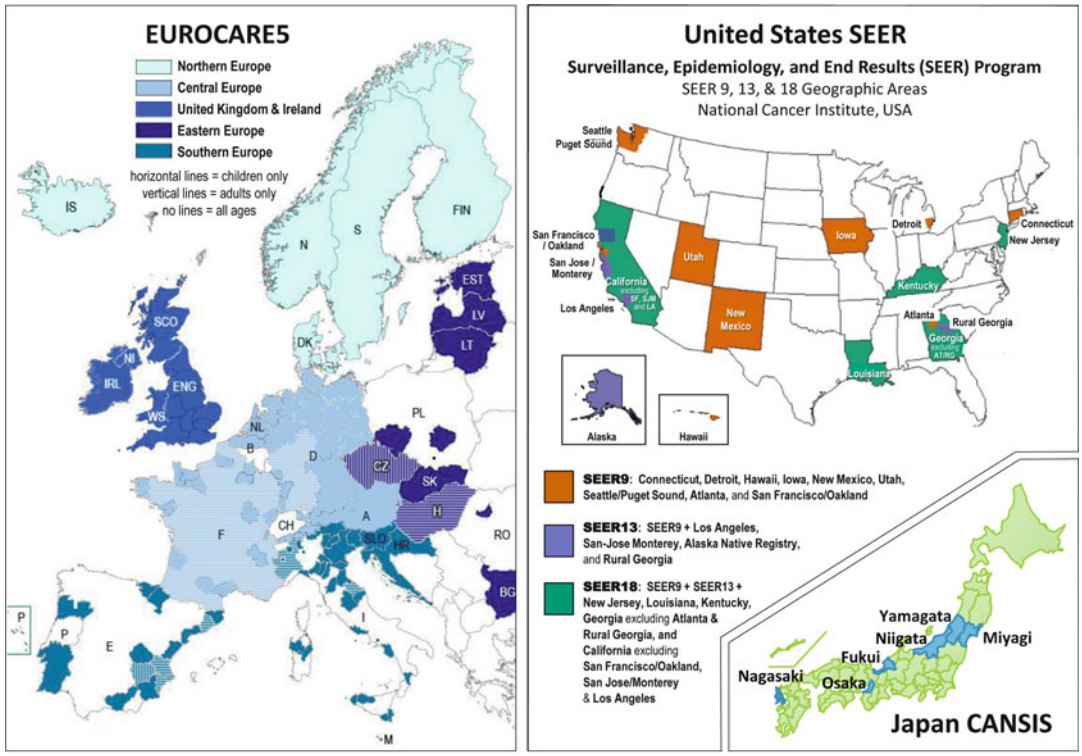


Fig. 2.1 Cancer registries included in EUROCARE-5, US SEER, and J-CANSIS

for Oncology 1976 (ICD-O-1) up to 1992 and International Classification of Diseases for Oncology second edition (ICD-O-2) [8] from 1992 to 2000. The ICD-O-3 hematopoietic codes were updated based on WHO classification of tumours of haematopoietic and lymphoid tissues (2008) [9]. Long-term trends were based on 9 SEER geographic areas (SEER9) [10] and more recent information since 2000 on 18 SEER geographic areas (SEER18) [5]. SEER*Stat (version 8.1.5), Excel 2007, and STATA 13 were used for analysis of SEER data.

In order to analyze site and histology, the SEER data were recoded into meaningful groups. For some chapters, the AYA recode based on Barr et al. [11] was used because it was designed to group site and histology with an emphasis on histology for the AYA age group. The AYA recode was adapted slightly to account for the new hematopoietic codes implemented in 2010 [12]. Since the upper age limit of the AYA age group was raised to 39 years of age [1], some of the chapters used the SEER site recode [13] to emphasize primary site, i.e., all histologies except lymphoma are included for each of the solid tumors. In the AYA recode, the histologies are usually limited to carcinomas for the solid tumors and excluded in situ tumors. In situ cancers of the bladder were combined with the invasive tumors, and pilocytic astrocytomas were excluded.

2.3.2 Survival

European survival data were obtained from EUROCARE (EUROpean CAncer REgistry-based study on survival and care of cancer patients) fifth edition [14]. EUROCARE is the widest collaborative research project on cancer survival in Europe. It started in 1989 to provide an updated description of cancer survival time trends and survival differences across European countries, measure cancer prevalence, and study patterns of care of cancer patients. The fifth edition, EUROCARE-5, included data on more than

21 million cancer diagnoses provided by 116 cancer registries (including 10 specialized childhood cancer registry) in 30 European countries from Jan 1, 1978, to Dec 31, 2007, with the date of death updated to at least December 31, 2008 (except for France cancer registries; December 31, 2007) (Fig. 2.1) [15].

Survival was analyzed for 56,505 cancer cases in European children (age <15 years), 312,483 cancer cases in AYAs (age 15–39 years), and 3,567,383 cancer cases in adults (40–69) diagnosed during the period 2000–2007. Only malignant cancers were included (pilocytic astrocytoma was excluded). Patients who had more than one type of cancer were included in the survival analyses; thus, if two or more cancers were diagnosed in a single patient, all were included in the analyses. More information on the database and the quality can be found in Trama et al. [16].

Individual types of AYA cancers were grouped into 19 diagnostic categories affecting AYAs and children and 20 carcinoma categories affecting AYAs and adults (Table 2.4) defined by the International Classification of Childhood Cancers (ICCC) third edition [17] with the addition of "all cancers combined." We estimated relative survival, the ratio of observed survival to the expected survival in the general population of the same age and sex, to correct for deaths from causes other than the cancer under investigation. We used the cohort approach, Ederer II method [18], to estimate survival for patients diagnosed in 2000–2007 and followed up until at least the end of 2008, enabling estimation of 5-year relative survival. We used a complete analysis which is a modification of traditional cohort analysis, in which more recently diagnosed patients are also included, even if they could not possibly have completed the entire follow-up interval of interest [19].

The differences in survival by age groups (0–14 vs 15–39 and 15–39 vs 40–69) were tested with a z test with a significance level $\alpha = 0.05$ [20]. The survival for the comparison of adults and AYAs was truncated at 69 years of age. To compare children and AYAs, survival in Europe as a whole was obtained by directly weighting the regional grouping survival estimates with weightings proportional to the population of 0–39 years in each regional grouping in 2000–2007. To provide the overall EU survival for adults, the weighting used to estimate survival in Europe was proportional to the adult population (15–99 years) [21].

Japanese survival data were obtained from J-CANSIS (Japanese CANcer Survival Information for Society), representing 14 % of the country's population. J-CANSIS data were provided by the population-based cancer registries of six prefectures (Yamagata, Miyagi, Fukui, Niigata, Osaka, and Nagasaki). These prefectural cancer registries have cancer records with high data quality (death certificate only = 3.9–17.7 %) and have been used to estimate national statistics for cancer survival in Japan for a long time. Survival was analyzed for 1852 Japanese children (aged 0–14 years) and 13, 190 AYAs (age 15–39 years) diagnosed with cancer during the period 2000–2006. The same site/histology groupings as in the European and SEER data were used (pilocytic astrocytoma was excluded). The maximum likelihood method was applied to estimate relative survival using the strel command in the publicly available STATA program. More information on the database and its quality can be found elsewhere [22].

To assess changes in survival over time from 1999 to 2007, 5-year relative survival was estimated by the period approach [19] for patients under observation/follow-up in 1999–2001 (diagnosed 1995–2001), 2002–2004 (diagnosed 1998–2004), and 2005–2007 (diagnosed 2001–2007). To assess the statistical significance of survival changes over time, the relative survival was modeled with a generalized linear model, which implies a Poisson distribution of the number of observed deaths in each interval. The Poisson regression model, with the year of diagnosis included as a continuous variable, was used to obtain the average yearly reduction in mortality for the period of diagnosis 1999–2007 expressed as the relative excess risk of death. The relative excess risk of death was estimated for each diagnostic group for Europe as a whole adjusted by country, age class, sex, and year of diagnosis.

The US survival data from 18 SEER geographic areas from 2000 to 2007 were used for the comparison of survival data from Europe and Japan. The same site/histology groupings were used as in the European data: in situ bladder cancers were included, and pilocytic astrocytomas were excluded. For urinary bladder, benign, in situ, and invasive tumors were included for Europe and in situ and invasive tumors for SEER. In addition, carcinoids (ICD-O-3 8240–8244) were excluded from the colon and appendix in both the European and SEER analyses.

Five-year survival trends in the United States were assessed from 1975 to 2012 by excluding Kaposi sarcoma and non-Hodgkin lymphoma in males and thyroid cancer in females. The former was necessary since the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic during the 1980s and early 1990s markedly increased the incidence of Kaposi sarcoma and non-Hodgkin lymphoma (NHL) in AYA males, cancers with such a poor prognosis that the overall survival rate substantively declined. The latter was necessary because of the overdiagnosis of thyroid cancer, predominantly in females, that began in the 1990s and has escalated since, progressively inflating the overall survival in AYA females.

2.3.3 Mortality

GLOBOCAN estimates for 2012 were used for the worldwide projections of cancer mortality counts and rates by sex and cancer site [10]. The US mortality data were from the National Center for Health Statistics (NCHS) as analyzed by the SEER Program which obtained files containing all deaths occurring in the United States by calendar year since 1969. Further details can be found elsewhere [6]. Only the underlying cause of death was used in the calculation of death rates. Cause of death was coded according to ICD-9 (1979–1988) and ICD-10 (1999+). Mortality groupings were used that correspond to the SEER site recode [17].

2.4 Global, Regional, and National Perspectives

2.4.1 Incidence

2.4.1.1 Cancer Incidence Worldwide

Worldwide over one million AYAs aged 15–39 years were diagnosed with malignant cancer in 2012 based on GLOBOCAN [4] (Table 2.1), which is 7 % of the 14.1 million new cancer cases of all ages worldwide estimated by GLOBOCAN for the same year [23].

The mix of malignant tumors in AYAs differs from that for all ages combined and from that in both younger and older persons. For all ages and both sexes, the top five cancers worldwide in 2012, in order of incidence, were cancer of the lung (13 %), breast (12 %), colorectum (10 %), prostate (8 %), and stomach (7 %) [23]. For AYAs, the order for the same year was breast cancer (18 %), cervix uteri cancer (11 %), thyroid cancer (8 %), leukemia (6 %), and central nervous system (CNS) tumors (4 %) (Table 2.2). In the United States, the predominant cancers in AYA males and females differ from the worldwide sequence in that, for the year 2012, the order was thyroid carcinoma (16 %), breast carcinoma (15 %), melanoma (9 %), cervix uteri carcinoma (7 %), and colorectal carcinoma (6 %).

Figures 2.2 and 2.3 illustrate with the United States data how the cancer mix in AYAs is highly age dependent within the AYA age span, as the cancers of childhood transit to those in adulthood (Fig. 2.2). From the youngest AYAs to the oldest, the incidence of breast cancer increases from extremely rare to the most frequent cancer. Cancer of the female genital tract (cervix, uterus, vagina, vulva) undergoes a similar increase. Leukemia on the other hand decreases from the most frequent type in children to a few percent in the oldest AYAs. When considered as a proportion of all cancer (Fig. 2.3), at least seven cancers have their highest percentage within the AYA age range: thyroid cancer, Hodgkin lymphoma, testis cancer, osteosarcoma, Ewing tumor, and Kaposi sarcoma. More than half of the cancers in AYAs are accounted for by those

Table 2.2 Worldwide estimated cancer incidence and mortality frequencies for ages 15–39 in 2012 based on GLOBOCAN

	Incidence					Mortality				
Cancer	Males and females	Males	Females	Overall rank	Male to female ratio	Males and females	Males	Females	Overall rank	Male to female ratio
All cancers[a]	1,048,821	383,209	665,612		0.6	390,579	183,116	207,463		0.9
Bladder	7401	4856	2545	21	1.9	1639	1149	490	22	2.3
Brain, nervous system	46,915	26,670	20,245	5	1.3	23,661	13,814	9847	5	1.4
Breast (female only)	191,844		191,844	1		48,961		48,961	1	
Cervix uteri	111,503		111,503	2		28,201		28,201	4	
Colorectum	42,647	21,947	20,700	7	1.1	21,474	10,979	10,495	6	1.0
Corpus uteri	15,535		15,535	18		1608		1608	23	
Gallbladder	3879	1401	2478	24	0.6	2411	958	1453	21	0.7
Hodgkin lymphoma	28,330	15,396	12,934	11	1.2	6199	3727	2472	14	1.5
Kaposi sarcoma	22,975	14,437	8538	16	1.7	8795	5032	3763	12	1.3
Kidney	13,660	7798	5862	19	1.3	3722	1912	1810	19	1.1
Larynx	3506	2575	931	25	2.8	1388	1002	386	24	2.6
Leukemia	61,432	35,313	26,119	4	1.4	45,169	26,322	18,847	2	1.4
Lip, oral cavity	24,251	15,267	8984	14	1.7	10,327	7836	2491	10	3.1
Liver	42,372	32,871	9501	8	3.5	37,528	29,765	7763	3	3.8
Lung	23,182	13,465	9717	15	1.4	15,977	9636	6341	9	1.5
Melanoma of the skin	26,600	10,055	16,545	12	0.6	3200	1642	1558	20	1.1
Multiple myeloma	2277	1444	833	26	1.7	743	497	246	27	2.0
Nasopharynx	15,949	10,340	5609	17	1.8	5547	3505	2042	15	1.7
Non-Hodgkin lymphoma	45,824	27,229	18,595	6	1.5	20,214	12,118	8096	7	1.5
Esophagus	8737	5362	3375	20	1.6	6986	3927	3059	13	1.3
Other pharynx	5727	3726	2001	22	1.9	3935	2680	1255	17	2.1
Ovary	31,492		31,492	10		9498		9498	11	
Pancreas	5310	2800	2510	23	1.1	3888	2243	1645	18	1.4
Prostate	1087	1087		27		978	978		26	
Stomach	26,313	13,598	12,715	13	1.1	18,697	9689	9008	8	1.1
Testis	33,871	33,871		9		4233	4233		16	
Thyroid	83,980	16,734	67,246	3	0.2	1116	251	865	25	0.3

Source: GLOBOCAN 2012 (19.3.2015v): http://globocan.iarc.fr, IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France

[a]All invasive cancers except basal and squamous skin cancer

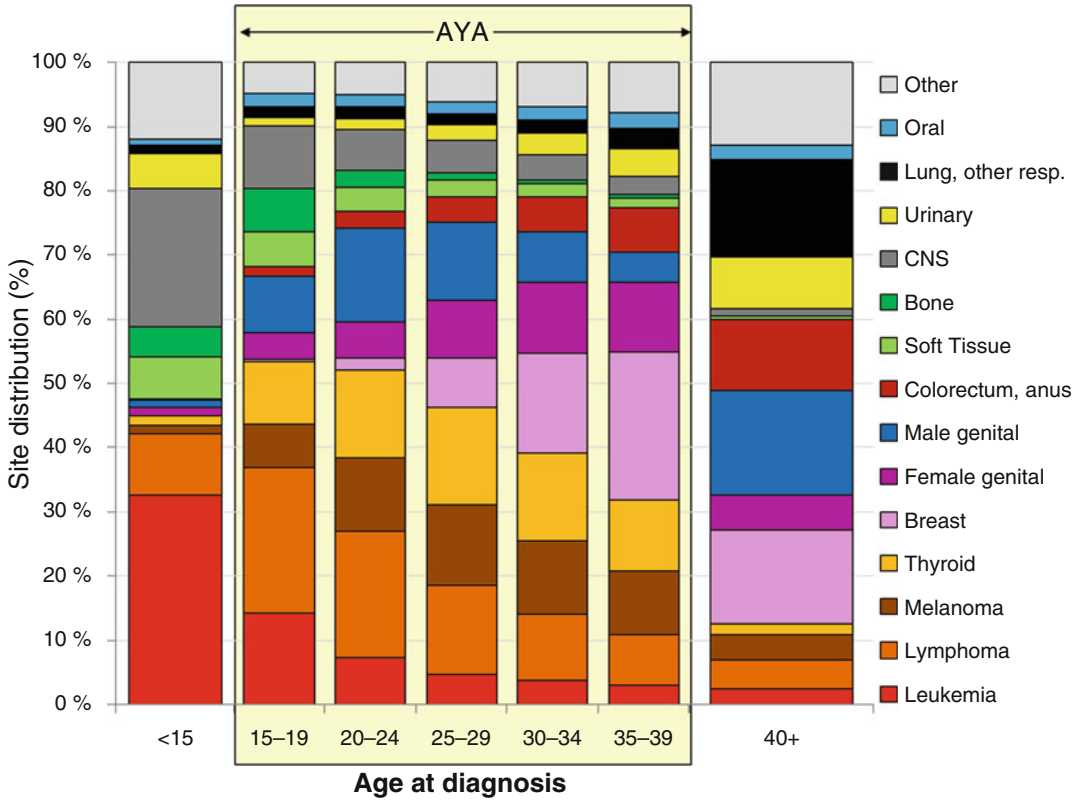


Fig. 2.2 Cancer site distribution, US SEER18, 2000–2011, by age

that peak in proportion during the AYAs years, further rendering the array of cancer types unique to the age group.

Nearly two-thirds of the incident cases were in females because the most common cancers in this age group are female-specific tumors (cervix uteri and other female gynecologic malignancies) or sites where the rates among females are much higher than for males (breast and thyroid) (Table 2.2). The most common cancer site for ages 15–39 years was female breast cancer with nearly 192,000 cases worldwide in 2012. The second most common was cancer of the cervix uteri and third was cancer of the thyroid, with 112,000 and 84,000 cases, respectively (Table 2.2). In AYA males, the most common was the leukemia, with 35,000 cases worldwide in 2012, followed by testis cancer and liver cancer with 34,000 and 33,000 cases, respectively (Table 2.2).

2.4.1.2 Worldwide Geographic Variation

A broad grouping was used as a first cut of MDR. Since the populations of the LDR are so much greater than the MDR, it is expected based on GLOBOCAN estimates that more than two-thirds of the cases among 15–39-year-olds will reside in LDR, while the incidence rate is lower in LDR than MDR (Table 2.1).

Worldwide, the cancer incidence rates for AYAs vary from country to country and continent to continent. Figures 2.4 and 2.5 show, for males and females, respectively, the higher rates of total invasive cancers for North America (N America) (United States and Canada) and Northern, Western, and Southern Europe (N, W, S Europe) compared to the overall world rate of Central and Eastern Europe (C and E Europe), South America (S America), Asia, and Africa. While the overall cancer rates for N America and N, W, S Europe

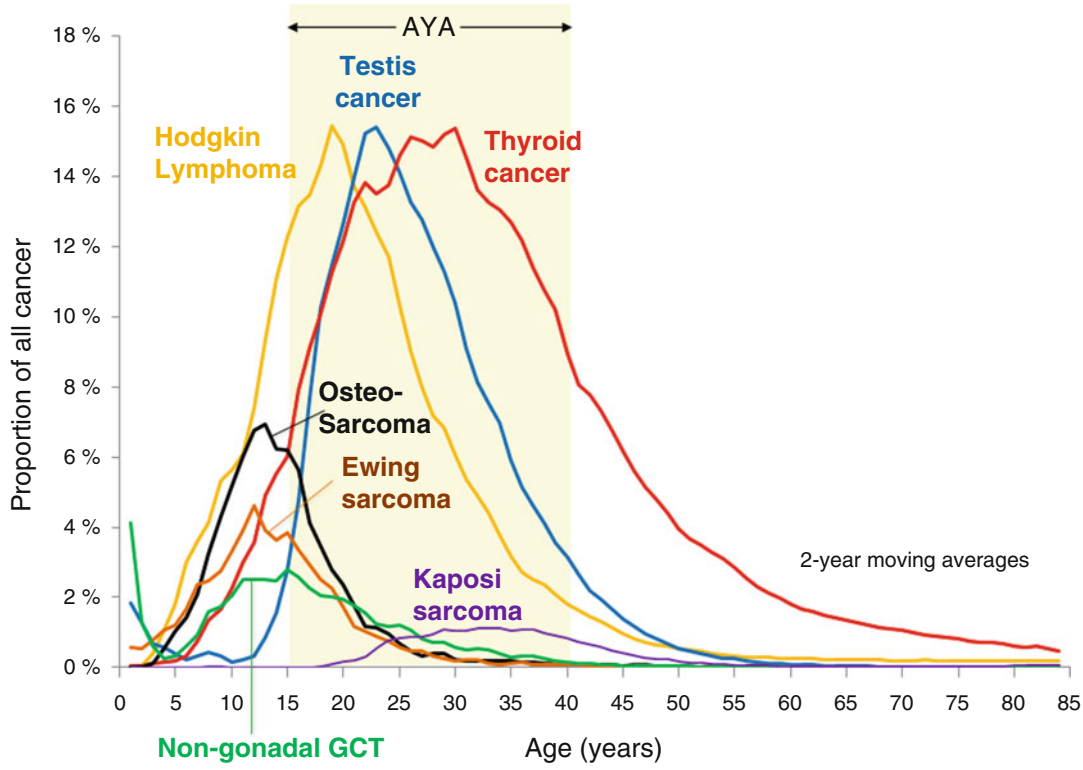


Fig. 2.3 Invasive cancers that have the highest proportion in AYAs, US SEER13, by single year of age

are similar, there are differences by site. In males, colorectal and renal cancer and leukemia and thyroid cancers are higher in N America, and melanoma and testicular cancer are higher in N, W, S Europe. The high rate in males of Kaposi sarcoma (KS) in Africa is in sharp contrast to the almost nonexistent KS rate in Asia and C and E Europe. Liver cancer is higher in Africa and Asia than in Europe (N, W, S and C and E Europe) and N America. In contrast, leukemia incidence rates in males are much lower in Africa than the other countries. Testicular cancer is much higher in N America and N, W, S Europe than in other regions. The incidence of nasopharyngeal cancer is higher in Asia than in any other regions.

For females (Fig. 2.5), the AYA breast cancer rates are similar between N, W, S Europe and N America, but nearly double those for the other regions. The rates for cancer of the cervix uteri range from a low of 6.7 in N America to a high of 14 per 100,000 females in S America and C and E Europe where it is the number one cancer among AYA females. The cervical cancer rates for N, W, S Europe are lower than for C and E Europe. However, in North Europe, cervix cancer incidence is also high in the Baltic countries which are included in the N, W, S Europe (data not shown). Thyroid cancer among AYA females in N America has more than double the rate of any other group of countries, and the thyroid cancer rate in Africa is one-twentieth that of N America. For females, N America has the highest rates for cancers of the colorectum, corpus uteri, and kidney and leukemia and NHL. S America has the highest rate for cancers of the ovary and the second highest rate for corpus uteri. While the KS rate among African females is lower than that for African males, the rate for African females is much higher than in the other country groups. Melanoma is higher in N, W, S Europe and N America and very low in Asia and Africa. For AYA females, nearly half of the

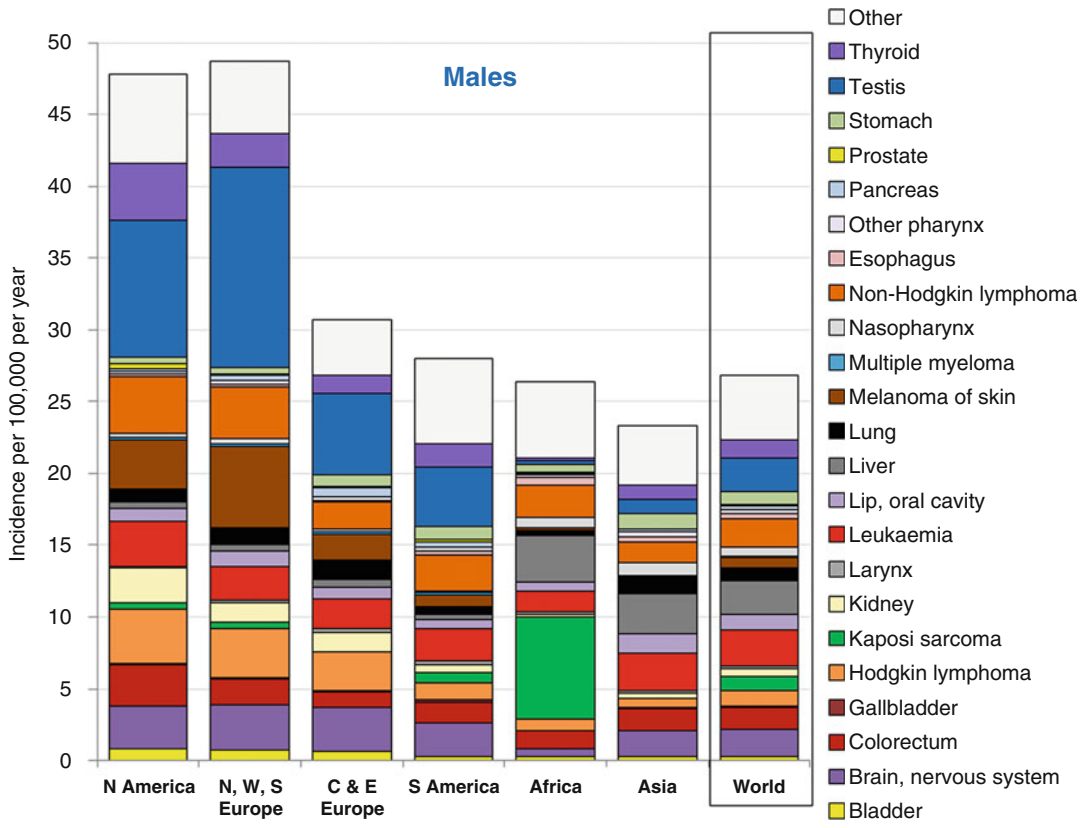


Fig. 2.4 World cancer crude incidence rates, age 15–39, 2012, by geographic area and site, males. GLOBOCAN, *N* North/Northern, *S* South/Southern, *W* Western, *C* Central, *E* Eastern

cancers are breast or thyroid in N America and breast or cervix in C and E Europe, S America, Africa, and Asia. While Asia has the lowest breast cancer rate, breast cancer comprises nearly 30 % of the cancer burden among AYA females.

2.4.1.3 Overall Incidence by Single Years of Age (US SEER)

Since GLOBOCAN data are not available in finer age breakdowns than 15–39 years of age, SEER data were used to show how the cancer sites can vary across the age groups comprising the AYA group. Figure 2.6 shows the incidence rates for males and females by single years of age. After the childhood cancer peak between 2 and 4 years of age, the incidence decreases until age 8 in girls and 10 in boys and then increases exponentially until age 60 after which the increase slows until it plateaus after age 80. In females, the incidence is a smoothly exponential phase from age 10 to 50, whereas in males it is triphasic with separate exponential phases from age 10 to 25, 25 to 40, and 40 to 60. Males have a higher incidence from infancy to age 20 and after age 55, whereas females have a distinctly higher rate in between and particularly during the older AYA years.

2.4.1.4 Individual Cancer Incidence by 5-Year Age Intervals (US SEER)

For ages 15–39 years, the overall cancer incidence rate increases with each 5-year age group from around 20 (ages 15–19) to 130 (ages 35–39) per 100,000 (Fig. 2.7). The rates for the 35–39-year-olds are much higher than the rates for other age groups for males and

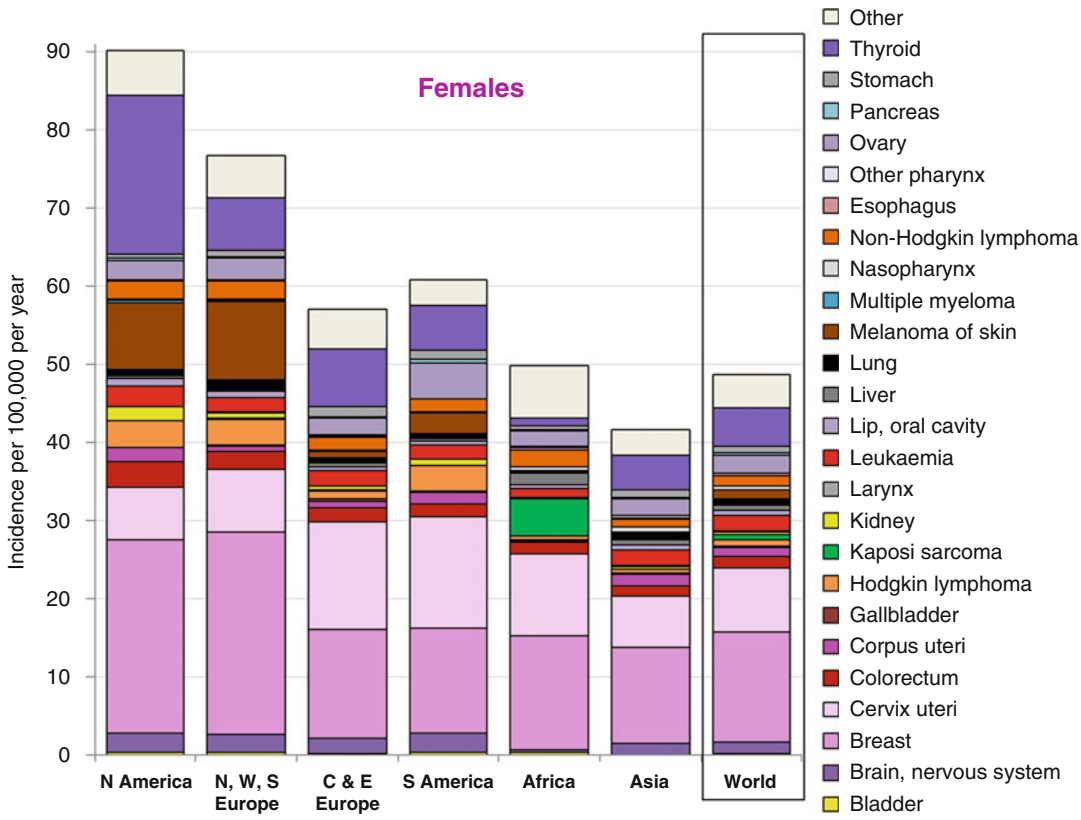


Fig. 2.5 World cancer crude incidence rates, age 15–39, 2012, by geographic area and site, females. GLOBOCAN, *N* North/Northern, *S* South/Southern, *W* Western, *C* Central, *E* Eastern

females. The rates for children under 15 years of age are less than the 15–19 age group and for those 40 and over are much greater (notice the scale break) than the 35–39 age group. For males (Fig. 2.8), the incidence rates range from less than 25–90 per 100,000 compared to a range of less than 25 to over 170 per 100,000 for females. For the older AYA age groups especially 35–39 years, the overall rates for males (Fig. 2.8) are lower than that for females (Fig. 2.9). Even though breast cancer is predominately a cancer for females, it remains the cancer with the highest rate for both males and females combined and females alone for the 35–39-year age group. The increase in the breast cancer rate across the female age groups is dramatic, and it ranges from 0.2 for ages 15–19 to 60.1 per 100,000 for females aged 35–39 (Fig. 2.9).

2.4.1.5 Individual Cancer Incidence by Age Group, Site, and Sex (US SEER)

In order to portray the incidence rates and trends more graphically, broader groups of sites were used in Figs. 2.7, 2.8, and 2.9. For males, genital (mostly testicular) cancer predominates for most age groups (from 20 years onward) except age group 35–39 in which three sites (lymphoma, male genital, and melanoma) dominate the picture.

For males aged 15–19 years, more than half of the cancers are leukemia, lymphoma, or genital tumors with corresponding rates of 3.6, 5.2, and 3.7 per 100,000. For males, the colorectal cancer rates increase from less than 1 per 100,000 for ages 15–19 to nearly 10 per 100,000 in 35–39-year-olds. Similarly, there is a large increase in cancer risk for melanoma between

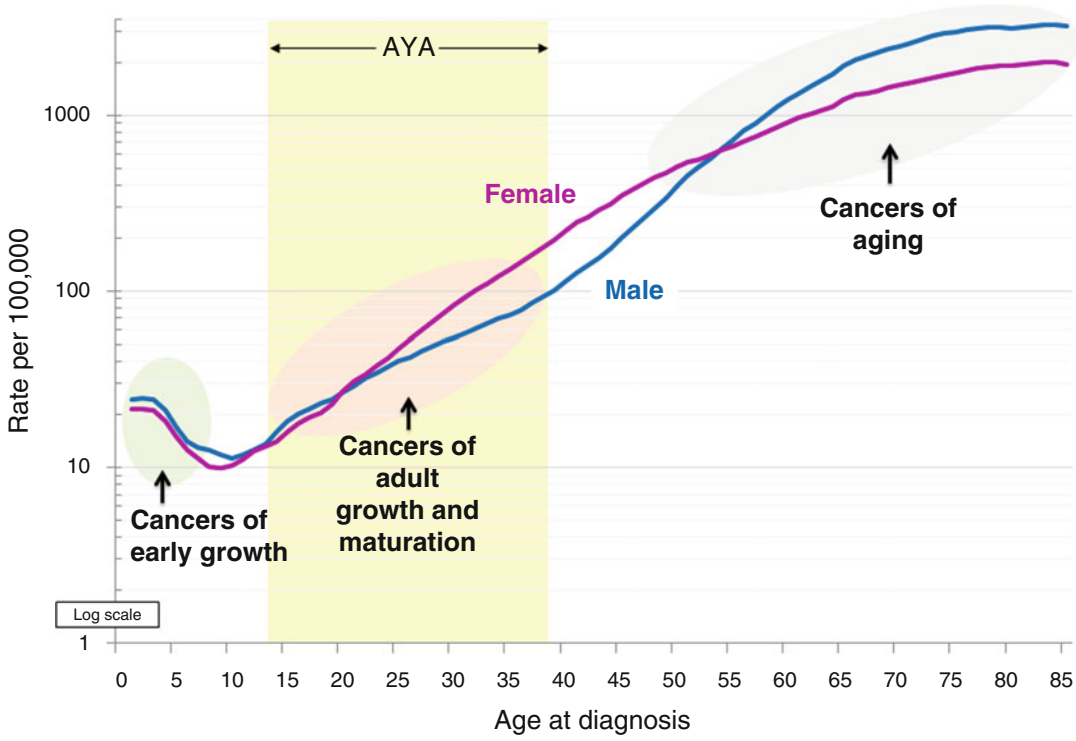


Fig. 2.6 Incidence of invasive cancer, 2000–2011, US SEER18, by single year of age and sex

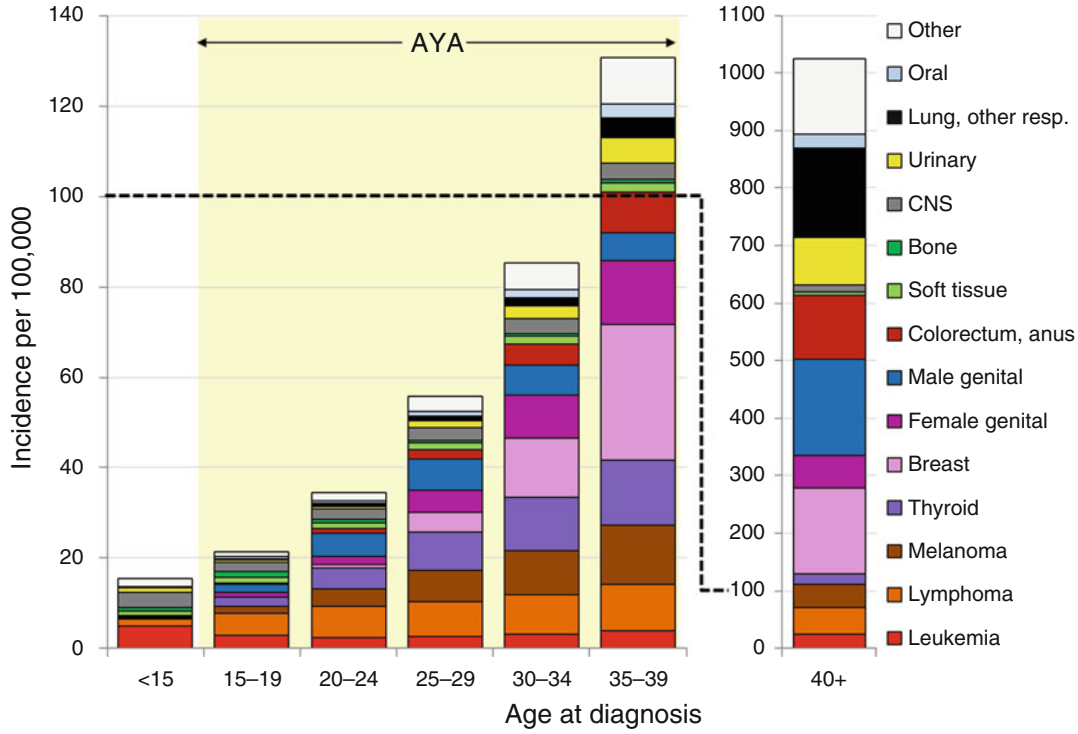


Fig. 2.7 Cancer incidence rates, 2000–2011, US SEER18, males and females, by site and age

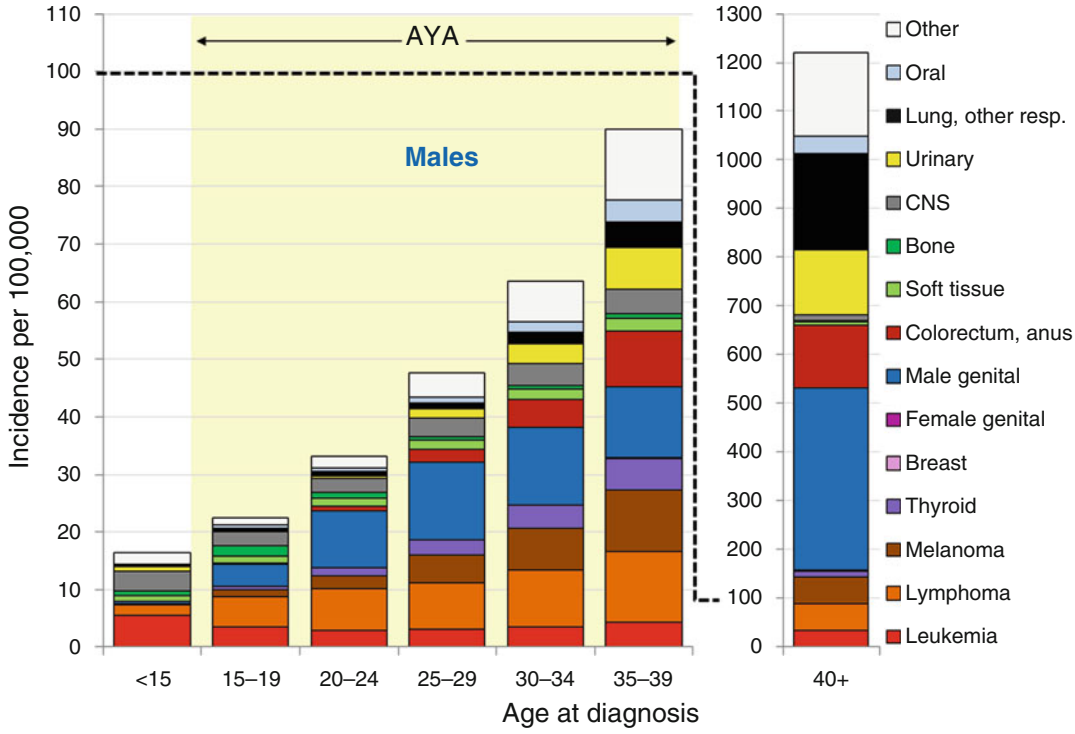


Fig. 2.8 Cancer incidence rates, 2000–2011, US SEER18, males, by site and age (Note that the ordinate scale is different here from that used in Fig. 2.9)

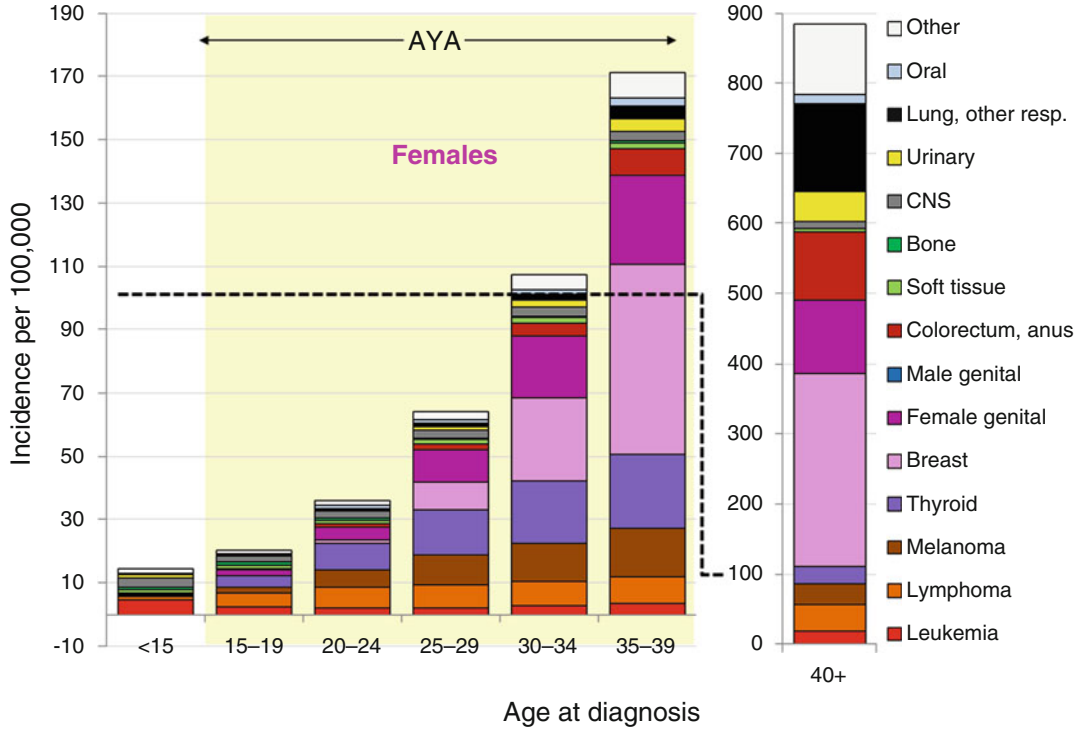


Fig. 2.9 Cancer incidence rates by site and age, 2000–2011, US SEER18, females (Note that the ordinate scale is different here from that used in Fig. 2.8)

ages 15–19 and 35–39. Invasive CNS tumor rates and leukemia rates varied between 2 and 4 per 100,000 across all AYA age groups.

In proportional terms, breast cancer alone comprises 35% of all female cancers in the 35–39-year age group and together with thyroid and genital cancers comprise over half of the cancers in this age group. Breast cancer is very rare for 15–19 (0.2) in comparison to 60 per 100,000 for ages 35–39. Large increases in rates across the age groups were seen for melanoma and cancers of the thyroid, genital tract, and colorectum.

Figure 2.10 shows the incidence rates for ages 15–39 combined by sex for a detailed list of over 25 cancer sites. Based on US SEER data, breast cancer is the number one cancer among AYA females with a rate of nearly 21 per 100,000, which is more than double the highest rate among males, cancer of the testis (10.17 per 100,000) (Fig. 2.10). For females, thyroid and melanoma complete the top three and for males, melanoma and NHL complete the top three. Cancer among AYAs is relatively rare with only female breast cancer, female thyroid cancer, and cancer of the testis with rates over 10 per 100,000 females/males.

2.4.1.6 Incidence Trends by Site (US SEER)

Figure 2.11 depicts for American AYAs the average annual percent change (APC) during 2000-2011 of the incidence rate of cancer and of 28 individual types of cancer for females and for males. The average was 1% per year in females and 0.25% per year in males. For females, about half of the cancers show decreasing incidence trends and half show increasing trends. For males, more cancers decreased than increased in incidence. Lung and cervix uteri showed the largest decreases for females, whereas Kaposi sarcoma, anus, eye, and urinary bladder had decreases of more than 2% per year for males. Two cancers, those of the kidney and thyroid, have had disproportionately greater increases in both females and males. For kidney cancer, the increases were 6.1% and 5.8% per year in males and females,

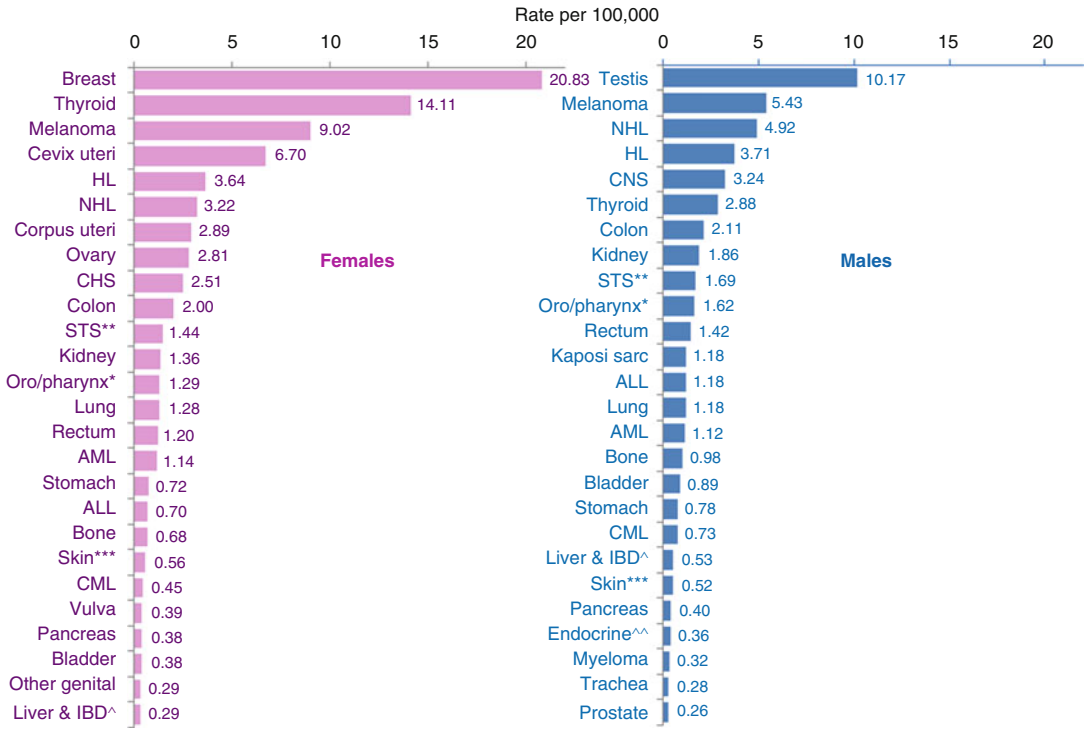


Fig. 2.10 Cancer incidence rates, 2000–2011, ages 15–39, US SEER18, by site and sex. *oral cavity and oropharynx **soft-tissue sarcoma ***nonmelanoma skin cancer ^intrahepatic bile duct ^^non-thyroid endocrine

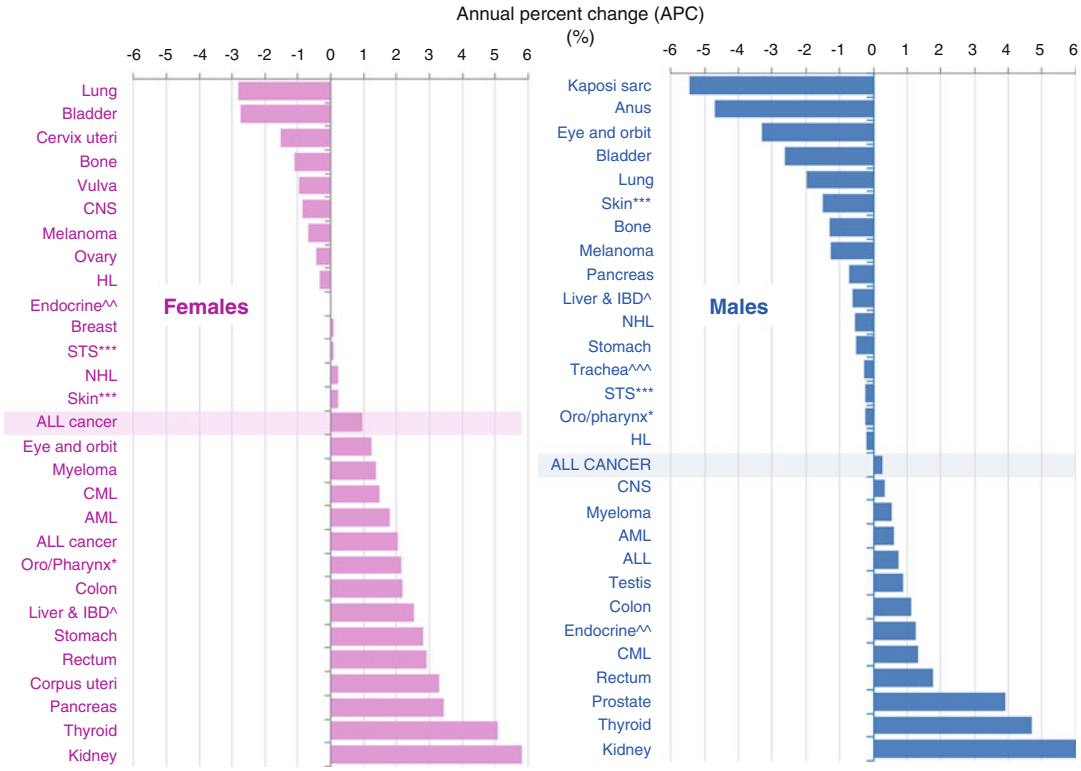


Fig. 2.11 Annual % change (APC) in cancer incidence, 2000–2011, age 15–39, US SEER18, by site and sex. *oral cavity and oropharynx **soft-tissue sarcoma ***nonmelanoma skin cancer ^intrahepatic bile duct ^^non-thyroid endocrine ^^^trachea and mediastinum

respectively. For thyroid cancer, the corresponding rates were 5.1 and 4.7 % per year. In the United States, the cancers with the greatest increase during 1975–2011 among the oldest AYAs, those 35–39 years of age, were cancer of the thyroid, kidney, anorectum, and prostate (Fig. 2.12), the last a previously unreported finding. In females, the thyroid cancer increase accounts for most of the total increase, 61 % of the total during 1975–2011 and 83 % of the total during 2000–2011.

2.4.2 Survival

2.4.2.1 Site Distribution and Survival (Europe, US SEER, Japan)

Table 2.3 lists the 5-year relative survival rates for the United States (SEER) and Europe by diagnostic group for each of the 5-year AYA age groups (15–19, 20–24, 25–29, 30–34, 35–39). To better understand the composition of the overall rates, the site distributions by age are presented in Table 2.4. Table 2.5 contrasts the survival for children (<15 years) and AYAs (15–39 years combined) by geographic area and is limited to site/histology groups affecting both AYAs and children. In contrast, Table 2.6 displays survival rates limited to carcinomas affecting AYAs (15–39 years) and adults (40–69 years). Obviously not all possible cancers are displayed in each table; the totals, however, include all cancers in that age group.

Site distribution between Europe and the United States is similar for the majority of diagnostic groups and carcinomas considered (Table 2.4). Some differences are apparent in Hodgkin lymphoma, germ cell, and cervix uteri tumors in Europe compared to thyroid cancer, sarcomas, and corpus uteri cancer in the United States.

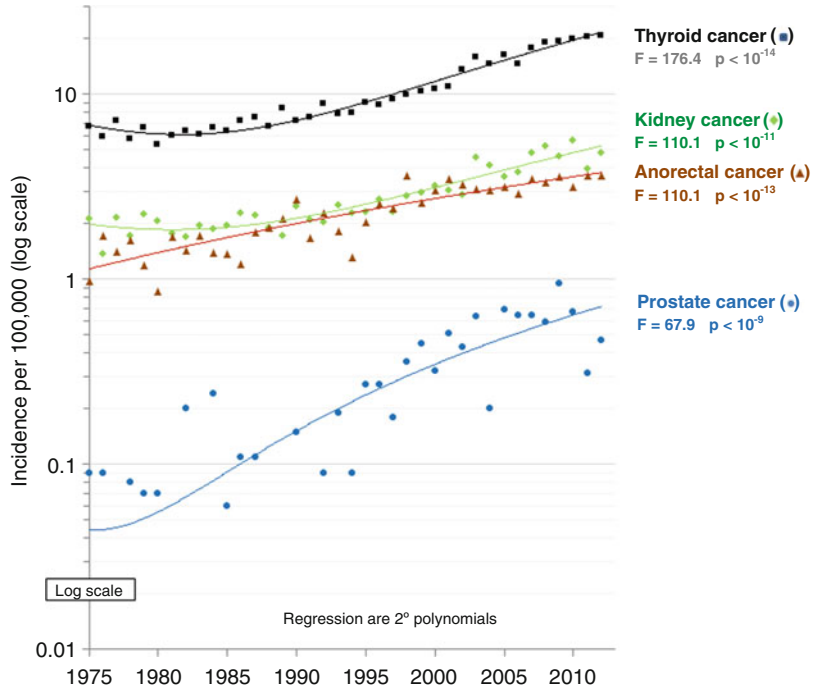


Fig. 2.12 Annual incidence of cancers in 35–39-year-olds with the greatest increase during 1975–2012, males and females, US SEER9

Survival rates in AYAs with cancer have been remarkably similar in the United States, Europe, and Japan for the vast majority of cancers that occur in AYAs (Figs. 2.13 and 2.14, Tables 2.3 and 2.4). The 5-year relative survival during 2000–2007 was comparable in Europe, the United States, and Japan (during 2000–2006) for all but a few of the 38 cancers common in AYAs and for which there were a sufficient number of cases to compare (Figs. 2.13 and 2.14). The exceptions include rhabdomyosarcoma, CNS tumors, and acute lymphoblastic leukemia, which had lower survival rates in Japan, prostate cancer with a lower survival in Europe, and melanoma which had a higher rate in the United States (Figs. 2.13 and 2.14). Rhabdomyosarcoma survival in AYAs was low in all three regions evaluated and among the lowest survival rates of all cancer in AYAs, however, especially in comparison to the much better rates in children.

Acute lymphoblastic leukemia is of special interest since it is one of the cancers in AYAs with the poorest survival rate (fourth worst of 38 cancers in Fig. 2.14), it has had the most research in comparison of pediatric and adult treatment regimens, and because of what appears to be a different biologic mix of acute lymphoblastic leukemias in AYAs than in either younger or older patients (see Acute Lymphoblastic Leukemia chapter). The 5-year survival rate appears to be better for AYAs in general in Europe and the United States than in Japan (Fig. 2.14, highest bars).

2.4.2.2 Survival for AYAs Compared to Children (Age <15 Years)

In Europe, the United States, and Japan, AYAs had worse survival than children (age <15 years) for most cancers that occur in both age groups. In Europe this was true for acute lymphoblastic leukemia (ALL), acute myelogenous leukemia, Hodgkin lymphoma, NHL, astrocytoma, Ewing sarcoma of the bone, and rhabdomyosarcoma ($p<0.001$ for each). The survival difference for osteosarcoma was also statistically significantly worse but relatively minor. In contrast, AYAs had

Table 2.3 Five-year relative survival of AYAs with cancer in the European (EUR) pool and US (SEER) diagnosed during 2000–2007, by type of cancer and 5-year age interval

	Age at diagnosis (years)									
	15–19		20–24		25–29		30–34		35–39	
	EUR	SEER	EUR	SEER	EUR	SEER	EUR	SEER	EUR	SEER
Diagnostic group[b]	5-year relative survival (%)									
Acute lymphoid leukemia	62.2	67.3	45.6	47.2	47.8	42.2	53.6	52.3	60.5	60.5
Acute myeloid leukemia	52.2	48.5	55.2	48.3	47.7	49.4	49.3	51.6	47.3	46.7
Hodgkin lymphoma	94.3	95.7	93.9	93.2	93.9	93.2	91.6	93.5	90.2	89.8
Non-Hodgkin lymphoma (except Burkitt)	78.0	77.6	76.3	76.6	77.8	76.8	78.0	77.7	76.9	76.2
CNS	61.8	64.7	63.4	65.6	60.1	66.4	57.4	61.1	49.8	57.8
Astrocytomas excluding pilocytic	50.8	53.3	54.2	53.8	51.5	54.8	47.6	45.8	38.7	40.3
Intracranial and intraspinal embryonal tumors	67.0	60.4	61.3	65.9	60.0	57.7	53.3	61.6	56.1	51.8
Medulloblastoma	72.8	66.8	63.3	74.2	69.0	66.7	65.7	76.7	66.2	62.9
Osteosarcoma	60.3	61.9	61.4	64.9	65.3	69.3	65.2	72.6	60.1	55.2
Chondrosarcoma	80.7	94.7	80.5	87.3	85.5	89.8	82.7	90.2	83.1	89.5
Ewing tumor and related sarcomas of the bone	51.1	56.2	50.4	54.2	45.3	44.1	47.7	23.6	42.9	38.9
Soft-tissue sarcomas (excluding Kaposi)	63.0	67.6	66.3	64.7	68.5	69.1	73.3	71.2	72.2	70.1
Rhabdomyosarcoma	39.6	46.7	35.8	41.1	30.9	24.8	39.0	30.7	43.2	27.3
Fibrosarcoma	72.8	67.5	88.6	70.4	78.9	68.3	88.4	68.3	74.7	66.3
Germ cell, trophoblastic and gonadal neoplasms	92.2	91.9	93.5	92.7	95.2	94.5	95.6	95.3	94.7	94.9
Gonadal germ cell tumors	93.6	94.4	94.3	94.3	95.9	96.0	96.1	96.5	95.4	96.0
Intracranial and intraspinal germ cell tumors	79.5	84.7	86.3	85.0	83.8	64.7	81.2	[a]	[a]	[a]
Malignant melanoma	90.8	95.0	90.9	95.1	90.5	95.1	89.4	94.4	87.1	94.0
Skin melanoma	91.2	95.2	91.2	95.3	91.3	95.3	90.2	94.6	88.1	94.3
Thyroid carcinoma	99.7	98.5	99.0	99.5	99.3	99.5	99.1	99.3	98.9	99.1
Breast carcinoma	87.3	72.5	82.9	77.4	78.1	80.2	81.4	82.0	84.9	85.1
Colon and rectum carcinoma	54.0	48.0	57.7	57.1	57.0	56.2	61.4	63.5	62.4	63.3
Appendix carcinoma	100.0	[a]	78.8	[a]	84.3	77.4	77.8	72.9	71.1	70.2
Male genital tract carcinomas	[a]	[a]	88.0	[a]	80.8	83.4	76.7	72.8	77.9	87.6
Prostate carcinoma	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	81.2	92.8
Female genital tract carcinomas	80.5	77.1	84.7	81.5	83.3	84.1	83.0	84.6	80.1	81.2
Carcinoma of the ovary	81.1	72.5	81.8	73.4	76.5	77.4	72.7	73.7	69.9	69.4
Carcinoma of the cervix uteri	76.0	[a]	87.1	83.1	84.8	83.7	84.9	84.5	81.6	79.8
Carcinoma of the corpus uteri and uterus NOS	[a]	[a]	81.0	98.1	89.3	93.9	91.9	93.1	89.5	92.6
Urinary tract carcinomas	83.8	90.1	82.0	83.4	84.4	85.6	84.6	87.3	81.8	86.0

(continued)

Table 2.3 (continued)

	Age at diagnosis (years)									
	15–19		20–24		25–29		30–34		35–39	
	EUR	SEER	EUR	SEER	EUR	SEER	EUR	SEER	EUR	SEER
Diagnostic group[b]	5-year relative survival (%)									
Kidney carcinomas	77.6	85.4	78.1	76.6	82.7	80.3	85.8	86.3	82.3	84.9
Urinary bladder carcinomas including in situ	98.7	95.3	85.1	91.9	84.4	95.6	81.0	91.5	79.9	88.7
Head and neck carcinomas	84.4	90.4	81.1	81.9	81.3	81.7	73.9	79.4	63.8	76.7
Nasopharyngeal carcinoma	74.5	87.5	76.3	65.7	71.3	68.1	66.5	65.4	68.1	75.9
Salivary gland carcinoma	94.0	92.5	93.5	96.4	92.3	98.2	87.0	93.1	83.0	93.6
Laryngeal carcinoma	[a]	[a]	[a]	[a]	89.5	83.4	72.6	91.6	71.3	74.9
Oral cavity carcinoma excluding the lip	87.0	85.3	74.0	75.7	77.6	76.5	71.3	74.8	61.6	71.0
Liver and intrahepatic bile duct carcinomas	16.0	41.1	31.4	24.8	35.5	20.2	21.1	23.5	26.1	21.9
Lung and trachea carcinomas	87.1	83.6	71.4	67.5	54.2	56.1	38.9	37.8	23.5	25.8
Total including other cancers not listed above	79.4	79.9	82.8	82.7	82.5	83.4	80.1	82.0	76.4	79.0

[a]Less than 25 cases
[b]Excludes pilocytic astrocytoma and carcinoids of the colon/rectum/appendix and includes bladder in situ

numerically better survival than children for medulloblastoma (69 % vs 63 %) and germ cell tumors (95 % vs 92 %).

2.4.2.3 Survival for AYAs Compared to Older Adults (Age 40–69)

With few exceptions, AYAs in Europe, the United States, and Japan had better survival than adults for the overlapping cancers (Table 2.6). AYAs had lower survival compared to adults for breast and prostate carcinomas in Europe and in the United States and similar survival for breast cancer in Japan. Colorectal cancer survival was lower in the United States in AYAs than in older persons, whereas neither Europe nor Japan had a difference.

2.4.2.4 Survival Trends

In the United States, the annual 5-year relative survival in AYAs increased steadily from 1975 to 2012, but at a much slower rate than in younger patients, such that both male and female AYAs lost their distinct survival advantage over younger patients two decades ago. For females the 20 % advantage in 5-year survival in 1975 dissipated by 1998, since when younger patients have a persistent advantage until as recently as 2007 (Fig. 2.15, left panel). For males a 9 % advantage in 5-year survival in 1975 dissipated by 1993 (Fig. 2.15, left panel). The survival deficit continued thereafter and until at least 2007 for both females and males (Fig. 2.15). The annual 5-year relative survival in AYAs for all cancer increased during 1975–2007 more in the oldest AYAs, age 30–39 (Fig. 2.16, right panel), than in the younger AYAs, age <30 (Fig. 2.16, left panel). Whereas the rates were originally worse in the older AYAs, by 2007 the rates were comparable and projected to be higher in older than younger AYAs since then.

Figure 2.17 shows 5-year relative survival time trends among AYAs in Europe and the United States during 1995–2007 for 4 of 19 cancers analyzed that are prevalent in both children and AYAs and that had statistically significant improvements in AYAs: acute lymphoblastic leukemia, NHL, astrocytomas, and melanoma.

Table 2.4 Distribution of types of cancer in AYAs in the European (EUR) pool and US SEER, 2000–2007, by 5-year age intervals (15–39)

Diagnostic group[a]	International classification of childhood cancer (ICCC) groupings and modifications	Age at diagnosis (years)									
		15–19		20–24		25–29		30–34		35–39	
		EUR %	SEER%	EUR %	SEER%	EUR %	SEER %	EUR %	SEER%	EUR %	SEER %
Acute lymphoid Leukemia	Ia	7.5	8.7	2.6	2.8	1.2	1.4	0.9	1.2	0.8	0.9
Acute myeloid leukemia	Ib	3.8	4.7	2.7	3.1	2.1	2.0	1.4	1.6	1.2	1.2
Hodgkin lymphoma	IIa	19.3	14.5	14.7	13.0	8.5	8.1	4.7	4.8	2.5	2.5
Non-Hodgkin lymphoma (except Burkitt)	IIb	6.6	7.5	5.5	6.1	4.8	5.7	4.6	5.8	4.6	5.6
CNS	III	8.0	7.4	6.0	5.7	5.4	4.9	4.6	3.7	3.4	2.9
Astrocytomas excluding pilocytic	IIIb	3.3	2.8	2.8	2.7	2.8	2.2	2.5	1.8	1.9	1.6
Intracranial and spinal embryonal tumors	IIIc	1.3	1.5	0.6	0.8	0.3	0.4	0.2	0.2	0.1	0.1
Medulloblastoma	Histology M9470-2,9474,9480	0.9	0.8	0.4	0.5	0.2	0.2	0.1	0.1	0.0	0.1
Osteosarcoma	VIIIa	4.2	4.3	1.2	1.3	0.4	0.4	0.2	0.2	0.1	0.1
Chondrosarcoma	VIIIb	0.8	0.4	0.5	0.4	0.3	0.3	0.3	0.2	0.2	0.2
Ewing tumor and related bone sarcomas	VIIIc	2.4	2.1	0.8	0.5	0.3	0.2	0.1	0.1	0.1	0.1
Soft-tissue sarcomas^	IX	6.5	8.0	4.6	5.9	3.5	5.4	2.7	4.6	2.3	4.0
Rhabdomyosarcoma	IXa	1.5	1.6	0.5	0.5	0.2	0.2	0.1	0.1	0.1	0.1
Fibrosarcoma	IXb	0.3	0.9	0.3	0.8	0.2	0.5	0.2	0.4	0.2	0.4
Germ cell, trophoblastic, gonadal neoplasms	Xa,b,c	12.2	13.2	19.7	17.0	18.4	13.5	11.8	8.8	6.7	4.8
Gonadal germ cell tumors	Xa	11.0	10.8	18.8	15.6	17.8	12.7	11.5	8.3	6.6	4.5
Intracranial and spinal germ cell tumors	Xc	0.9	1.4	0.3	0.4	0.1	0.1	0.0	0.0	0.0	0.0
Malignant melanoma	XId	7.1	8.1	12.6	12.5	13.7	13.7	13.0	12.1	10.7	10.5
Skin melanoma	XId (C44.0–44.9)	6.8	7.9	12.2	12.3	13.3	13.5	12.5	11.9	10.3	10.2
Thyroid carcinoma	XIb	5.8	8.8	7.3	13.1	7.7	14.4	6.7	12.6	5.2	10.1

(continued)

Table 2.4 (continued)

Diagnostic group[a]	International classification of childhood cancer (ICCC) groupings and modifications	Age at diagnosis (years)									
		15–19		20–24		25–29		30–34		35–39	
		EUR %	SEER%	EUR %	SEER%	EUR %	SEER %	EUR %	SEER%	EUR %	SEER %
Breast carcinoma	XIf (C50.0–50.9)	0.3	0.3	1.8	2.0	7.8	7.3	17.1	15.7	26.1	23.4
Colon and rectum carcinoma	XIf (C18.0,18.2–18.9, 19.9, 20.9–21.8)[b]	0.5	0.9	1.9	1.9	2.5	3.0	3.6	4.5	4.9	6.0
Appendix carcinoma	XIf (C18.1)[b]	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.2
Male genital tract carcinomas	Xd (C62.0–62.9), XIf (C60.0–61.9, 63.0–63.9)	0.1	0.1	0.3	0.1	0.3	0.1	0.2	0.2	0.3	0.5
Prostate carcinoma	XIf (C61.9)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3
Female genital tract carcinomas	Xd (C56.9), XIf (C51.0–55.9, 57.0–58.9)	1.1	0.9	4.4	3.6	9.7	7.6	12.3	10.3	11.5	10.0
Carcinoma of the ovary	Xd (C56.9)	0.8	0.6	1.4	1.1	1.7	1.1	1.8	1.4	2.2	1.7
Carcinoma of the cervix uteri	XIf (C53.0–53.9)	0.2	0.2	2.8	2.1	7.6	5.3	9.6	6.8	8.0	5.5
Carcinoma of the corpus uteri and uterus NOS	XIf (C54.0–54.9, 55.9)	0.0	0.1	0.1	0.3	0.2	1.1	0.5	1.9	0.9	2.4
Urinary tract carcinomas	VIb, XIf (C65.9–C68.9)	0.8	0.9	1.1	1.4	1.5	2.1	2.2	3.0	3.0	4.0
Kidney carcinoma	VIb	0.5	0.5	0.6	0.7	1.0	1.3	1.4	2.0	2.0	2.7
Urinary bladder carcinoma^^	XIf (C67.0–67.9)	0.3	0.4	0.4	0.6	0.5	0.7	0.8	1.0	1.0	1.3
Head and neck carcinomas	XIc, XIf (C00.0–14.8, 30.0–30.1, 31.0–32.9)	1.8	2.1	1.6	2.1	16	2.1	2.0	2.3	2.8	2.8
Nasopharyngeal carcinoma	XIc	0.7	0.7	0.4	0.5	0.3	0.3	0.2	0.3	0.3	0.4
Salivary gland carcinoma	XIf (C07.9–08.9)	0.6	0.8	0.5	0.9	0.5	0.6	0.4	0.6	0.4	0.4
Laryngeal carcinoma	XIf (C32.0–32.9)	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.4	0.3
Oral cavity carcinoma excluding the lip	XIf (C02.0–02.3, 02.9, 03.0–05.0, 06.0–06.9)	0.3	0.3	0.4	0.3	0.5	0.6	0.7	0.6	0.8	0.7

Diagnostic group[a]	International classification of childhood cancer (ICCC) groupings and modifications	Age at diagnosis (years)									
		15–19		20–24		25–29		30–34		35–39	
		EUR %	SEER%	EUR %	SEER%	EUR %	SEER %	EUR %	SEER%	EUR %	SEER %
Liver and intrahepatic bile duct carcinomas	VIIb	0.5	0.6	0.4	0.5	0.4	0.5	0.4	0.5	0.4	0.7
Lung and trachea carcinomas	XIf (C33.9–34.9)	0.6	0.5	0.7	0.8	0.9	1.0	1.4	1.5	2.7	2.7
Total number of cases including other cancers not listed above[b]		18,403	9558	30,248	15,314	49,208	23,706	81,471	37,976	133,153	61,501

[a]Excludes pilocytic astrocytoma and carcinoids of the colon/rectum/appendix and includes bladder in situ
[b]All morphologies except 8240–8244 ^excluding Kaposi sarcoma ^^ including in situ

Table 2.5 Comparison of 5-year relative survival (RS) of children (age <15) and AYAs (age 15–39) with cancer diagnosed during 2000–2007 in Europe and US SEER and 2000–2006 in Japan, by type of cancer

	5-year relative survival						Site distribution (%)					
	Age <15			Age 15–39			Age <15			Age 15–39		
Diagnostic group[c]	Europe	SEER	Japan	Europe	SEER	Japan	Europe	SEER	Japan	Europe	SEER	Japan
Acute lymphoid leukemia	85.8	88.1	84.0	55.6	56.8	44.2	26.7	27.6	21.4	1.5	1.8	1.7
Acute myeloid leukemia	60.5	61.3	71.7	49.8	48.9	55.1	5.2	5.4	8.3	1.7	1.9	2.5
Hodgkin lymphoma	95.1	95.6	100.0	92.9	93.1	91.7	5.3	4.0	0.6	6.2	5.9	1.2
Non-Hodgkin lymphoma (except Burkitt)	83.0	83.8	84.8	77.4	76.9	75.6	4.3	4.3	4.3	4.8	5.9	3.4
CNS	57.2	62.8	63.4	56.8	62.2	61.3	15.7	16.4	17.3	4.6	4.0	3.4
Astrocytomas excluding pilocytic	61.9	69.6	55.4	46.4	47.5	47.3	4.6	4.8	4.3	2.4	1.9	1.6
Intracranial and intraspinal embryonal tumors	56.3	61.6	64.7	60.3	60.4	45.2	5.2	5.2	3.7	0.3	0.3	0.2
Medulloblastoma	63.2	68.9	71.0	69.3	70.1	53.7	3.8	3.0	3.0	0.2	0.2	0.1
Osteosarcoma	66.8	69.2	71.1	61.5	63.7	69.4	2.5	2.7	2.8	0.5	0.6	0.6
Chondrosarcoma	89.4	[a]	[a]	82.6	90.0	80.7	0.1	0.1	0.4	0.3	0.2	0.3
Ewing tumor and related sarcomas of the bone	66.6	73.4	59.6	49.3	50.7	45.6	2.3	1.5	1.2	0.3	0.3	0.2
Soft-tissue and other extraosseous sarcomas[d]	69.3	72.5	67.9	69.8	69.3	70.8	6.9	7.5	5.3	3.1	4.8	2.4
Rhabdomyosarcoma	66.6	67.1	63.8	37.8	38.8	22.9	3.8	3.7	2.9	0.2	0.3	0.2
Fibrosarcoma	83.8	81.7	55.4	81.4	67.9	61.6	0.4	0.8	0.5	0.2	0.5	0.3
Germ cell, trophoblastic and gonadal neoplasms	91.5	91.3	95.8	94.7	94.2	91.7	3.2	3.9	6.6	11.4	9.0	6.5
Gonadal germ cell tumors	96.8	97.4	100.0	95.4	95.6	94.4	1.5	1.7	2.6	11.1	8.3	0.4
Intracranial and intraspinal germ cell tumors	85.9	86.7	93.9	79.5	81.6	86.3	0.8	1.1	2.3	0.1	0.2	5.5
Malignant melanoma	90.1	95.9	[a]	88.9	94.5	82.2	0.8	1.5	0.4	11.7	11.5	0.7
Skin melanoma	92.2	96.4	[a]	89.7	94.7	85.6	0.7	1.4	0.4	11.3	11.2	0.7
Total number of cases including other cancers not listed above							56,505	20,094	1852	312,483	147,518	13,190

[a]<25 cases
[b]Including other cancers not listed above
[c]Excludes pilocytic astrocytoma and carcinoids of the colon/rectum/appendix and includes bladder in situ
[d]Excluding Kaposi sarcoma

Table 2.6 Comparison of 5-year relative survival of AYAs (age 15–39) and middle-aged adults (40–69) with cancer diagnosed during 2000–2007 in Europe and US SEER and 2000–2006 in Japan, by type of cancer

	5-year relative survival (%)						Site distribution (%)					
	Age 15–39			Age 40–69			Age 15–39			Age 40–69		
Diagnostic group[a]	Europe	SEER	Japan	Europe	SEER	Japan	Europe	SEER	Japan	Europe	SEER	Japan
Thyroid carcinoma	99.2	99.3	99.7	93.1	96.8	96.1	6.2	11.7	6.7	1.3	2.4	1.8
Breast carcinoma	83.5	83.9	87.3	87.0	89.4	89.3	17.0	15.1	19.5	18.7	18.4	11.9
Colon and rectum carcinoma	61.3	62.1	70.3	60.8	67.0	71.0	3.6	4.4	7.3	11.1	9.2	15.7
Appendix carcinoma	77.2	74.7	60.4	61.0	58.0	49.9	0.1	0.2	0.1	0.1	0.1	0.1
Male genital tract carcinomas	80.1	85.0	–	89.6	98.6	–	0.3	0.3	–	11.4	17.7	–
Prostate carcinoma	79.9	92.0	–	89.8	98.7	92.9	0.1	0.2	0.0	11.2	17.6	3.7
Female genital tract carcinomas	81.6	82.7	84.7	69.1	74.3	71.0	10.1	8.5	15.8	6.7	6.1	4.7
Carcinoma of the ovary	72.8	71.9	71.5	47.1	50.5	55.8	1.8	1.4	3.1	2.1	1.6	1.5
Carcinoma of the cervix uteri	83.3	82.2	87.0	67.7	67.7	69.5	7.4	5.1	10.8	1.4	1.1	1.5
Carcinoma of corpus uteri and uterus NOS	90.0	93.0	94.6	86.7	89.5	86.5	0.6	1.7	1.9	2.8	3.1	1.7
Urinary tract carcinomas	82.9	86.3	88.9	69.5	77.1	78.5	2.2	3.0	2.3	5.8	6.7	3.8
Kidney carcinomas	83.0	84.4	91.2	70.7	73.3	79.5	1.4	2.0	1.3	2.6	3.1	1.5
Urinary bladder carcinomas including in situ	81.4	90.8	87.4	69.1	81.6	83.6	0.8	1.0	0.8	3.0	3.5	1.8
Head and neck carcinomas	69.9	79.4	73.9	51.5	61.0	63.0	2.2	2.4	2.9	4.7	3.9	3.0
Nasopharyngeal carcinoma	69.9	72.7	70.6	51.2	57.8	61.0	0.3	0.4	0.4	0.1	0.2	0.1
Salivary gland carcinoma	88.2	94.6	88.6	64.4	74.6	63.2	0.4	0.6	0.5	0.2	0.2	0.1

(continued)

Table 2.6 (continued)

	5-year relative survival (%)						Site distribution (%)					
	Age 15–39			Age 40–69			Age 15–39			Age 40–69		
Diagnostic group[a]	Europe	SEER	Japan	Europe	SEER	Japan	Europe	SEER	Japan	Europe	SEER	Japan
Laryngeal carcinoma	72.9	80.7	62.4	61.8	59.7	80.1	0.2	0.2	0.1	1.4	1.0	0.8
Oral cavity carcinoma excluding the lip	66.7	73.6	72.5	48.3	59.3	65.7	0.7	0.6	1.4	1.1	0.8	0.9
Liver and intrahepatic bile duct carcinomas	25.2	23.6	31.7	14.2	16.3	27.8	0.4	0.6	1.3	1.0	1.7	6.3
Lung and trachea carcinomas	32.1	34.0	29.6	14.9	18.9	33.5	1.7	1.8	0.0	10.7	12.3	10.3
Malignant melanoma	88.9	94.5	82.2	82.4	90.1	64.8	11.7	11.5	0.73	3.6	4.8	0.2
Total number of cases including other cancers not listed above							312,483	147,518	13,190	3,567,383	1,440,620	215,565

[a]Excludes pilocytic astrocytoma and carcinoids of the colon/rectum/appendix and includes bladder in situ

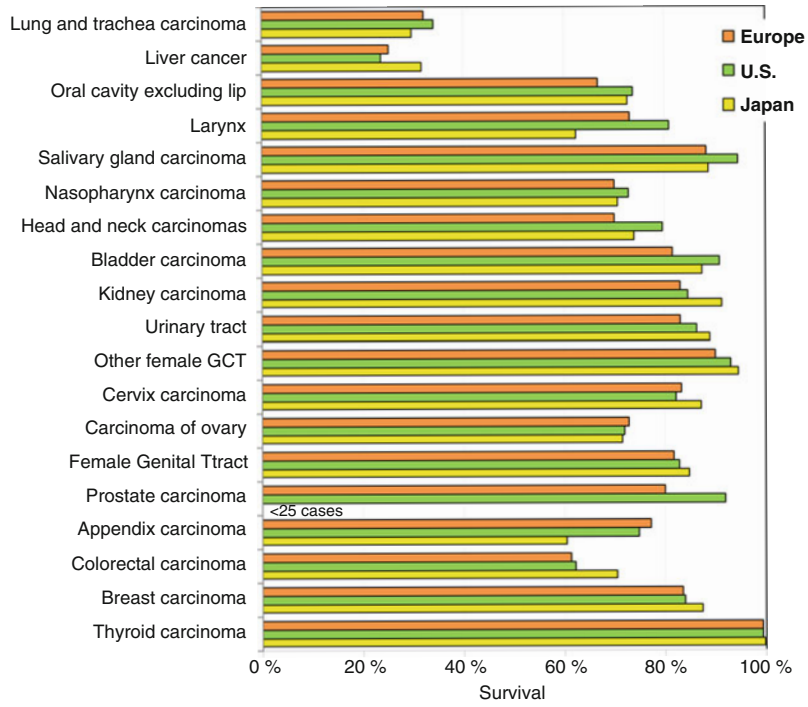


Fig. 2.13 Five-year relative survival, age 15–39, carcinomas, 2000–2007, Europe, US SEER, and Japan, by cancer type

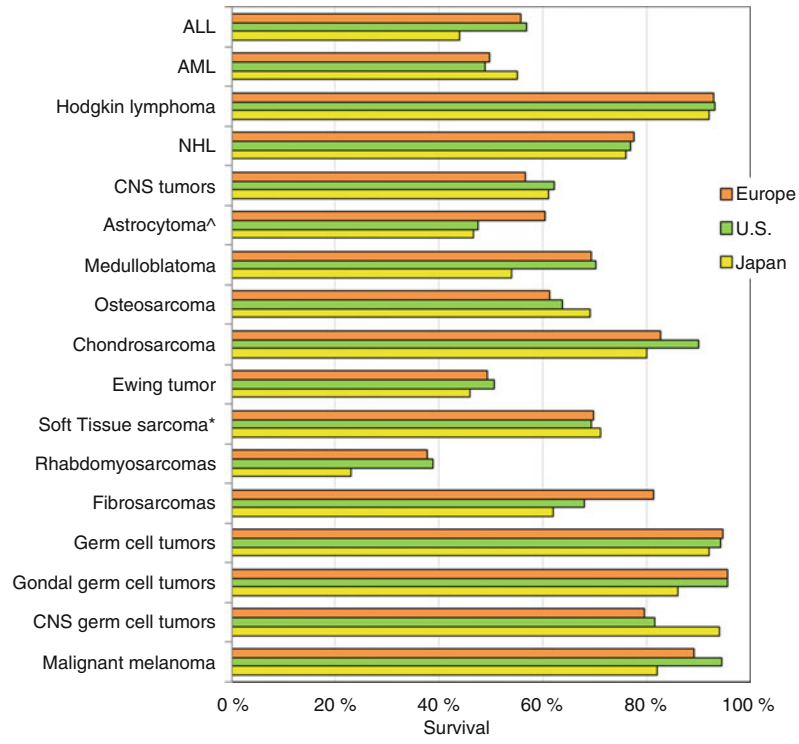


Fig. 2.14 Five-year relative survival, age 15–39, noncarcinoma AYA cancers, 2000–2007, Europe, US SEER, and Japan, by cancer type. ^excluding pilocytic astrocytoma *excluding Kaposi sarcoma

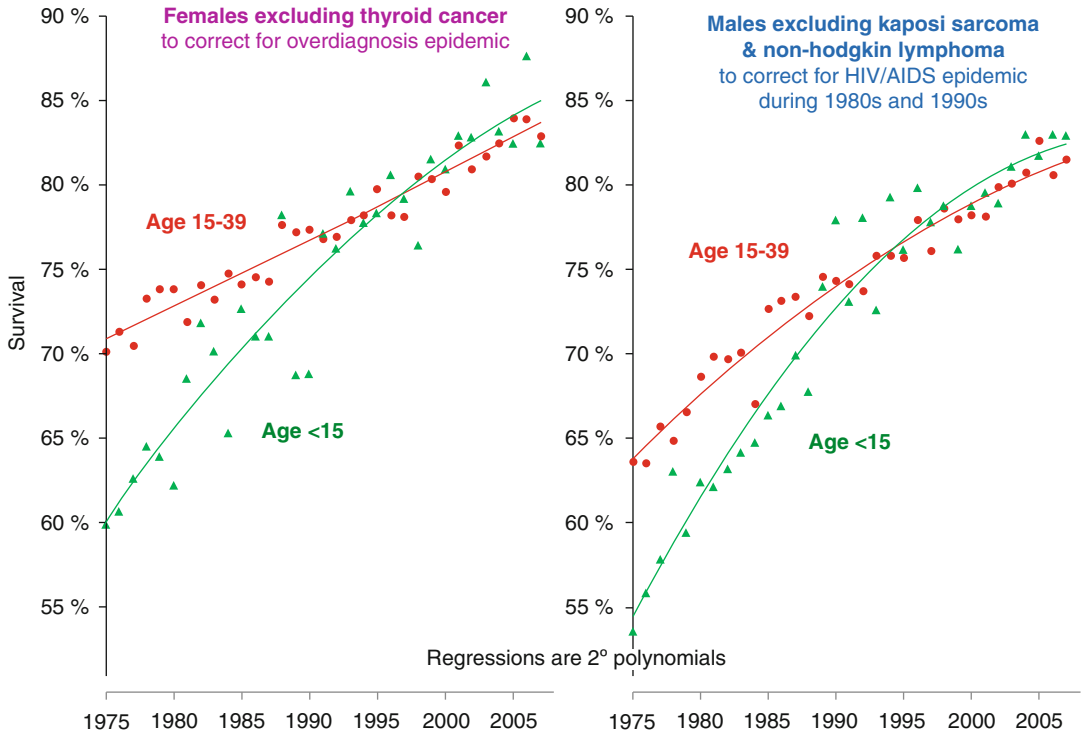


Fig. 2.15 Annual 5-year relative survival rates, 1975–2007, US SEER9, age <15 and 15-39, by sex. Exclusion of Kaposi sarcoma and non-Hodgkin lymphoma in males and thyroid cancer in females is explained in methods

Acute lymphoblastic leukemia and NHL had the greatest absolute and relative increases. Astrocytoma and melanoma had minor increases, but the melanoma rates were high at the outset (85–94 %).

2.4.3 Mortality

2.4.3.1 Cancer Mortality Worldwide

Worldwide, cancer deaths in AYAs were estimated by GLOBOCAN 2012 at nearly 400,000: 53 % females and 47 % males (Table 2.1). Nearly 5 % of the worldwide cancer deaths were among 15–39-year-olds (Table 2.1). For deaths, the overall ranking was the same as the incidence for #1 (female breast) and #5 (brain/other nervous system) (Table 2.2). The order in between changed with leukemia #2, liver #3, and cervix uteri #4 (Table 2.2). There were several sites in which the male deaths were more than twice as frequent as those in females: bladder, larynx, lip/oral cavity, liver, multiple myeloma, and pharynx other than nasopharynx. Since the survival rates for thyroid cancer are high, there were very few deaths estimated in comparison to the large numbers of cases.

2.4.3.2 Death Rates and Trends by Site

Since cancer among AYAs is uncommon overall and survival rates are high for many of the major cancers, the cancer mortality rates are very low in the United States (Fig. 2.18). The highest death rate is for female breast cancer at 2.5 per 100,000 females, and death rates for the remaining sites are less than 1 per 100,000 females. For males, with the exception of invasive tumors of the CNS (1.2 per 100,000), the death rates are below 1 per 100,000 males. For many AYA cancers, the US death rates are decreasing (Fig. 2.18). For several cancers, the death rates are decreasing rapidly between 2000 and 2011: >8 % per year for chronic myeloid leukemia, >4 % for lung and bronchus, NHL, and Hodgkin lymphoma (females) (Fig. 2.19).

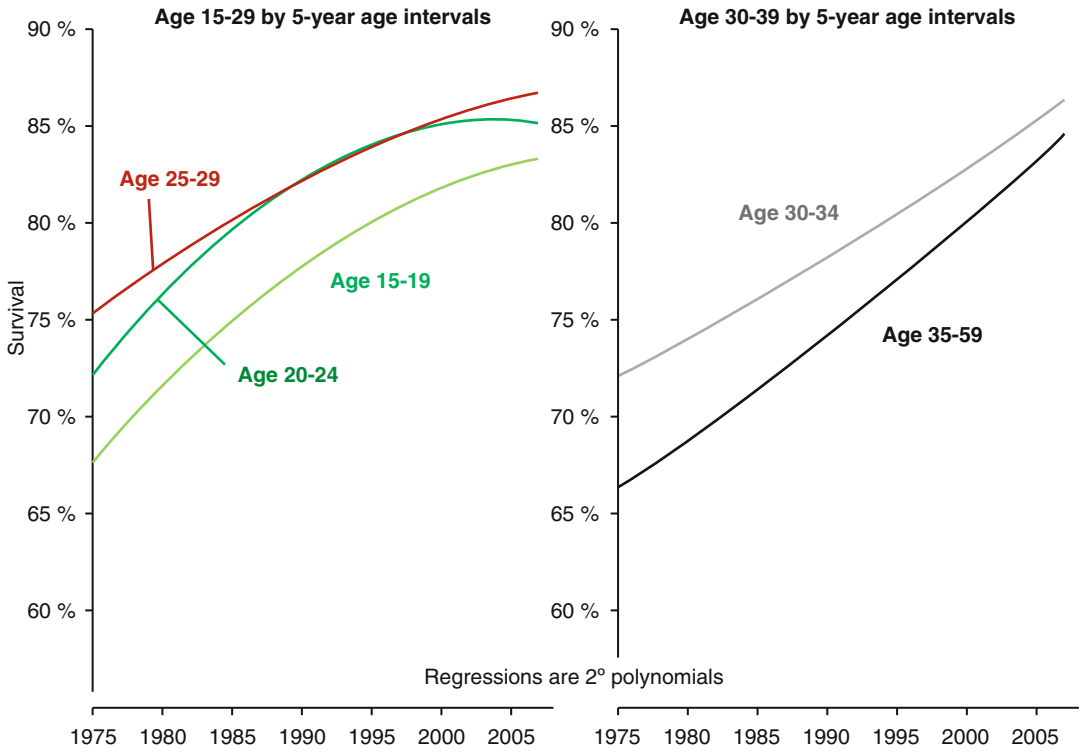


Fig. 2.16 Annual 5-year relative survival rates in males and females excluding Kaposi sarcoma and NHL in males, 1975–2007, US SEER9, age 15–39 by 5-year age intervals. Exclusion of Kaposi sarcoma and non-Hodgkin lymphoma in males is explained in methods

In the United States, cancer is the fourth most common cause of death among AYAs and the second most common cause of death due to disease (Fig. 2.20), after suicide. Accidents, homicides, and suicides are most common. The oldest AYA subgroup, 35–39 years of age, has by far the highest cancer death rate, 20 %, and is the greatest contributor to the overall increase in deaths in the age group (Fig. 2.20). Among AYAs, females have a higher cancer death rate than males that is due primarily to a higher rate in the older AYAs (Fig. 2.21). Among 35- to 39-year-old females, cancer is the most common of all causes of death. Among AYA males, suicide is the number one disease killer over the entire AYA age range including 15- to 19-year-olds, with cancer #3 behind heart disease overall and above age 25 (Fig. 2.21).

Cancer accounts for 9 % of AYA deaths in the United States, behind homicide at 10 %, suicide at 14 %, and accidents at 35 % (Fig. 2.22). The youngest AYAs, those 15–19 years of age, have the greatest proportion of cancer deaths, 17 %. It's also the age with the greatest proportion of homicides and suicides. Cancer accounts for 15 % of all deaths among AYA females in the United States (Fig. 2.23). The fraction in females is directly proportional to age from 8 % in 15- to 19-year-olds to 22 % in 35- to 39-year-olds, whereas the suicide and accident fractions are inversely proportional (Fig. 2.23). Among the oldest AYA females, more deaths occur from cancer than accidents, suicides and homicides combined.

Cancer accounts for 6 % of all deaths among AYA males in the United States, with accidents six times more common, suicides nearly threefold more common, and homicides twice as common (Fig. 2.24). Suicides and homicides account for 1 in every 6 AYA deaths and more than a third for those 15–29 years of age (Figs. 2.22–2.24).

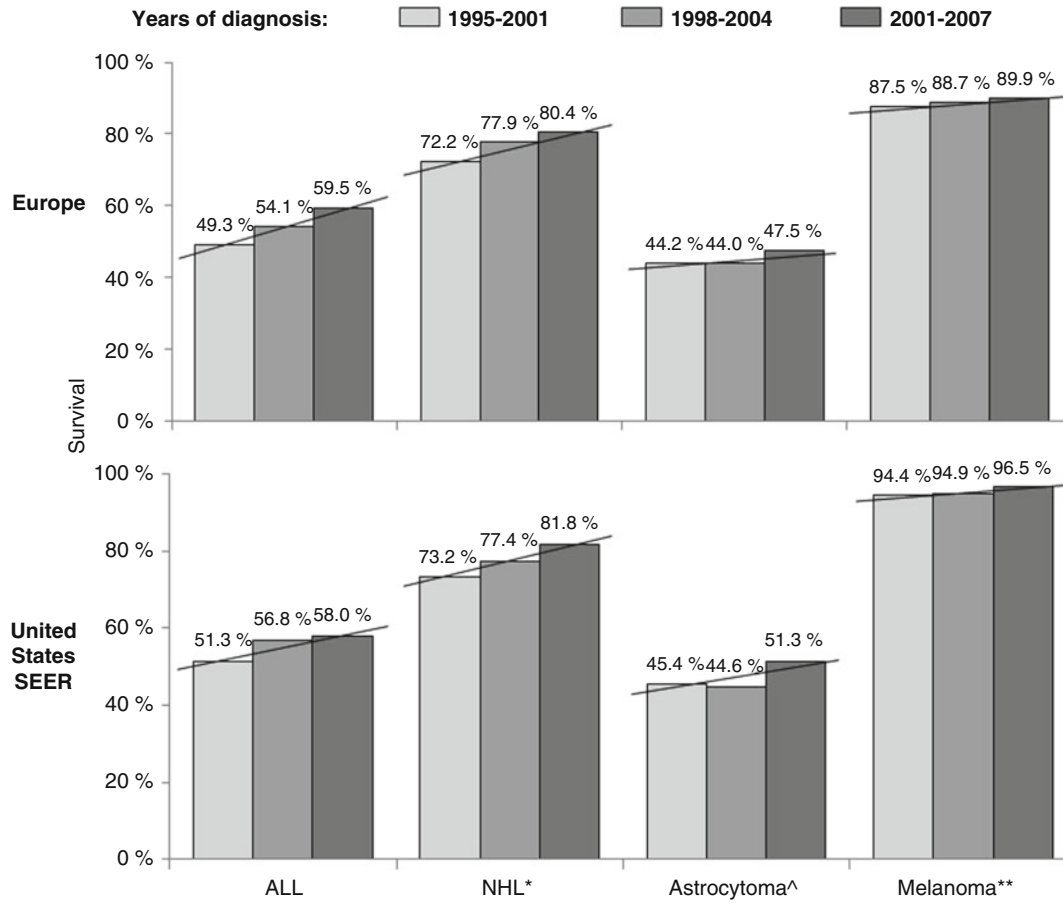


Fig. 2.17 Five-year relative survival in Europe and the US (SEER18) of cancers prevalent in both AYAs and children that had a statistically significant increase in their survival rate during 2000–2007 *excluding Burkitt lymphoma ^excluding pilocytic astrocytoma **malignant melanoma

2.5 Etiology, Biology, Trends, and International Progress

Cancer is predominantly a disease of aging, with a dramatic increase from age 10 to 80 years and an exponential phase from 40 to 80 years (Fig. 2.6). In economically advantaged countries, the median age is between 65 and 70 years. Thus, most of cancer can be considered as *cancers of aging*. During the first 5 years of life, there is a peak in incidence, with an entirely different group of cancers that appear to have their origin prenatally, during embryogenesis and fetal development. These early cancers may be regarded as embryonal/fetal cancers or *cancers of early growth*. Many of these cancers are small, round blue-cell tumors that are characteristic of pediatric malignancies [24, 25]. A nadir in incidence occurs at age 10, followed by a second peak during adolescence and early adulthood, most apparent in males (Fig. 2.6). In this phase, there is another set of cancers unique to the age group and to organ systems that, as a group, do not occur at any other age (Fig. 2.2). This second set of age-dependent cancers may be regarded as *cancers of adult growth and maturation* or young adult cancers (Fig. 2.6).

As a consequence of the age relatedness, the array of cancer types in AYAs is distinctly different from that of any other ages (Fig. 2.2). The array also varies greatly by age *within* the age range. For some cancers, there are few cases in

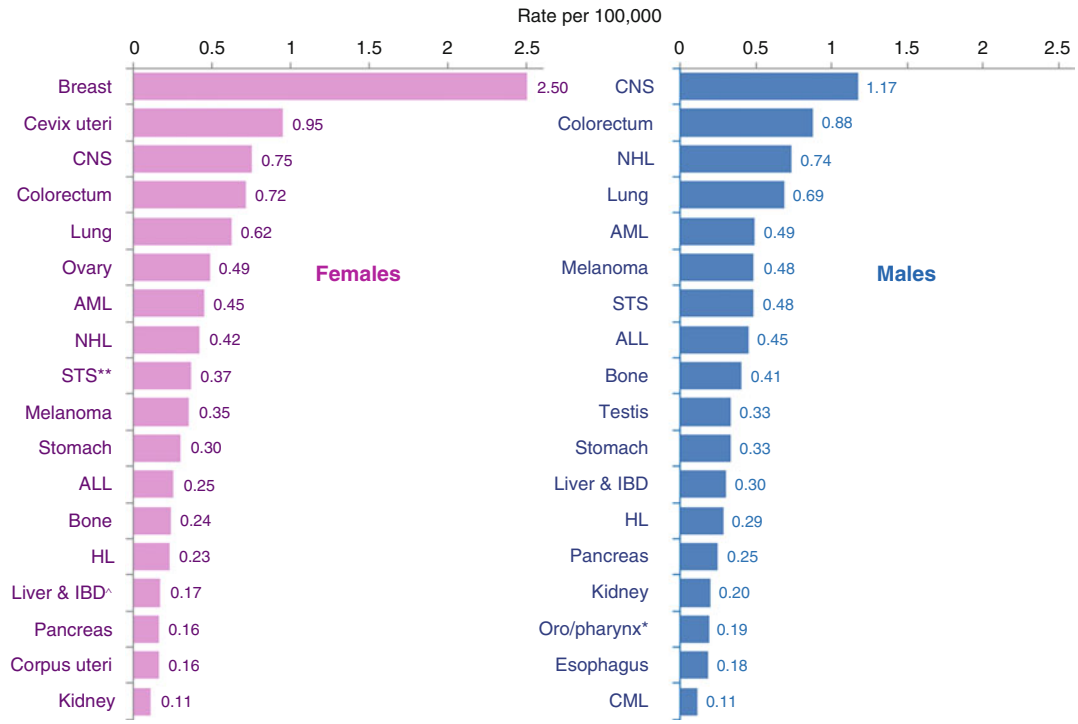


Fig. 2.18 Cancer death rates (NCHS), 2000–2011, age 15–39, US SEER 18, by site and sex. *oral cavity and oropharynx **soft-tissue sarcoma ^intrahepatic bile duct

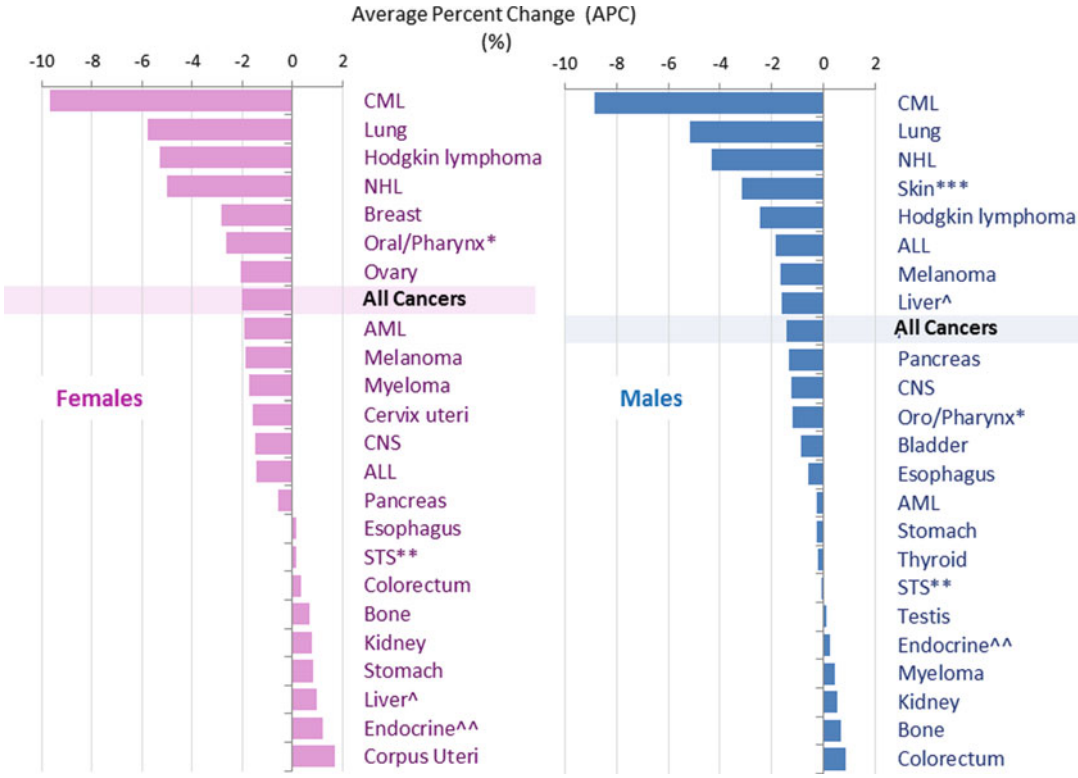
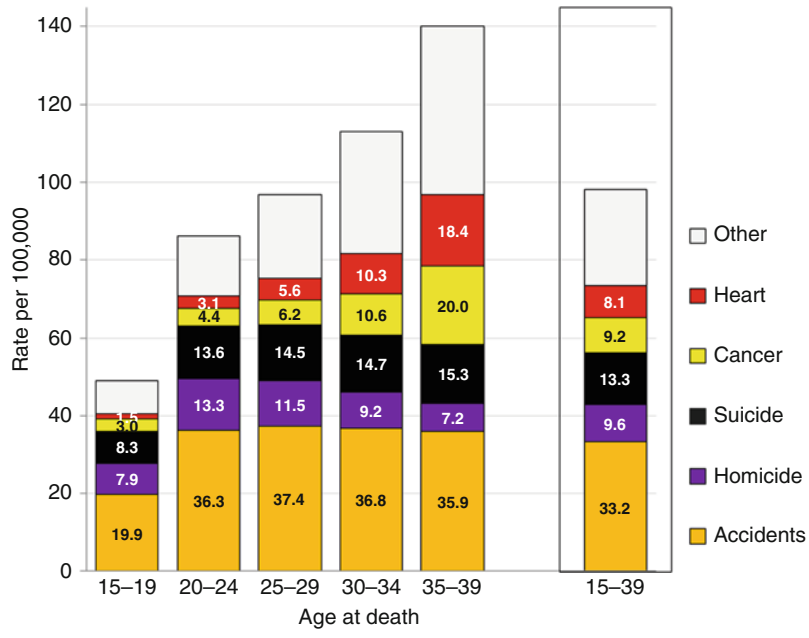


Fig. 2.19 Annual % change (APC) in cancer death rates (NCHS) 2000–2011, age 15–39, US SEER 18, by site and sex. *oral cavity and oropharynx **soft-tissue sarcoma ***nonmelanoma skin cancer ^includes intrahepatic bile duct ^^non-thyroid endocrine



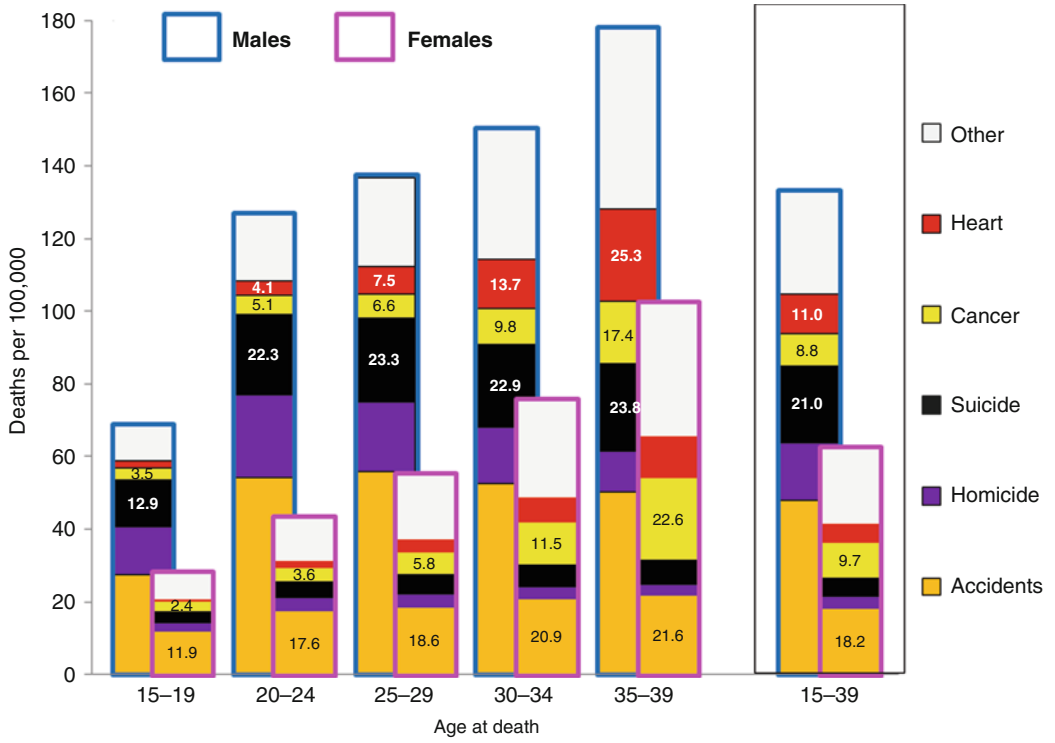


Fig. 2.20 Cause of death (COD) rates (NCHS), United States, 2011, males and females, age 15–39 by age

Fig. 2.21 Cause of death (COD) rates (NCHS), United States, 2011, age 15–39 by age and sex

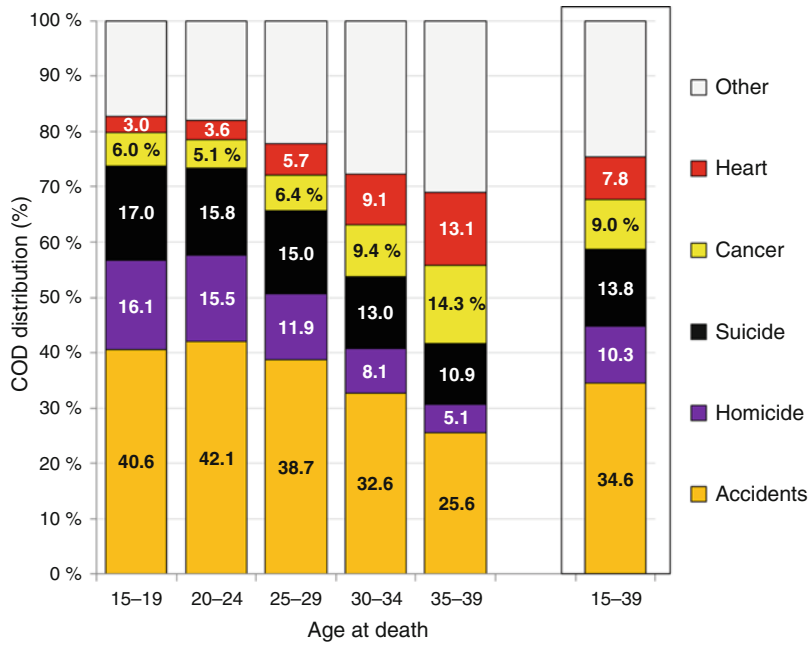


Fig. 2.22 Cause of death (COD) distribution, United States, 2011, males and females, age 15–39 by age

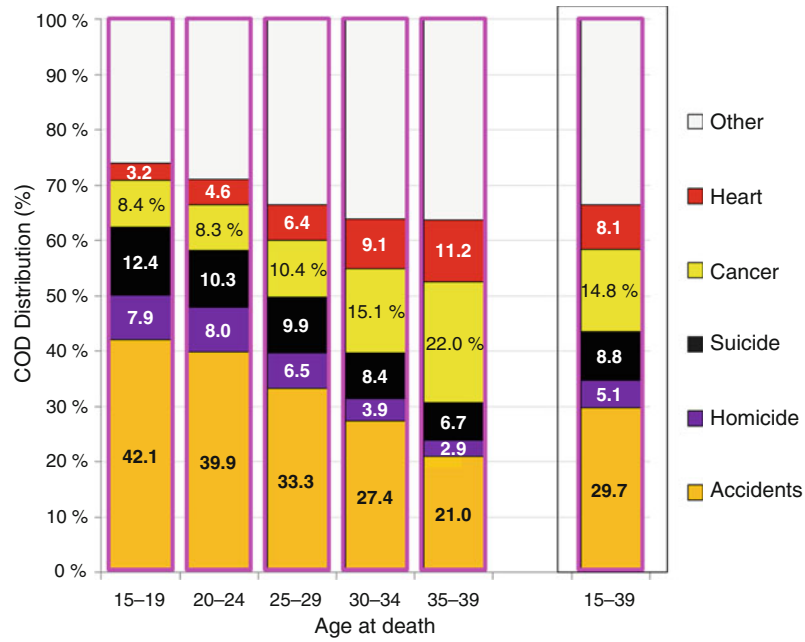


Fig. 2.23 Cause of death (COD) distribution, age 15–39, United States, 2011, females, by age

the youngest AYAs and a predominance by age 40 (e.g., breast and female genital cancers) and vice versa (e.g., lymphoma and leukemia) (Fig. 2.2). Others predominate in the middle of the AYA age range and are of lower incidence in younger and older persons (e.g., thyroid and testis cancer) (Fig. 2.2). This epidemiologic uniqueness renders the AYA age group deficient in specialists and experts and relatively understudied and understood. Fortunately, an AYA oncology discipline is in evolution and expected to mend the gap.

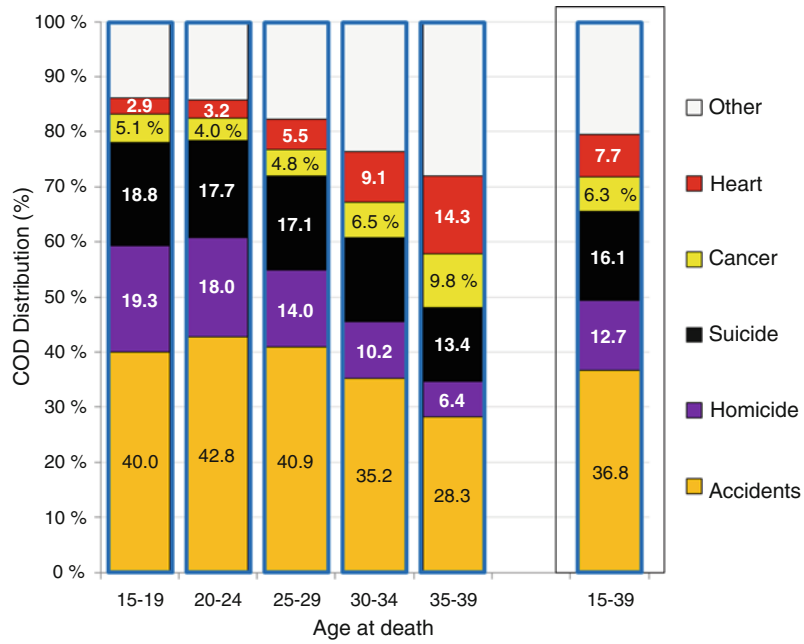


Fig. 2.24 Cause of death (COD) distribution, age 15–39, United States, 2011, males, by age

Among the more than million new cases of invasive cancer in AYAs each year worldwide, the incidence of all cancer varies dramatically from continent to continent. That the overall rate is nearly twice as high in North America and Northern, Western, and Southern Europe than it is in the rest of the world (Figs. 2.4 and 2.5) may to some degree be due to variation in recording and reporting, but is most likely due to the global variation in the mix of cancer types that is either genetic (racial/ethnic) or environmental in origin. Most of the global variation in AYA cancer is accounted for by melanoma and cancer of the testis and breast.

Thyroid cancer accounts for most of the difference in AYAs between cancer in North American females and females elsewhere, with >60 % of the increase in all cancer since 1992 and >80 % of the increase since 2000 in American females due to thyroid cancer. The likely explanation for this difference is overdiagnosis [26], albeit overdiagnosis is also problematic in other high-resource countries [27–29].

Other inter-geographic variations among AYAs exist, such as the world's highest incidence of Kaposi sarcoma in Africa, the highest rates of liver cancer in African and Asian males, and an excess of Hodgkin lymphoma in North America, Europe, and South America (Fig. 2.4). Each of these patterns has either a genetic or environmental underpinning, or both, such as the HIV prevalence in Africa (Kaposi sarcoma), solar exposure in persons of light-skinned heritage in the northern hemisphere (melanoma), and hepatitis B and C infection in Asia (hepatocellular carcinoma) [30].

The increase in incidence of all cancer in AYAs since 2000 is due mostly to overdiagnosis of thyroid and renal cancer, the two most rapidly increasing cancer diagnoses in both female and male AYAs (Fig. 2.11). The decrease in lung cancer and Kaposi sarcoma in AYAs is attributable to the reduction in AYAs of cigarette smoking and HIV infection [31]. The decline in melanoma incidence, albeit less than that for lung cancer and Kaposi sarcoma, may be due to public campaigns that have increased sunscreen usage and reduced indoor tanning device use by adolescents such that by the late AYA years melanoma incidence has declined [31]. Among older AYAs, prostate and anorectal cancer have also increased in incidence, suggesting a human papillomavirus etiology (Fig. 2.12). That the 5-year survival

rates are so high (92 % in the United States and 80 % in Europe) is consistent with HPV-related carcinomas that have a more favorable prognosis than the corresponding non-HPV type [32]. The increase in prostate cancer in AYA men has not been previously reported; it is highly significant ($p < 10^{-13}$ in the 35- to 39-year age group) (Fig. 2.12). The reason for the increase is not known, although with the history of overdiagnosis of prostate cancer in older men and the increasing overdiagnosis of other cancers in AYAs (especially thyroid and renal cancer), it is a possibility. Prostate-specific antigen (PSA) screening would have to be done in young men for overdiagnosis to be a factor, which is not obviously being done but should be evaluated.

A variety of environmental factors have been implicated in childhood leukemia and lymphoma [33, 34]. Overall cancer incidence is directly proportional to lower socioeconomic status [35, 36]. The same is true for AYAs (Figs. 2.4 and 2.5). Hodgkin lymphoma has been particularly associated with socioeconomic status [35, 36], which is clearly apparent in much lower incidences in Africa in both male and female AYAs (Figs. 2.9 and 2.10) and in females in Central and Eastern Europe (Fig. 2.5). Testis cancer also appears to be associated with socioeconomic status (Fig. 2.4), higher rates in higher SES countries. The childhood ALL incidence peak is rare in countries with lower socioeconomic status [37, 38], which may also be true for AYAs since Africa has the lowest incidence of leukemia in AYAs and virtually no apparent rate in female AYAs (Fig. 2.5).

National cancer screening programs also explain some of the global variation in cancer incidence. Countries with thyroid screening have higher incidences of these cancers, such that overdiagnosis also contributes to a higher incidence rate [26–29]. The strikingly higher rate of thyroid cancer in American female AYAs (Fig. 2.5), attributable to overdiagnosis, may also be partially due to screening. That cervix cancer is more frequent in AYAs in South America, Africa, and Central and Eastern Europe speaks to different etiology, most likely HPV prevalence [39].

The better survival of AYAs than older adults for most cancers is partially explained by the fact that AYAs have fewer comorbidities and are able to tolerate more treatment. This is not true for a number of cancers that in general have a worse survival in AYAs than in older patients (breast cancer, colorectal cancer, soft-tissue sarcoma, leukemia) [40], suggesting that these cancers are biologically different in AYAs than in older persons. Both breast cancer and colorectal cancer appear to have a different biologic mix in AYAs, with forms that are more difficult to treat or for whom treatments have not been developed because this difference was not known. Young women with breast cancer are more likely to have larger, less hormone-sensitive tumors of higher grade, with more frequent spread to lymph nodes and a greater number of involved lymph nodes than older women. Young women have the highest incidence of the so-called "triple-negative" tumors [40, 41]. Colon carcinoma in young adults appears to be a distinct disease characterized by biological aggressiveness, but prognosis is not worse due to a better performance status at the time of surgical intervention [42].

Early-onset prostate cancer, that is prostate cancer diagnosed under the age of 55 years, differs from prostate cancer diagnosed at an older age in several ways. Autopsy studies have shown a high prevalence of Gleason score 6 prostate cancers in men under 55 years of age, yet mortality of prostate cancer at this young age is almost negligible [43], as mentioned above.

That the rate of improvement in survival of AYAs with cancer has not improved as rapidly as it has in younger and older patients has been apparent for a couple of decades [44]. There has been recent reassuring progress in accelerating the survival improvement in the United States, at least in older AYAs (Fig. 2.15). The slower rate in younger AYAs, particularly those 20–25 years of age (Fig. 2.15), is concerning and may be related in part to the loss of healthcare insurance at the age of 18 that most AYAs sustained in, and only in, the United States until passage of the Health Protection and Affordable Care Act in 2010. Since passage of the Affordable Care Act, many

thousands of AYAs have been diagnosed with cancer while being covered with health insurance they otherwise would not have had. As more and more AYAs benefit from the expanded health insurance availability, their overall rate of survival improvement should accelerate [45, 46].

Because the types and distribution of malignancies presenting in AYAs are markedly different compared with those seen in younger or older patients, the development of specialist services targeted to AYA cancer patients is desirable and necessary to improve all aspects of outcome. In order to develop services tailored to the needs of this age group, it is necessary to define the extent and nature of the patient population through precise analyses of relevant population-based data. These data will be relevant not only for planning but also for better understanding global differences and trends. The chapters on special AYA services and care in this book provide the essentials to accommodate the occurrence and survival of cancer in AYAs.

Appendix

Notes on which sites/histologies were used for incidence and survival except for international comparisons. For the definitions used for the international survival comparisons, see Table 2.4. Note that some chapters were limited to invasive cases while other chapters also included in situ cases separately:

- Breast: based on SEER site recode and includes all histologies except lymphoma. Limited to female breast cancer. In situ is also presented.
- Colon: based on the primary site codes for all segments of the colon and limited to carcinomas (8010–8599). This is different from AYA recode in that it included in situ separately and different from SEER site recode in that it excluded large intestine not otherwise specified (NOS) and is limited to carcinomas.
- Rectum: based on the primary site codes for rectum and rectosigmoid and limited to carcinomas (8010–8599). SEER site recode for rectum which includes the rectum and all histologies except lymphoma. This is different from AYA recode in that it included in situ separately and different from SEER site recode in that it is limited to carcinomas.
- Anus, anal canal, and anorectum: based on SEER site recode and includes invasive tumors and all histologies except lymphoma. This is included in the colon and rectum chapter. This is different from AYA recode in that it included in situ separately and different from SEER site recode in that it is limited to carcinomas.
- Liver and intrahepatic bile duct: based on SEER site recode and includes invasive tumors only and all histologies except lymphoma.
- Bones and joints: based on AYA recode for bone which included invasive tumors of the bone plus any site with a bone-specific histology such as osteosarcoma, chondrosarcoma, Ewing sarcoma, etc.
- Soft-tissue sarcoma (STS): the STS chapter used the AYA definition and included all invasive STS histologies without regard to primary site. It includes Kaposi sarcoma of all sites. Invasive only. Some of these cases may also be included in other chapters. For example, leiomyosarcoma of the breast would be included in the breast and STS chapter.
- Kaposi sarcoma: is included in STS chapter and is for all sites.
- Melanoma: this included melanomas of all sites. In situ is also presented.
- Ovary: based on SEER site recode and includes all histologies including epithelial and non-epithelial except lymphomas. Tables show the histology distribution.
- Testis: based on SEER site recode and limited to invasive only. Included all histologies (except lymphoma), and very few histologies are carcinomas.
- Brain and other nervous system: chapter included benign/borderline and invasive tumors and was limited to 2004–2011. It also included pituitary gland, craniopharyngeal duct, and pineal gland (C75.1-75.3) which is usually grouped with other endocrine and included primary brain/ONS lymphomas which were excluded from most other

chapters. The histologies and sites were grouped based on CBTRUS definitions. For both malignant and benign brain tumors, the histologies were grouped with slight modification based on Table 2.2a–c from the Central Brain Tumor Registry of the United States (CBTRUS) report.

- Thyroid: invasive cancer limited to carcinomas (AYA definition).
- Hodgkin and non-Hodgkin lymphoma: same definition was used in AYA recode and SEER site recode.
- Acute lymphoblastic leukemia: same definition was used in AYA recode and SEER site recode.
- Acute myelogenous leukemia: AYA definition used which includes acute monocytic leukemia (9961) which is a separate group in the SEER site recode.
- Chronic myelogenous leukemia: same definition was used in AYA recode and SEER site recode.
- Urinary bladder, prostate, cervix, vagina, vulva: included in genitourinary.

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The Biology of AYA Cancers

3

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Abstract

Investigating the potential biological basis of age-related differences in outcome for AYA with cancer could lead to a better understanding of the biology, facilitate the development of new diagnostic and predictive markers, and identify novel therapeutic targets and treatment approaches for AYA patients. The evidence that cancers in AYA patients may differ biologically from those in older and younger populations includes data from numerous laboratories. However, much of this evidence is preliminary, and large comprehensive studies to confirm and validate these findings are only now beginning to get underway. Indeed, there may be substantial differences in biological and molecular features between different age groups even within the population of AYA patients with a specific cancer type. If age is a good surrogate for a unique tumor biology associated with AYA cancers, then studies of cancers in AYA patients will almost certainly illuminate alternative tumorigenic pathways and will also likely benefit patients in other age groups whose tumors exhibit similar biological/molecular features. The biologic, molecular, and clinical features of five AYA cancers (colon, breast, acute lymphoblastic leukemia, melanoma, and sarcoma) are highlighted in this chapter, and the current state of research for each of them is examined. What will be required to better diagnose, treat, and predict response in patients with AYA cancer is also discussed.

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3.1 Introduction

One potential reason for the limited progress in improving outcomes for cancers among AYA patients compared to the same diseases in younger and older individuals may be that AYA cancers have biological characteristics that are unique compared to other age groups. Investigating the potential biological basis of age-related differences in outcome for AYA cancers could lead to a better understanding of the biology, facilitate the development of new diagnostic and predictive markers, and identify novel therapeutic targets and treatment approaches for AYA patients. The evidence that AYA cancers may differ biologically from those in older and younger populations includes data from numerous laboratories. However, much of this evidence is preliminary, and large comprehensive studies to confirm and validate these findings are only now beginning to get underway. Indeed, there may be substantial differences in biological and molecular features between different age groups even within the population of AYA patients with a specific cancer type. If age is a good surrogate for a unique tumor biology associated with AYA cancers, then studies of cancers in AYA patients will almost certainly illuminate alternative tumorigenic pathways and will also likely benefit patients in other age groups whose tumors exhibit similar biological/molecular features. This chapter will describe the evidence for the existence of unique biological and molecular features associated with cancers that were reviewed at the two US National Cancer Institute (NCI) workshops on AYA cancer biology [1] and their implications for the biology of AYA cancer in general. The cancers are acute lymphoblastic leukemia, breast cancer, melanoma, and fusion-positive sarcomas. If it is possible to elucidate and confirm such differences, we can then begin to utilize this information to develop novel therapies for treating AYA cancers, as well as the companion diagnostics to accompany these treatments. This evidence may also impact our understanding and treatment of adult cancers that may, in some cases, share specific molecular features found in AYA cancers.

3.2 Old Questions and New Technologies

The question of whether AYA cancers have unique pathological and biological features compared to what appears to be the same cancers in older adults and children has been around for several decades [2]. Some of the earliest evidence for the possible unique nature of AYA tumor biology came from studies of colorectal cancer (CRC) in AYA patients. Hereditary nonpolyposis colon cancer (HNPCC) is an inherited form of CRC, also known as Lynch syndrome, the hallmark of which is microsatellite instability (MSI) due to mutations in the mismatch repair genes *MLH1* and *MSH2*. Some of these studies have been revealing. One such study performed an analysis of MSI in 189 CRC patients with no familial evidence of HNPCC using four to five microsatellite markers per tumor [3]. The results demonstrated that of the tumors in 31 patients who were 35 years old or younger, 18 (58 %) displayed microsatellite instability (MSI). In 46 patients who were 36–55 years old, only 8 (17 %) displayed MSI, while in 112 patients who were 55 or older, only 11 % or 10 % displayed MSI. In addition, studies using EBV-transformed lymphoblastoid cell lines also indicated that mutations in mismatch repair genes were not inherited but rather de novo somatic mutations. In another study, a group of investigators compared 126 CRC patients of age 13–39 years with 126 CRC patients >60 years of age. The tumors in younger patients displayed a number of unique characteristics including poorer differentiation, higher incidence of mucinous tumors, signet ring cells, and more advanced tumor stage at diagnosis [4]. This study also found that the percentage of tumors with p53 overexpression was significantly lower among the younger CRC patients. Another study [5] examined 77 CRC tumors in patients aged 7–19 years at St. Jude Children's Hospital in which 48/77 (62 %) displayed mucinous histology compared to 11–13 % of CRC tumors diagnosed in adults. In addition, the disease outcomes for these patients were significantly inferior to those expected for adult CRC patients despite being on adult treatment protocols.

Non-mucinous tumors showed a distinct survival advantage in AYA CRC compared to those of mucinous histology. This suggests that mucinous histology is an independent negative predictor for survival in AYA CRC patients and is indicative of more aggressive disease. The general conclusions from these and similar studies are that MSI frequency is greater among younger CRC patients as displayed by five microsatellite markers [6] and that a greater percentage of tumors characterized by MSI are mucinous compared to tumors without MSI. It is noteworthy that there is no difference between MSI and non-MSI subgroups of young patients with respect to a family history of cancer.

In breast cancer, the hypothesis that AYA patients display a unique biology has been the topic of considerably more debate and has less supporting evidence than the case for AYA CRC [7]. Breast cancer is one of the most common cancers in the AYA population, representing 15 % of all diagnosed cases and nearly one fourth of all cases of invasive cancer diagnosed in American AYA females during 2000–2012 [8]. In the USA, 5 % of all invasive breast cancer in women is diagnosed before 40 years of age [8]. When they do occur, breast tumors in AYAs are on average of higher grade than those found in older adults [9]. In addition, AYA breast cancers often exhibit an absence of estrogen, progesterone, and Her2 receptors, the so-called triple-negative subtype [10]. These tumors are in general more aggressive and have a poorer prognosis than other subtypes. At the same time, the incidence of the more aggressive luminal B tumors is greater in AYA females than in older women [11, 12]. However, unlike AYA colon cancer, unique molecular or biological features have not been definitively associated with AYA breast cancer per se.

In acute lymphoblastic leukemia (ALL), the impact of age on relapse-free and overall survival is striking, and age remains one of the most important prognostic factors for outcome [13]. In childhood, up to 25 % of ALL patients still relapse and often die of resistant disease; the frequency of relapse increases with patient age [14–16]. Data from the NCI Surveillance Epidemiology and End Results program and the Children's Oncology Group demonstrate that survival from ALL begins to decrease dramatically after puberty [17, 18] and that the incidence of AYA ALL has increased significantly since 1975 [19]. While the genetics of pediatric ALL have been studied in great detail, the biologic determinants of treatment failure in ALL patients of any age remain poorly understood. ALL may be of B- or T-cell lineage and is characterized by recurring chromosomal alterations and sequence alterations that have, until recently, been identified using primarily low-resolution genetic approaches such as standard karyotyping or fluorescence in situ hybridization (FISH) and candidate gene sequencing of a limited number of genes. These alterations include aneuploidy and chromosomal rearrangements that commonly disrupt hematopoietic regulators or aberrantly activate oncogenes and tyrosine kinases. Some examples of these chromosomal rearrangements are *ETV6-RUNX* – t(12;21), *TCF3-PBX1*- t(1;19), *BCR-ABL1* – t(9;22), and *MLL* – frequently t(4;11) and other variants in B-ALL and rearrangement of *TAL1*, *TLX1*, and *TLX3* in T-ALL [20, 21].

In melanoma, a highly aggressive form of skin cancer, pediatric and AYA melanoma may be clinically similar to adult melanoma. However, some differences in clinical presentation and outcome in children and AYA with localized disease are evident [22]. Stage by stage the prognosis in the pediatric and AYA groups is generally believed to be similar to that in adults [23]. Phenotypically, melanomas appear to be thicker in young patients, and metastases to sentinel nodes (SLN) occur more frequently in children and AYA groups than would be expected in adults with the same stage of disease. High mitotic rate and younger age are considered to be predictors of SLN positivity [24]. Melanoma in young patients is also less likely to recur in distant organs, implying that pediatric and AYA melanomas display biological differences compared with adult melanoma [25]. However, whether there is an inherent biological uniqueness associated with AYA melanomas is currently unknown.

Among the sarcomas, AYA patients generally do more poorly than younger patients [1]. In one of the first multivariate analyses of

prognostic factors in patients 18 or more years of age with Ewing sarcoma, age was found to be one of the three independent factors, with adults older than 26 having a worse survival [26]. The other factors were metastatic disease at presentation and primary origin in extraosseous tissue [26]. In a review of 975 children and AYAs in Europe with Ewing sarcoma of bone, patients with localized disease who were 15 years or more of age had a worse survival than those who were younger [27]. Host age, tumor biology, enrollment on clinical trials, and treatment intensity may all play a role in the prognosis of AYA patients with soft-tissue sarcomas. There are numerous gene fusion events known to occur in soft-tissue sarcomas. These are represented in a heterogeneous group of soft-tissue sarcomas described below.

The data available to support a unique biology for these and other AYA cancers, described in more detail below, has come mainly from more traditional molecular analysis methodologies such as FISH, in situ hybridization, immunohistochemistry, reverse transcriptase-polymerase chain reaction (RT-PCR), and methylation-specific PCR studies. In general new technologies for molecular analysis such as whole-exome/whole-genome (WEG) sequencing of DNA, RNA sequencing (RNASeq), digital PCR, microarray expression analysis for mRNA, and miRNA, whole-genome methylation analysis and proteomic analysis have yet to be applied to this question.

3.3 Four AYA Cancers with Biologic Distinction

The following sections provide more specific existing data in support of a unique biological and clinical phenotype for the above-cited AYA cancers and further elucidate the essential questions to be explored that may reveal the unique biological characteristics inherent in AYA cancers. This section will also consider how the new advanced technologies mentioned above may assist in this effort and the clinical implications for new discoveries in AYA cancer biology.

3.3.1 Colorectal Cancer

The evidence for AYA cancers presenting a unique biology compared to the same cancers in adults (or children) varies based on the specific cancer being considered. As mentioned previously, some of the best evidence for this is in colon cancer. The current studies investigating the molecular characterization of this tumor include those summarized in a publication from an NCI workshop that focused on several AYA cancers [1].

The incidence of digestive tract cancer in AYAs is low compared to that in older adults. Based on the 2000–2012 incidence of invasive cancer in the 18 SEER regions of the USA, CRC accounted for 5.2 % of all new cases diagnosed as a first malignancy in AYAs, whereas in adults over 40 years of age, the incidence proportion was 9.4 % [8]. The corresponding proportions for cancer of subgroup of the anus, anal canal, and anorectum were 2.0 % and 2.8 %, respectively [8]. During 2000–2012, the USA had an average of 6,000 new cases of invasive digestive tract cancer yearly in AYAs, of which 3,660 were in CRC and 1,100 in the anus, anal canal, and anorectum [8]. The incidence of new cases in AYAs was higher in females throughout the digestive tract, except for the proximal colon and anal regions in which male AYAs had a higher rate than females [8].

However, CRC is the sixth leading cause of AYA cancer mortality resulting in an average of 805 deaths annually in the USA during 2000–2012 [28]. Of all cancer deaths in AYAs during 2000–2012, invasive cancers of the digestive tract, including the anus, liver, stomach, and esophagus, ranked #1 [28]. In terms of all cancer mortality, deaths due to CRC accounted for 9 % overall during 2000–2012 in both AYAs and adults over 40 years of age [28].

Figure 3.1 depicts the all-stage, 5-year cancer-specific survival rate in patients with CRC and cancer of the anus, anal canal, and anorectum as a function of sex and age at diagnosis during 2000–2012 and sex in the 18 SEER regions of the USA [28]. Most sites distal to the ascending colon had a worse prognosis in AYAs than in older adults up to the age of 70–75, with the absolute rate ranging

Fig. 3.1 Incidence of invasive cancer of the colon, rectum, and anus, SEER18, 2000–2012 by age, site, and sex. Age groups with <10 patients excluded. *Includes rectosigmoid junction

from 30% lower for hepatic flexure primaries in females to 10% lower for rectal primaries in females [28]. Among AYAs, the survival rate was inversely proportional to patient age for all primaries distal to the ascending colon and the ascending colon in females. AYA females had a distinctly worse survival than older females for cancer of the anus, anal canal, and anorectum, whereas this was not true in male AYAs [28]. Survival of AYAs with cancer of the proximal large intestine, including the appendix and cecum, was more favorable in AYAs than in older patients (data not shown). In general, AYAs exhibit a more aggressive disease phenotype, stage by stage, than the equivalent sites in older adults [18].

AYA CRC is known to exhibit a greater frequency of mucinous histology, the presence of signet ring cells, high MSI, and a higher incidence of mutations in mismatch repair (MMR) genes [3–5, 29–31]. Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant syndrome that is associated with an approximately 70% lifetime risk of CRC (often right sided) and a 50–70% risk of endometrial cancer [32]. It is caused by heterozygous mutations in one of four MMR genes *MSH2*, *MLH1*, *MSH6*, or *PMS2* (predominantly *MLH1* and *MSH2*) and is associated with colon cancer that can appear in patients as young as their mid-20s, as well as in older adults. Silencing of the *MLH1* gene by methylation is observed in 20% of sporadic CRC. Colorectal tumors with *MLH1* silencing or from patients with HNPCC exhibit MSI. While some cases of AYA CRC exhibit MSI due to a hereditary component, many do not have a history of genetic predisposition, suggesting that de novo somatic mutations in MMR genes may be a molecular feature of AYA CRC. Relatively few molecular genetic studies have been conducted in this age group, perhaps due to the fact that these cases are few in number and tissue samples are difficult to procure. Recent work by the Cancer Genome Atlas (TCGA) study has provided data on genes that are frequently mutated in adult CRC [33]. This and other studies have identified several genes that exhibit amplification and elevated expression in adult CRC, including IGF-2 [34]. There are also consensus gene sets exhibiting mutations in adult CRC that have been identified [35, 36]. These data provide a baseline for pathway analysis that could direct us toward novel signaling pathways in AYA CRC tumors. While AYA CRC tends to have a more mucinous phenotype and appears to have a higher frequency of MSI even in the absence of a hereditary component, molecular targets that would make the AYA CRC more vulnerable to a specific therapeutic target have yet to be identified. The only molecular marker at this time, which could be considered a predictor in AYA CRC, is MSI. However, this falls more into the category of descriptor than predictor, as does the mucinous histology phenotype. As true diagnostic markers that are specific to AYA CRC have yet to be identified, there is a need for both basic biological and translational research studies to elucidate any fundamental differences between adult and AYA CRC. The biological questions include whether there are signaling pathway differences between the two types of CRC and, if so, how unique are they to each form of the disease and how dependent are the tumor cells on these pathways for their proliferation and survival. High-throughput methodologies for gene expression and mutational analysis are expected to provide initial clues as to whether there are unique molecular characteristics associated with AYA CRC compared to that found in adults. These studies could include microarray analysis for mRNA and miRNA expression signatures and whole-exome sequencing studies for identification of unique somatic mutation patterns. Studies could also include single-nucleotide polymorphisms, methylation, and proteomic analyses to compare adult and AYA forms of the disease. The results from these studies will provide a foundation from which novel diagnostic, prognostic, and predictive markers can be identified in the AYA CRC population and perhaps reveal preferred signaling pathways that can be used as targets for therapy.

3.3.2 Acute Lymphoblastic Leukemia

As mentioned in the "Introduction," ALL is another cancer in which there are significant data supporting a biological uniqueness to the disease in AYA patients. ALL is the most common cancer

in individuals from birth to 21 years of age and is one of the leading causes of cancer-related mortality in AYAs [13, 37–39]. While the incidence of ALL in the USA, in children from 1 to 10 years of age, has remained relatively constant over the past several decades, data from the NCI SEER program reveal a continual increase in the incidence of ALL in the AYA population (ranging in age from 15 to 29 years) from 1975 to 2010 (Fig. 7.5, Chap. 7). Unfortunately, in contrast to pediatric ALL in which scientific and clinical advances have led to impressive improvements in overall survival with more than 80 % of children (depending on race, ethnicity, and age) now achieving cure on contemporary chemotherapy regimens, overall survival in AYA ALL remains poor. Less than 45 % of AYA ALL patients currently achieve long-term remissions. While ALL is one of several cancers with a poor outcome in the AYA population, ranked as 4th among the AYA cancers with the lowest overall survival rates [40], it remains the most common cause of AYA cancer-related mortality due to its high incidence in this age group [41]. The impact of age on relapse-free and overall survival in ALL is striking [17]. In addition, the annual average percent change in the death rate during 1998–2011 shows the least improvement in the AYA age range (25–44 years) compared to improvements in children and in older adults (Fig. 7.9, Chap. 7).

The reasons for the differences in outcome observed in pediatric vs. AYA ALL patients are due to distinct genetic and biologic features of the disease at different ages, differences in therapeutic approach and therapeutic intensity, possible differences in compliance with therapy at different ages, and/or other social and behavioral factors and are now under intensive investigation. The identification of genomic lesions has provided critical insights into leukemogenesis and is central to accurate diagnosis and current methods of risk stratification for pediatric ALL patients participating in clinical trials. Several of these genetic alterations are typically associated with a very high risk of treatment failure and relapse on current treatment regimens, the most important of which are the Philadelphia-like mutations that are analogous to Ph-1 (*BCR-ABL1*) but are different at the molecular level (*CRLF2*, *JAK-1*, etc.). The Ph-like mutations have a peak incidence during the AYA years (Fig. 3.2) [42, 43]. Other mutations that are more common in AYAs than children include *MLL* rearrangements and *BCR-ABL1* itself. Importantly, as shown in Fig. 3.3, the frequency of genomic rearrangements (e.g., *ETV6-RUNX1*- t(12;21)) and hyperploidy associated with a superior outcome in pediatric ALL decrease in AYA ALL patients. Conversely, those genetic abnormalities associated with a poorer outcome (*BCR-ABL1*- t(9;22), *MLL* rearrangements) increase [20]. It has been found that a substantial number of children with ALL, in particular those who are older than 10 years of age, including many who relapse, lack one of these well-known chromosomal alterations associated with better outcome. This suggests that genomic/biological differences in AYA ALL may contribute to a more aggressive and treatment-refractory form of the disease.

Ongoing studies in ALL xenograft/primagraft models and in human patients have demonstrated that some of the gene fusions in Ph-like ALL involving tyrosine kinases are particularly sensitive to various tyrosine kinase inhibitors (TKIs), such as imatinib or dasatinib [20, 44–46]. These observations underscore the importance of rapid translation of these genomic studies to prospective identification of patients with Ph-like ALL and therapeutic targeting of these patients with TKIs in the context of clinical trials. The identification of these patients at diagnosis will provide an opportunity to incorporate TKI inhibitor treatment to current chemotherapeutic regimens that for some has already prolonged survival [43] and as such exemplifies how a better understanding of the genomics and biology of AYA cancer can lead to better diagnostics and treatment.

The discovery of *RAS* mutations in a distinct cohort of 10 % of AYA ALL patients [48] also underscores the importance of developing effective treatments targeted to activated RAS and opens up avenues of investigation into the contribution of RAS pathways [20, 47–49]. Such studies will provide the mutational profiles and associated pathways that may distinguish AYA ALL from pediatric and adult forms of the disease.

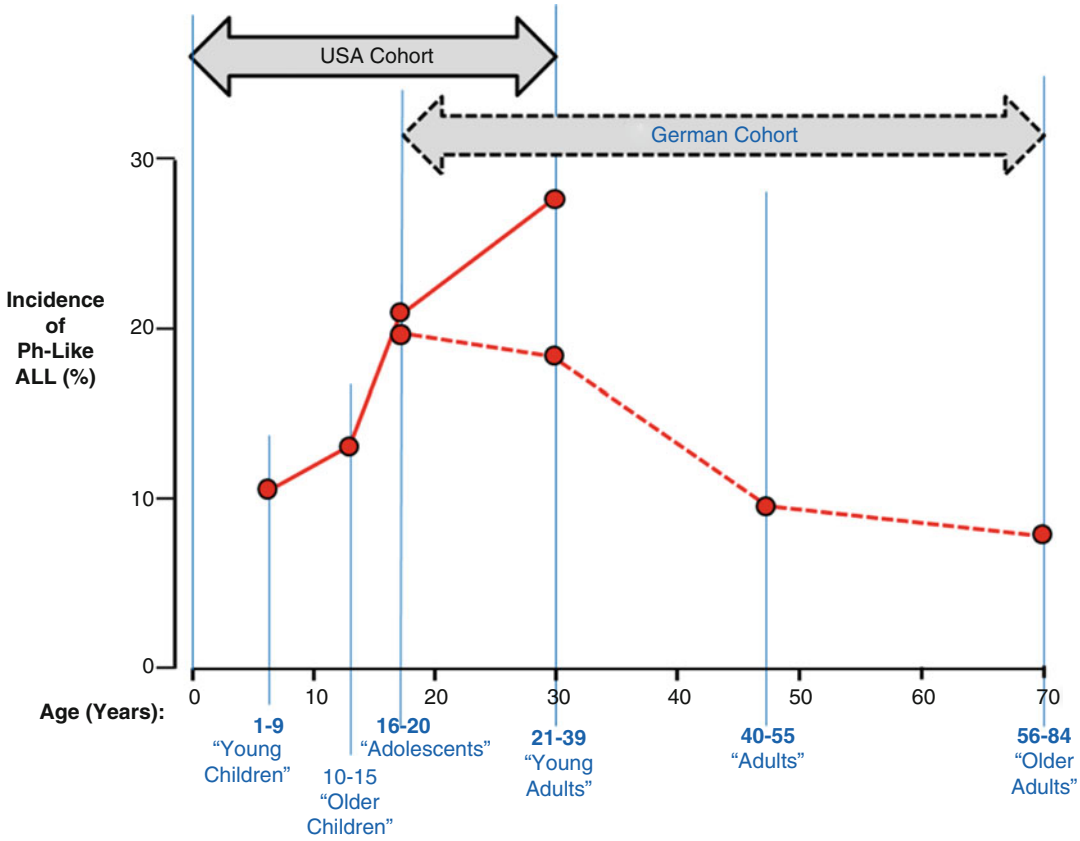

Fig. 3.2 Proportion of all pre-B-ALL that is Ph-like by age at diagnosis. The German cohort was composed of patients who received treatment on the German Multicenter Study Group for Adult ALL trials [42] and the US cohort was composed of the patients of the Children's Oncology Group and St. Jude Children's Research Hospital [43]

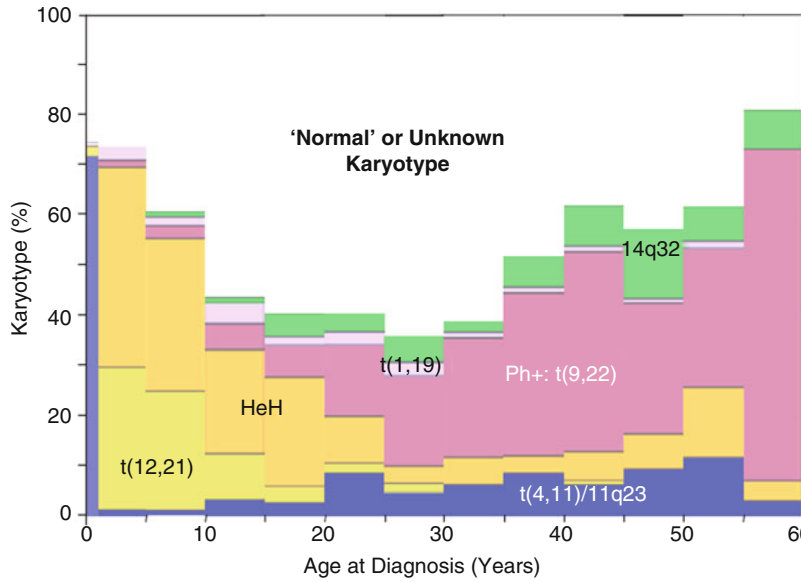

Fig. 3.3 ALL karyotype by age (Modified from Harrison and Moorman [20])

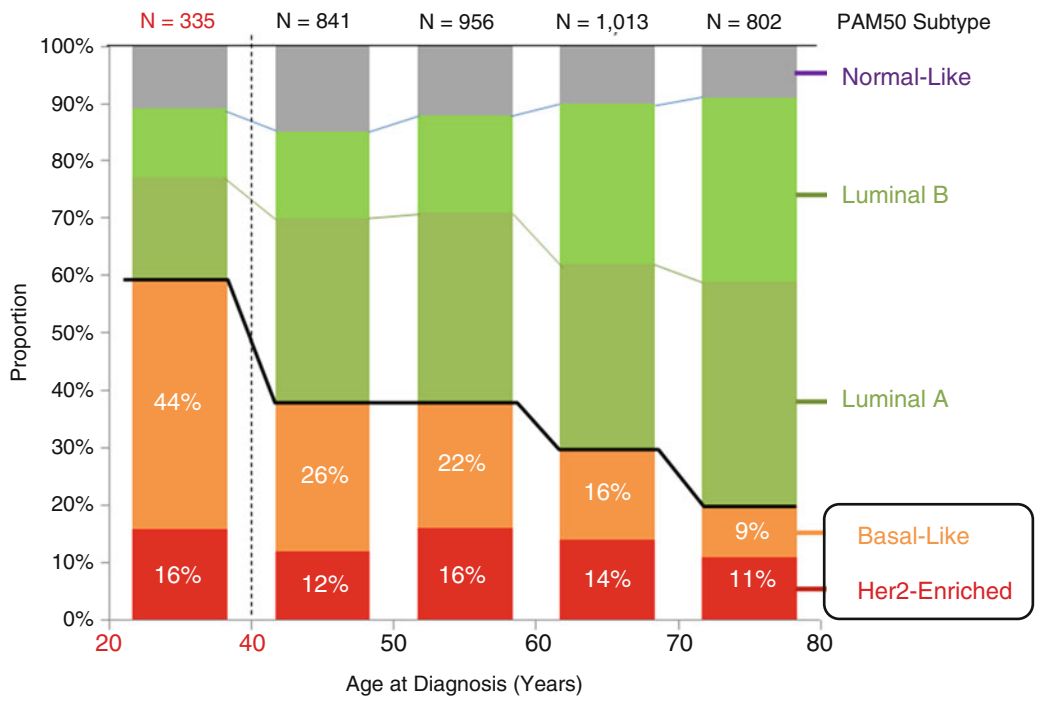

Fig. 3.4 Age-specific changes in intrinsic breast cancer subtypes [55]

3.3.3 Breast Cancer

Breast cancer is the most frequent form of cancer in women in the AYA age group throughout the world [2, 50–52, Chap. 2]. In recent years, the proportion of women presenting with distant involvement, which is associated with a poorer prognosis, has shown a statistically significant increase [53]. Age at diagnosis is an independent factor in prognosis, and cumulative evidence has suggested, but not demonstrated, that AYA breast cancer exhibits differences in type, grade, and aggressiveness in comparison to the disease in older women [2, 54]. Young women have nearly twice the rate of the basal type of breast cancer than that of any other age group (Fig. 3.4) and a peak incidence of *HER-2-NEU*-positive and triple-negative subtypes (Fig. 3.5) [8]. Ductal carcinoma in situ (DCIS) is 3–5× more likely to be either triple negative or *HER-2-NEU* positive in 25- to 30-year-olds than at any other age [8].

However, the hypothesis that this is due to a *unique* biology continues to be debated [7]. Current studies utilize gene expression profile comparisons in order to identify specific genes and molecular profiles that could identify unique factors involved in younger women with breast cancer [55–59]. The results have suggested that there are some detectable expression pattern differences between tumors in young and older women, but reanalysis of these studies has led to questions about some of the earlier conclusions [51]. Ongoing studies have focused on specific genes such as *BRCA1*, *TP53*, and others that have been linked to the early incidence of aggressive breast cancer [60, 61]. There is also a growing interest in the role of an apparent difference in tumor-associated stroma in AYA breast cancer [62]. Studies of the molecular mechanisms of different breast cancer subgroups identified in adults are likely to be informative for AYA breast cancer as well, since no consistently unique molecular or biological factors have been identified definitively [63]. Detailed studies of triple-negative/basal subgroups [64] are particularly relevant since these have been associated more frequently with breast cancers in the AYA population. This is illustrated in Fig. 3.5 showing the relative proportions of invasive breast

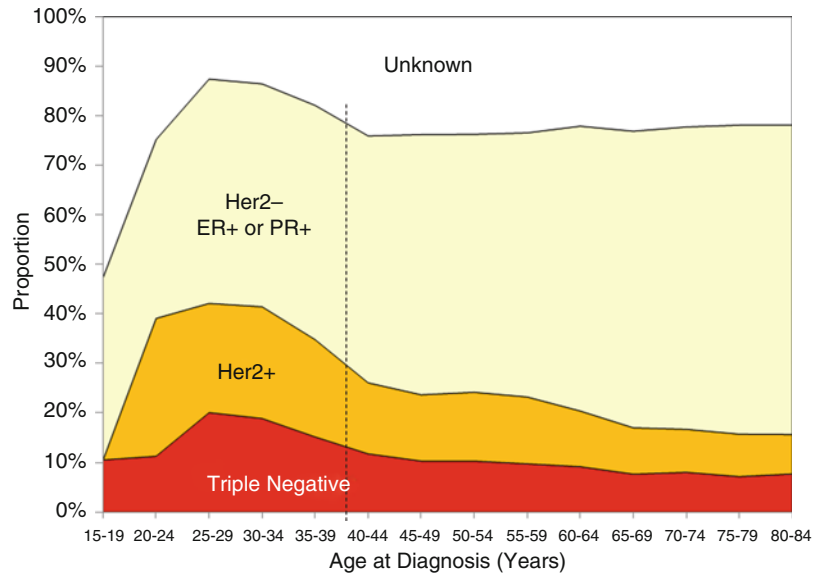

Fig. 3.5 Incidence of invasive breast cancer and ductal carcinoma in situ, SEER18, 2010–2011, by surface receptor type and age [8]

carcinomas and DCIS as they relate to Herceptin, estrogen receptor, and progesterone receptor status. Studies on the role of the microenvironment/stroma in tumor initiation and progression will be informative for studies of AYA tumors. More extensive, carefully controlled analysis of gene expression signatures in AYA tumors relative to the same subtypes in older patients is needed to determine definitively whether a specific pattern is linked to AYA breast cancers [65]. Whole-genome analysis with deep sequencing could also help to identify mutations or polymorphic patterns that could be linked to susceptibility to early-onset breast cancer [66, 67].

3.3.4 Melanoma

The incidence rate of melanoma in children and adolescents is rising yearly and increases with age. Melanoma accounts for <1 % of all malignancies in patients less than 15 years of age compared with 8 % among AYAs and a peak of 13 % between 25 and 30 years of age. In AYAs, the incidence is higher in females than in males, whereas in older adults, melanoma is far more frequent in males (Fig. 10.1 in Chap. 10). The etiology of melanoma in the AYA population is not clear, and while diagnosis at an older age is linked to lifelong exposure in genetically less susceptible individuals, in AYAs it is likely that melanomas result from genetic and/or environmental factor interactions involving excessive UV exposure among susceptible individuals. Known predisposing factors in pediatric melanoma include rare conditions such as large congenital nevi, giant hairy nevi, acquired dysplastic nevus syndrome, xeroderma pigmentosum (XP), Werner syndrome, retinoblastoma, immunosuppression, familial melanoma syndrome, and, to a lesser extent, exposure to UV radiation [22]. How this may relate to the biology of AYA melanoma is unclear. According to staging criteria for adult melanoma, important prognostic criteria are thickness of the primary tumor, presence or absence of ulceration, nodal status, and presence or absence of metastasis. The 2007 guidelines also include using mitotic rate as a prognostic factor in staging, particularly for lesions <1 mm thick (T1) [68]. To date, however, there has been no validated staging system for melanoma in the children and AYAs. Diagnosis of melanoma in children and AYAs can be difficult since many pediatric skin lesions (such as pyogenic granulomas, Spitz nevi, and benign nevi) share some features of adult melanomas.

Molecular techniques such as comparative genomic hybridization (CGH), array-CGH,

FISH, PCR-based loss of heterozygosity studies, and immunohistochemical markers have all been applied to formalin-fixed, paraffin-embedded archived clinical specimens. These approaches promise more accurate classification to discriminate a nevus from melanoma, especially in the cases of melanocytic tumors with ambiguous histology [69]. In particular, CGH may be helpful when routine histologic examination does not permit distinguishing melanoma from these lesions. However, these approaches have not been validated in children and AYAs.

Although contradictory data have been reported regarding outcome in pediatric patients [23], prognosis in the pediatric and AYA groups is generally believed to be similar to that in adults. Melanomas appear to be thicker in young patients, and metastases to sentinel nodes (SNL) are found more frequently in children and AYAs with melanoma than would be expected in adults with the same stage of disease. High mitotic rate and younger age are considered to be predictors of SLN positivity [24]. Interestingly, melanoma in young patients is also less likely to recur in distant organs. This implies that melanoma in children and AYA patients display biological differences compared with adult melanoma. For example, melanomas in young patients are more prone to progression and subsequent metastasis than in adults [25].

Marked differences exist between the patterns of melanomas and melanocytic nevi, such that neoplasms of Spitzoid morphology commonly seen in younger patients and the genetic differences between melanoma and benign Spitzoid neoplasms identified by CGH may be used to distinguish these lesions when pathological features are in question. Spitz nevus, blue nevi, proliferating congenital nevi, or other benign melanocytic lesions are characterized by fewer or absence of chromosomal aberrations or have a restricted set of aberrations with no overlap to melanoma. More information is known about genomic differences between pediatric and adult melanoma than for AYA melanoma. Some chromosomal and genomic alterations differentiate between adult and AYA melanoma. For example, frequent deletions of chromosomes 9p (the most common aberration in melanoma harboring *CDKN2A*), 1p, 6q, 10q, and 8p and gains of chromosomes 7, 8, 6p, and 1q are present in adult melanoma cases. Recurrent Spitz nevi revealed higher frequencies of 11p gain implicating *HRAS* as a candidate oncogene on 11p [70]. Pediatric melanomas demonstrate higher levels of MSI than melanomas in adults [71].

Melanoma development has been linked to germline mutations in genes encoding *CDKN2A*, *CDK4*, and *MCIR* and to somatic mutations in proto-oncogenes *BRAF*, *NRAS*, and *KIT* and tumor suppressor genes *CDKN2A*, *TP53*, and *PTEN* [72]. A recent study revealed that *BRAF* mutations that are common in melanocytic nevi and melanomas were not detected in typical Spitz nevi. Somatic mutations in *BRAF* are the most common genetic alterations, occurring in up to 66 % of adult malignant melanomas and 21 % of common benign melanocytic nevi with non-Spitzoid morphology [73, 74]. The most common *BRAF* V600E mutation occurred more frequently among patients who were 50 years of age or younger when compared with those over age 50 years. Similarly to *BRAF*, *NRAS* is mutated more frequently in melanomas than Spitz nevi, whereas no *HRAS* mutations have been found in Spitzoid melanomas. Approximately 67 % of Spitz nevi with increased copy number of chromosome 11p harbor an activating mutation of this oncogene that is part of RAS/RAF/MEK/ERK kinase signaling pathway. This is in contrast with rare *HRAS* mutations in Spitz nevi with normal *HRAS* copy number.

Pediatric melanomas demonstrate more frequent loss of *INK4A* and gain of *KIT* oncogenes compared with familial melanoma cases. Gain of KIT may be associated with metastasis of pediatric melanoma [75]. Early development of melanoma in children and AYAs occurs following loss of key regulators of melanocyte function. Currently, the *p16INK4* tumor suppressor gene on chromosome 9p21 is postulated as a strong candidate melanoma gene, with particular relevance to early-onset familial melanoma. Spitz nevi, as a group, show high levels of p16 expression [76]. Whether sporadic melanomas occurring in childhood and AYAs are associated with

aberration of this gene needs to be confirmed. In addition, expression of cyclins D1, D3 A, and CDK4 in adult and young adult/pediatric melanomas should be explored for comparison of melanoma specimens across age groups.

Recent findings suggest that the differential biology of melanoma at different ages is driven partly by deregulation of microRNA (miRNA) expression that target proliferation genes including *MAP3K5*, RAS-related protein *RAB32*, and the suppressor of cytokine signaling (*SOC1*), inflammation (cytokines and chemokines) EMT transition, and stroma (disintegrin and metalloproteinase precursors and TNF-related proteins) [77]. Several miRNA species have been identified to be either up- or downregulated in melanomas from different age groups. miRNA profiles in the primary melanomas may be associated with the clinical parameters of stage and nodal involvement that differ in adult and young populations, suggesting that melanomas in older adults rely on different pathways of invasion than young adult melanomas. The outcome for younger patients may be improved, but stratification for pediatric and AYA age groups should occur in biology studies and clinical trials so that prospective data are obtained for this population in which the incidence of melanoma is rising. Improved knowledge of the biology of tumors in this population and formal testing of novel-targeted therapies and immunotherapy approaches are required to improve outcomes of melanoma in AYA patients.

3.3.5 Sarcoma

In AYA patients, sarcomas represent 5.3 % of all invasive cancers, with more sarcomas in the age group located in soft tissue (3.9 %) than in bone (1.3 %) (SEER18, 2000–2012) [8]. Derived from the mesenchyme of connective tissues, they are the most diverse and heterogeneous of cancers grouped by standard classification systems. The most common sarcomas in AYAs, in descending order of incidence according to the US SEER database for 2000–2012, are Kaposi sarcoma, dermatofibrosarcoma protuberans, leiomyosarcoma, osteosarcoma, peripheral primitive neuroectodermal tumor (PNET) (originally called Ewing sarcoma), myxoid chondrosarcoma, myxoid liposarcoma, gastrointestinal stromal tumor (GIST), fibrous histiocytoma, synovial sarcoma, phyllodes tumor, spindle cell sarcoma, fibromyxosarcoma, alveolar rhabdomyosarcoma (ARMS), hemangiosarcoma, epithelioid sarcoma, desmoplastic small round-cell tumor (DSRCT), embryonal rhabdomyosarcoma, fibrosarcoma, liposarcoma, angiomatoid fibrous histiocytoma, alveolar soft part sarcoma, inflammatory myofibroblastic tumor, and giant cell tumor of bone [8]. The incidence of each of these types of sarcoma with respect to age varies with diagnosis (Figs. 3.6 and 3.7).

More than 50 morphological subtypes of sarcoma exist that in 2013 were recategorized by the WHO Classification of Tumors of Soft Tissue and Bone [78]. This revision was driven primarily by the rapidly increasing knowledge of the genetics of sarcomas, two aspects of which are particularly important for AYA patients. First, this classification is more reproducible and provides a universal nomenclature that helps to ensure comparability of international trials, facilitation of translational research, and ultimately more effective treatment. In addition, more than 60 hereditary syndromes related to bone and soft-tissue sarcomas have been recognized in this volume [78], most of which are detectable early in life and allow earlier diagnosis of the related malignancy and some of which primarily affect AYAs. In addition, many of these sarcomas have been identified to have gene fusions (Table 3.1).

Figures 3.6 and 3.7 show for 2000–2012 in the USA the incidence and distribution of the major soft-tissue and bone sarcoma classifications as a function of age within each of the 5-year age groups in AYAs compared with younger and older patients. The two figures depict different ways to classify the sarcomas. There is not only a distinct late adolescence incidence peak in sarcomas, among 15- to 19-year-olds (upper panels), there is also a striking variation in the distribution of sarcoma types within the age range of AYAs (lower panels). Each of the 5-year age groups of AYAs has a unique distribution, and all are

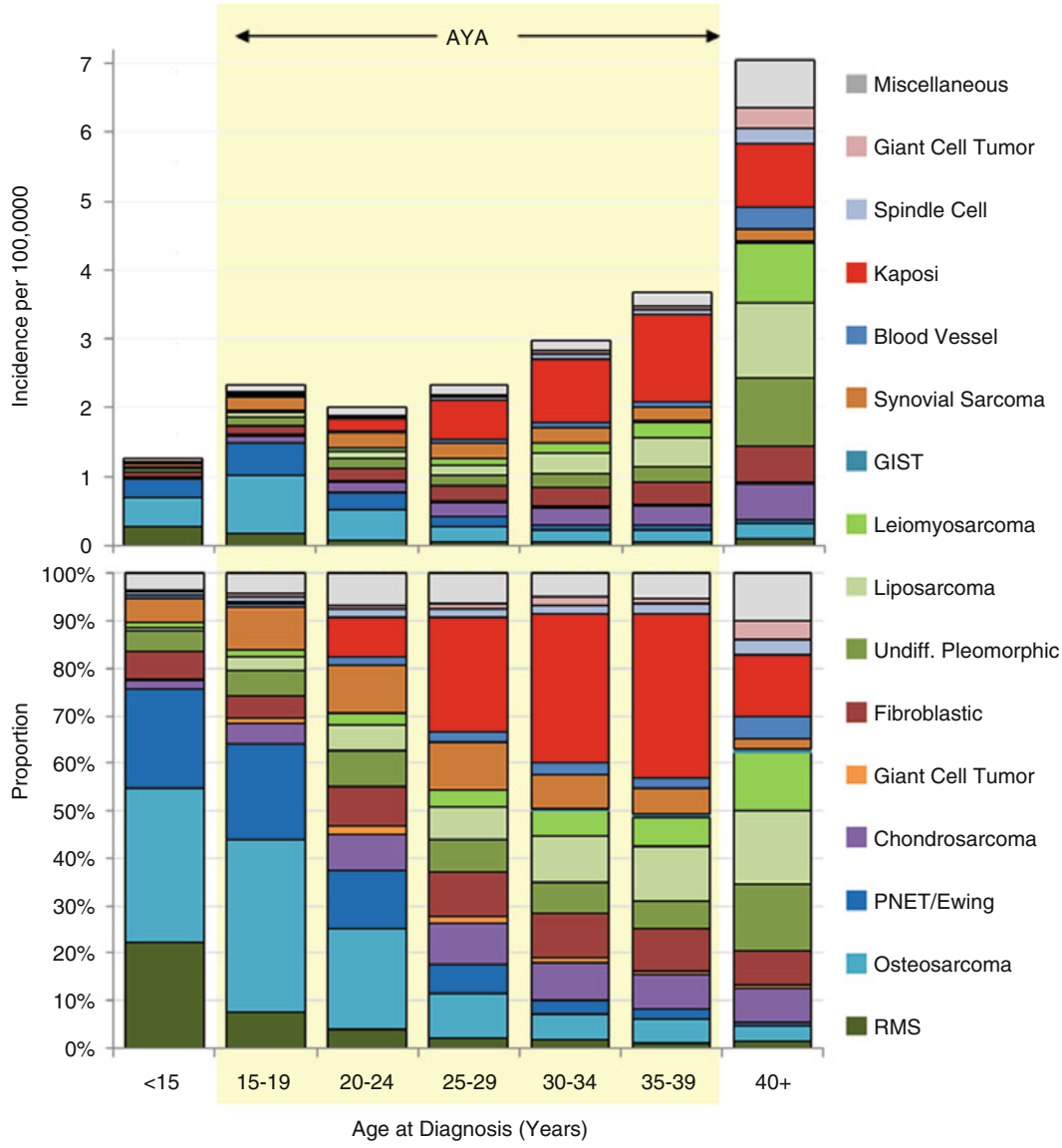

Fig. 3.6 Incidence and distribution by ICD-O-3 histology code of soft-tissue and bone sarcomas, US SEER18, 2000–2012, by 5-year age intervals in AYAs and younger and older patients. GIST-gastrointestinal stromal tumor

distinctly different from younger and older patients. Bone sarcomas predominate in 15- to 19-year-olds and represent nearly half of the sarcomas in 20- to 24-year-olds. Chondrosarcoma is the most common bone sarcoma in older AYAs, 30 to 39 years of age. Of the soft-tissue sarcomas, synovial sarcoma predominates in younger AYAs and Kaposi sarcoma in older AYAs, with the latter occurring almost entirely in males and diminishing in incidence in the most recent years. In 2010–2012, Kaposi sarcoma was replaced by DSRCT as the most common sarcoma in the oldest AYAs. The next most common soft-tissue sarcomas in AYAs are undifferentiated pleomorphic sarcoma (previous fibrohistiocytic sarcoma), fibroblastic sarcoma, leiomyosarcoma, liposarcoma, malignant peripheral nerve sheath tumors, and alveolar soft part sarcoma (ASPS). Rhabdomyosarcoma (RMS), the most common soft-tissue sarcoma in children, occurs in AYAs

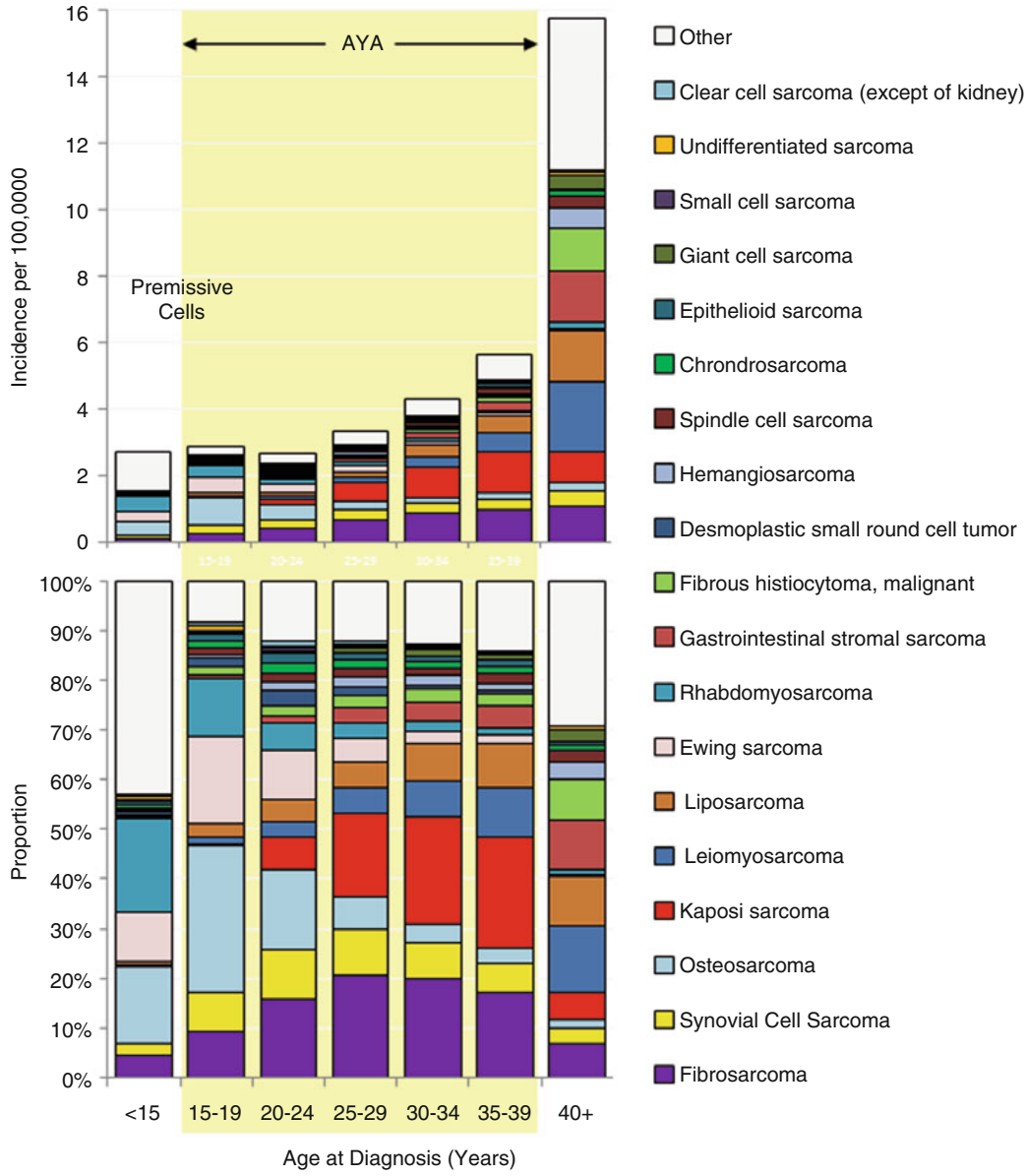

Fig. 3.7 Incidence and distribution by ICD-O-3 histology code of soft-tissue and bone sarcomas, US SEER18, 2000–2012, by 5-year age intervals in AYAs and younger and older patients. Sarcoma classification differs from Fig. 3.6

but at an incidence inversely proportional to age, such that by age 40, it is distinctly rare. Its importance is highlighted by the strikingly worse survival rate in AYAs despite what appears to be the same cancer, with the superior results in children (Chap. 15). Several other sarcomas have a worse outcome in AYAs compared to children, such as PNET.

All of this underscores the need for new treatment modalities based on a better understanding of the biology of sarcomas. Molecular profiling using the latest genomic techniques is a powerful tool to detect actionable mutations in as many as 60% of the soft-tissue sarcomas. In the next sections, the molecular biology of bone and soft-tissue sarcomas will be discussed, with emphasis on the

Table 3.1 Associated gene fusions in sarcoma

Sarcoma type	Cytogenetics	Fusion genes	Gene	Frequency
Angiomatoid fibrous histiocytoma	t(2;16)(q34;p11)	FUS-CREB1	bZIP	89 %
	t(12;16)(q13;p11)	FUS-ATF1	bZIP	11 %
Alveolar soft part sarcoma	t(X;17)(p11;q25)	ASPSCR1- TFE3	Microphthalmia-TFE, basic helix-loop helix, leucine zipper	100 %
Alveolar rhabdomyosarcoma	t(2;2)(q35;p23)	PAX3-NCOA1	Paired box/homeodomain	Rare
	t(2;13)(q35;q14)	PAX3-FKHR	Paired box/homeodomain	95 %
	t(1;13)(p36;q14)	PAX7-FKHR	Paired box/homeodomain	5 %
Ewing sarcoma	t(11;22)(q24;q12)	EWSR1-FLI1	Ets-like	85 %
	t(21;22)(q22;q12)	EWSR1-ERG	Ets-like	10 %
	t(7;22)(p22;q12)	EWSR1-ETV1	Ets-like	Rare
	t(17;22)(q12;q12)	EWSR1-ETV4	Ets-like	Rare
	t(2;22)(q33;q12)	EWSR1-FEV	Ets-like	Rare
Desmoplastic small round-cell tumor	t(11;22)(p13;q12)	EWSR1-WT1	Zinc finger	95 %
Inflammatory myofibroblastic tumor	t(1;2)(q25;p23)	ALK-TPM3	Tyrosine kinase	N/A
	t(2;19)(p23;p13)	ALK-TPM4	Tyrosine kinase	N/A
	t(2;17)(p23;q23)	ALK-CLTC	Tyrosine kinase	N/A
Myxoid liposarcoma	t(12;16)(q13;p11)	FUS-DDIT3	bZIP	95 %
	t(12;22)(q13;q12)	EWSR1-ATF1	bZIP	5 %
Myxoid chondrosarcoma	t(9;22)(q22;q12)	EWSR1-NR4A3	bZIP	75 %
	t(9;15)(q22;q21)	TFC12-NR4A3	Basic helix-loop helix	N/A
	t(9;17)(q22;q11)	TAF15-NR4A3	bZIP	N/A
Clear cell sarcoma	t(12;22)(q13;q12)	EWSR1-ATF1	bZIP	N/A
Liposarcoma	t(12;16)(q13,p11)	FUS-ATF1	Bzip	N/A
Synovial sarcoma	t(X;18)(p11;q11)	SYT-SSX1	Kruppel-associated box	65 %
	t(X;18)(p11;q11)	SYT-SSX2	Kruppel-associated box	35 %
	t(X;18)(p11;q11)	SYT-SSX4	Kruppel-associated box	Rare
	t(X;20)	SS18L1-SSX1	Kruppel-associated box	Rare
	t(X;20)	SS18L1-SSX2	Kruppel-associated box	Rare
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	COL1A1-PDGFB	Tyrosine kinase	N/A
Endometrial stromal sarcoma	t(7;17)(p15;q21)	JAZF1-JJAZ1	Polycomb group complexes	N/A
Congenital fibrosarcoma and mesoblastic nephroma	t(12;15)(p13;q25)	EVT6-NTRK3	HLH, tyrosine kinase	N/A

N/A not known

fusion-positive sarcomas, most of which involve transcription factors that are of particularly interest to AYA cancer biology. Studies to date indicate that many of these tumors are dependent for their survival on fusion genes so that interruption of the pathways associated with these genes may lead to novel therapeutic targets. Osteosarcoma, PNET (Ewing sarcoma), and synovial sarcoma are discussed separately to illustrate the potential impact of the biologic underpinnings.

Tumor-specific fusion proteins that are not expressed in normal cells and appear to be required for oncogenesis in most fusion-positive soft-tissue sarcomas make them ideal targets for therapeutic intervention. However, the ability to target these fusions remains a challenge. Unlike the commonly targeted receptor tyrosine kinases, fusion protein transcription factors have been more difficult to target. For example, peptides spanning the unique fusions in Ewing sarcoma

and alveolar rhabdomyosarcoma have been used as part of vaccine strategies in consolidative immunotherapy [79], but did not result in robust immune responses.

Comprehensive genomic analyses, including whole-exome sequencing, RNASeq analysis, microarray analysis, and methylation analysis, will all be required for a complete molecular characterization in order to reveal the downstream impact of the fusion genes and provide important insights into the biology of these cancers. In addition, high-throughput siRNA and drug screening in isogenic cell lines harboring these fusion genes will identify specific vulnerabilities for cells harboring these fusion genes.

Osteosarcoma Osteosarcoma (OS) is an osteoid-producing sarcoma [80]. Most cases of osteosarcoma are high grade and are described herein. OS has two age-incidence peaks, one at age 15 and another in elderly adults (Fig. 3.8) [81] that is associated with Paget disease or occurs as a secondary malignancy [81, 82].Whereas OS can appear to arise in soft tissue in the older adult population, it rarely if ever does in AYAs (Fig. 3.8). As described in Chap. 16, the incidence in young adolescents is similar for boys and girls, but in AYAs males have a distinctly higher incidence. All of these factors suggest that OS must have a different biology in AYAs than in children or older adults.

Most cases of OS occur sporadically, but in a number of genetic conditions, a higher incidence of OS is present. Among these are Li-Fraumeni syndrome (*TP-53* mutations), hereditary retinoblastoma, and progeria syndromes such as *RECQL4* (Rothmund-Thomson syndrome), *RECQL3* (Bloom syndrome), and *RECQL2* (Werner syndrome) [83]. Sporadic OS is genetically an unstable tumor, with frequent numerical

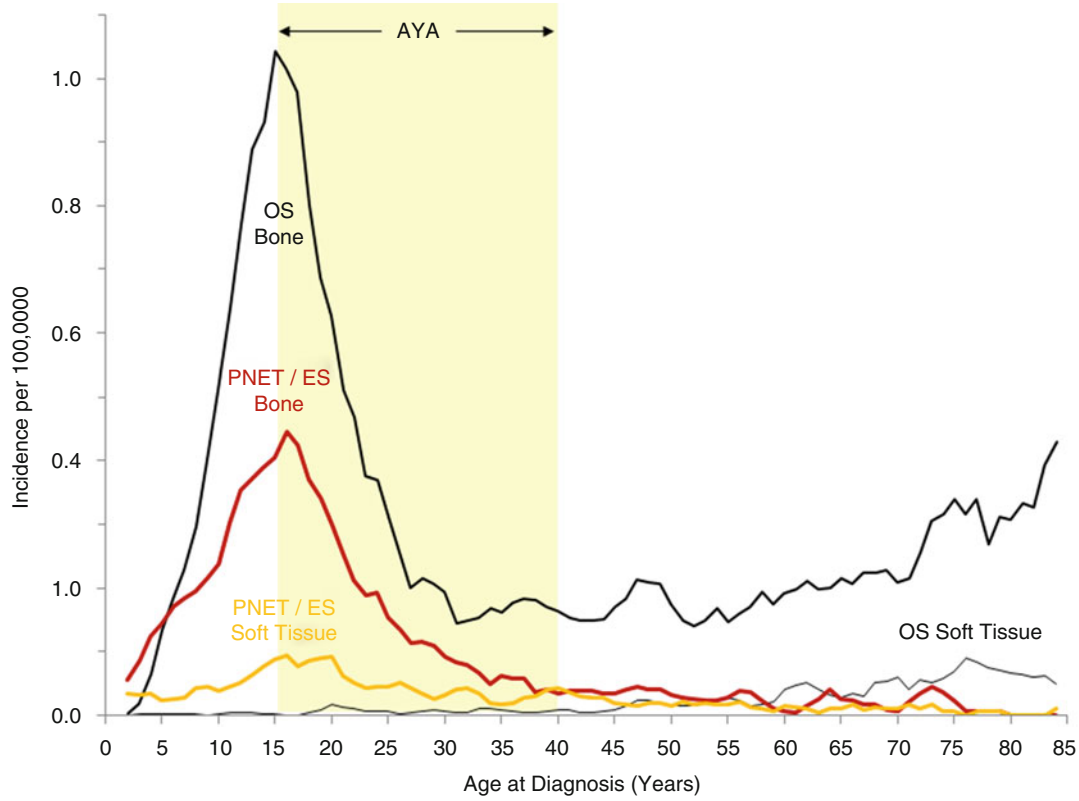

Fig. 3.8 Incidence of osteosarcoma and PNET/Ewing sarcoma, SEER18, 2000–2012, by bone or soft-tissue origin and by single year of age. *Curves* are 3-year moving averages

and structural chromosomal defects [84, 85]. In a recent whole-genome sequencing (WGS) study, regional clusters of hypermutation (kataegis) were found in 50 % of the OS samples [86]. One of the remarkable features of this kataegis in OS is that these hypermutations consisted of enriched C→T substitutions, one of the mutational signatures in cancer that is typically related to age [85]. In addition to the hypermutable regions, p53 pathway lesions were found in all OS tumor samples and recurrent somatic alterations in the *RB1*, *ATXR*, and *DLG* genes in one-third to two-thirds of the tumors [85]. Studies of gene expression, microRNA expression, gene methylation, or gene-copy number data have been reviewed [84] and showed that IGFBP5 was downregulated in metastatic cell lines and tumor samples. Genes like *RUNX2*, *DLX5*, and *WIFI5* (Wnt-inhibiting factor) were involved in tumor growth; miR-16 was validated as a tumor suppressor and miRNA-27 as pro-metastatic miRNA. Expression studies also showed that a profile associated with macrophages was related to a better survival, suggesting a potential role for immune modulation as therapeutic target. However, in a large collaborative trial (EURAMOS-1), initial results did not show a significant beneficial effect of the immune-modulator interferon-alpha added to the standard chemotherapy regimen [87]. Another randomized study, using the immune-modulator liposomal muramyl tripeptide (L-MTP-PE) had mixed results [88].

A recent review suggests that OS harbors few actionable mutations. However, new insights referring genomic instability, the expected discovery of new genes involved in osteosarcoma genesis, and the view that the bone microenvironment represents a unique compartment of the immune system with cross talk between the developing bone cells and cells of immune competent cells may give rise to a new biologic and therapeutic approach for this tumor.

PNET (Ewing Sarcoma, ES) PNET/ES is one of the few sarcomas that occur in AYAs in both bone and soft tissue, with both having a peak incidence between ages 15 and 19 (Figs. 3.8). In AYAs it is far more common to arise in bone, whereas in older adult, the two sites of origin have similar incidences (Fig. 3.8), suggesting a different biology in older adults than in AYAs [89, 90]. The bone incidence peak is sharp, at age 15 (Fig. 3.8), in the middle of the growth spurt of adolescence. This pattern implicates skeletal maturation as a major factor in oncogenesis and the related underlying developmental biologic dynamics. In general, PNET/ES has a predominant specific translocation and a relatively simple karyotype, in contrast to OS that, as described above, is characterized by genetic instability [91].

PNET/ES is characterized by CD99+ small round blue cells [92]. In 85 % of cases, PNET/ES has a specific translocation consisting of a reciprocal somatic translocation, *EWS-FLI1*, that fuses the N-terminal portion of the EWSR1 gene located on the long arm of chromosome 22 (22q12) with the C-terminal portion of the FLI-1 gene on chromosome 11q24 [93, 94]. The *EWSR1* gene belongs to the so-called TET family of proteins that bind to RNA and contribute to the control of transcription and RNA processing and play a role in DNA damage response [95]. The human ETS family of transcription factors consists of 27 genes that encode for ETS proteins which are defined by an ETS domain and recognize a GGAA-containing microsatellite sequence [93, 96]. These proteins regulate the expression of genes involved in signaling pathways, development, cell proliferation, differentiation, migration, angiogenesis, and apoptosis.

The *EWS-FLI1* fusion gene yields a protein with a constitutive activated EWSR1-amino-terminal domain, juxtaposed to a lineage-restricted ETS-DNA-binding part [94]. The other ETS family members the *EWSR1* gene fuses with are the *ERG* gene (21q22)(*EWSR1-ERG*) in 10 % of the cases or rarely with *ETV1* (t(7;22)(p22;q12), *ETV4* (t(17;22)(q21;q12), or *FEV* (t(2;22)(q33;q12). Although the early concept of tumorigenesis from this fusion gene was considered to be a transcriptional activator, later studies showed that the fusion protein acts in at least the same magnitude as a transcriptional repressor at target genes.

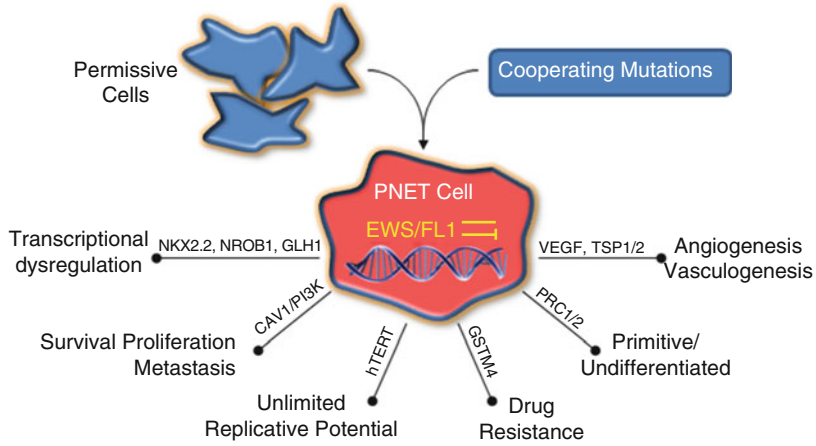

Fig. 3.9 Ewing's sarcoma transformation requires several distinct events. The EWS/FLI (or other TET/ETS) translocation is the central mediator of this process, dysregulating a number of genes that contribute to oncogenesis and tumor progression. A permissive cell type for EWS/FLI expression is also required. Cooperating mutations such as those in the RB and p53 pathways as well as growth factor signaling (including IGF) likely contribute to the fully transformed phenotype (Modified from Toomey et al. [93])

Genomic approaches identified thousands of genes that are dysregulated by the EWS-FLI1 oncoprotein, which are involved in growth promotion and proliferation and in blockade of development and differentiation [93, 97, 98]. Identification of these target genes is complicated by the fact that, in experimental models, the tolerance to *EWS-FLI1* expression and the pattern of responsive genes depend on the cellular context [98] and that the responsive genes are regulated, either directly or indirectly, when these genes are part of signaling pathways. Examples of direct upregulated genes are *RBP7*, *UPP1*, *ID2*, *TERT*, *GLI1*, *PLD2*, and *AURORA A/B*, whereas p21/*CDKN1A*, *TGFBR2*, and *IGFBP3* are downregulated genes [99]. Examples of indirect upregulated targets are *CCND1*, *MYC*, *NKX2.2*, *CCK*, *CAV1*, *VEGF-A*, *EZH2*, *IGF1/IGF1R*, and *DAX/NR0B1* and indirectly downregulated genes are p27/*CDKN1B*, p57/*CDKN1C*, *NOTCH-TP53*, and *ZYX*. The matter becomes even more complicated, because it has been shown that the *EWS-FLI1* transcript induces chromatin opening and creates in this way de novo enhancers that interact physically with target promoters [100, 101]. New genomic techniques rapidly add new structural variants, mutations, epigenomic modifications, or transcribed proteins to the already extensive list of genes [98]. A model that evolves from these studies, and is built upon the organizational principle of the complexity of tumors, is shown in Fig. 3.9.

The intensive research deciphering the molecular complexity in PNET/ES has diagnostic, prognostic, and therapeutic consequences. *EWS-FLI1's* transcription factor requires binding to RNA helicase A for oncogenic function. Strategies to inhibit interaction with RNA helicase A are underway [102], and novel agents targeting the MET pathway are in clinical development. These agents are being evaluated as a potential therapy for tumors carrying the ASPL-TFE-3 fusion transcript [103]. The exact function of the TFE3 protein in ASPS is not known; however, the tumor-specific *ASPL-TFE-3* fusion transcription factor is known to directly upregulate the *MET* gene [104]. Similarly, FGFR4, MET, and other tyrosine kinases are known downstream targets of the *PAX3/7-FOXO1* fusion product found in ARMS [105–107].

The *TET-ETS* translocation is not only relevant for ES, but similar fusions have been shown to be pathognomonic in other EWS-like or not-EWS-related tumors (see "Synovial Sarcoma" below). Two studies have shown that several

EWS-ETS translocation variants (*EWS-FLI1* types 1 and 2, nontype 1/nontype 2, and *EWS-ERG*) are not prognostically significant with current chemotherapy protocols [108, 109]. In vitro studies show that the transforming potential of *EWS-FLI1* relies on the presence of a functional IGF-1R pathway. Subsequent studies showed rapid developing resistance to IGF-1R-targeting antibodies or switch to an IGF-2/insulin receptor A loop to evade from receptor inhibition [110]. Inhibition of mTOR or HDAC with multi-kinase inhibitors, such as ABT-263, to treat resistance is also promising [110, 111].

Synovial Sarcoma Synovial sarcoma (SyS) is a high-grade soft-tissue sarcoma, displaying a variable degree of epithelial differentiation, and more than 50 % of patients with SyS are AYAs (Fig. 3.7) [112]. In contrast to what the name suggests, this tumor does not originate from synovial precursor cells, but instead is located in the juxta-articular deep soft tissues of the upper and lower extremities. Several studies have shown that SyS has a similar clinical presentation in children, AYAs, and middle-aged adults, but with a survival rate that is inversely proportional to age [113], suggesting differences in biology [113, 114].

Histologically there are two subtypes, a biphasic and a monophasic variant. Cytogenetically SyS is characterized in 90–95 % of cases by a specific chromosomal t(X;18)(p11;q11) translocation involving the *SS18* gene (formerly *SYT*-gene) and one of the synovial sarcoma genes (*SSX*) on chromosome X, usually *SSX1*, *SSX2*, or *SSX4* [112, 115, 116]. The biphasic form consists of epithelial and spindle cell components, and nearly all harbor the *SS18-SSX1* translocation. In the monophasic form, spindle cells predominate, and these may carry either the form of *SSX-SS18* gene fusion, but the *SSX1* and *SSX2* fusion types are mutually exclusive. In a recent meta-analysis, no significant differences were shown in the overall survival or disease-specific survival between *SS18–SSX1* and *SS18–SSX2* types, but there were indications of *SS18–SSX1* being an unfavorable prognostic factor for progression-free survival or metastasis-free survival [117]. Established poor prognostic factors for SyS are large tumor size (>5 cm), poorly differentiated (>20 %) histology, and older age. Despite the lack of evidence as a prognostic marker, it is assumed that the *SS18-SSX* mutations act as drivers for tumorigenesis in SyS. The mutations occur in nearly all cases of SyS, with only a few additional mutations in the tumors, are present in both primary and metastatic lesions, and have the ability to induce tumors in conditional mouse models with high penetrance [118]. The *SS18-SSX* translocation creates an in-frame fusion of the N-terminal part of the *SS18* gene with the C-terminus of the SSX-fusion partner. This complex associates with the SWI/SNF chromatin remodeling complex and usurps SWI/SNF-like BAF complexes, resulting in the activation of *SOX2*, which drives proliferation [119]. In addition, epigenetic-induced repression of tumor suppressor genes, like *EGR1*, *ATF3*, and *CDKN2A* by involvement of chromatin remodeling, is also believed to be implicated in the tumorigenesis of SyS [119, 120].

Additional molecular changes in SyS can be divided into chromosomal changes, secondary mutations and alterations of gene and protein expression [118]. SyS is known as a tumor with low genetic complexity [121], but additional copy number changes have been demonstrated more in adults than in younger patients and were associated with the development of metastases and local recurrences [122, 123]. Secondary mutations have been detected in only 8–14 % of the cases, comprising mutations in *PTEN*, *CTNNB1*, and *APC*. Next-generation sequencing showed additional mutations in *KRAS* and *CCND1*, *RNF213*, *SEPT9*, *KDR*, *CSM3*, *MLH1*, *and ERBB4* [114]. Another study showed genetic alterations in *TP53* and a truncating mutation in *SETD2* that encodes a histone methyltransferase [124]. Finally, in SyS, high expression of genes involved in the Wnt pathway (e.g., *LEF1*, *AXIN2*, *WNT5A*), the Notch pathway (e.g., *HES1*, *JAG1/2 NRARP*), the Hedgehog (e.g., *PTCH1*, *GLI1/2*), FGF (e.g., *FGFR2/3*, *FGF18*) and BMP pathways (e.g., *BMP5/7*, *SOSTDC1*), and early embryonic markers (e.g., *TLE1*, *SIX1/4*, *DLX2*)

has been reported [118]. Other markers that were highly expressed in SyS are neural (e.g., NPTX2, NTNG2) and chondrocyte (e.g., COL2A1, COL9A3, SOX9) lineage markers. High expression of BCL2 and the receptor tyrosine kinases PDGFRA, EGFR, and ERBB2 has also been shown to be upregulated. More recent results show deregulated Wnt pathways, AKT/mTOR signaling, and antiapoptotic pathways that might be targets for treatment.

3.4 Summary

There is a paucity of data on molecular characterization comparing AYA cancers with their counterparts occurring in either children or older adults. Thus, our knowledge of AYA cancer biology and what may distinguish tumors in AYAs from cancers diagnosed outside this age range remains limited. Certainly, in some cases, tumors in the AYA population display clinical differences, being more aggressive and more refractory to various forms of treatment than the adult form of the same cancer. However, this is not always the case. In AYA colon cancer, the MSI form of the disease actually has a better prognosis than the MSS form, and stage-for-stage prognosis in general is about the same for AYA patients as for older adults [31]. In another study, despite higher rates of stage III and IV disease and poorer tumor differentiation, young patients with CRC had an equivalent and in some cases better prognosis than older patients [125]. Even so, 5-year survival rates are worse in AYA CRC patients, 40 % compared to 60 % for older adults, and the 10-year survival rates are even more disparate, 31 % for AYAs and 54 % for older adults [31, 126]. The only way to determine definitively whether AYA cancers truly present with a unique biology is to directly compare cohorts of tumor specimens from cancers in AYAs and older adults, and their normal counterparts, using a variety of molecular analytical approaches. These include WGS and WES analyses to discern differences in somatic mutational profiles, RNASeq and microarray expression to determine differences in transcript expression patterns, miRNA and lncRNA analyses to identify differences in non-coding RNA profiles, and proteomic and phosphoproteome analyses to determine the impact of any alterations at the genomic and RNA levels. In order to accomplish this, access to high-quality annotated AYA tumor tissue will be required. The challenge is that the incidence of the cancers discussed in this chapter is relatively rare in the AYA population. There is an urgent need to register all patients with AYA cancers centrally, to establish a tissue repository of normal (germline) and malignant tissues, and to develop patient-derived xenografts from the most aggressive subtypes of tumors. There is also a need for basic biological, genomic, and model development for these cancers, as well as translational research studies to elucidate any fundamental differences between pediatric, AYA, and adult cancers. The biological question of whether there are mutational or signaling pathway differences between cancers in older adults and AYAs needs to be answered. If we are able to elucidate such differences, we can then begin to utilize this information to develop novel therapies for treating AYA cancers and companion diagnostics to accompany these treatments. Only then will we be able to better diagnose, treat, and predict responses in AYAs with cancer.

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Non-Hodgkin Lymphoma

4

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Abstract

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid malignancies accounting for a significant portion of cancers occurring in children, adolescents, and young adults. The incidence increases with age as children grow into young adults. While there are greater than 30 distinct diagnostic NHL entities classified by the World Health Organization (WHO), five diseases account for >90 % of cases in CAYA—Burkitt lymphoma, lymphoblastic lymphoma, diffuse large B-cell lymphoma, anaplastic large cell lymphoma, and primary mediastinal B-cell lymphoma. Other B-cell, T-cell, and NK-cell lymphomas have been described in CAYA, but the incidence is relatively low. Cure rates for CAYA with NHL range from 75 % to 90 % depending on risk stratification and are generally superior to outcomes in comparison to adult data. Inasmuch, there has been a paradigm shift to treat older adolescents and young adults on pediatric protocols, resulting in encouraging results. This chapter will review the clinical and biological characteristics of NHL occurring in CAYA, with particular focus on the nuances of disease in adolescents and young

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adults. The ultimate goal is to achieve the same excellent curative outcomes in adolescents and young adults that have been established in the pediatric literature.

4.1 Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid malignancies. The overall incidence and frequency of the different histologic types vary according to age at diagnosis. Adolescence is at the junction of childhood and adulthood in the sense that in adolescents, the lymphomas frequent in children and rare in adults may still be seen (the Burkitt lymphoma [BL] and the lymphoblastic lymphoma [LL] types), but the incidence of the large cell subtypes, especially the diffuse large B-cell lymphomas (DLBCL), frequent in adults, increases greatly in young adults (to 30 years of age).

In many countries, as for other malignant diseases, the minority of adolescents are referred to either pediatric departments where they are generally included in trials, but the majority are referred to adult departments where a minority are registered in trials. So far, there is little data on adolescents and young adults (AYA) with NHL. The questions are: Is there a difference in results when patients are treated with childhood versus adult NHL protocols and their respective departments? If yes, is it related to the type of treatment? Is there a prognostic value of age of onset and treatment with similar therapeutic strategies? Is this related to different biology? In this chapter we will present what is presently known, but many questions are still without answers, which indicates the need for further studies directed specifically toward adolescents and young adults with NHL.

4.2 Epidemiology

4.2.1 Age-Specific Incidence

The overall incidence of NHL increases steadily with and is predominantly higher in males vs. females (Fig. 4.1) [1]. The incidence of NHL increases in AYA more in Blacks over the AYA age range than any of the other race/ethnicities. Blacks have the highest incidence from age 25 to 40, but declines in older age until it is the fourth most common by age 70 (Fig. 4.2). During the past quarter century in the United States, the incidence of NHL has increased in each age group through to age 30 years (Table 4.1). In 10- to 29-year-olds, the increase was dramatic, averaging 4–19 % per year over 25 years. Most of the increase was in the non-Burkitt, NHL category II(b), according to the International Classification of Childhood Cancer (ICCC), which was in part due to human immunodeficiency virus (HIV) epidemic that occurred during the 1980s and early 1990s (Table 4.1). In the 1979–1997 English registry, NHL represented 7 % of all cancers in adolescents, very similar to the corresponding proportion in the United States.

4.2.2 Incidence of Histologic Types

The predominant NHL in AYA were DLBCL and anaplastic large cell lymphoma (ALCL) which accounted for 55–70 % and 20–25 % of the NHL in AYA, respectively. Furthermore, primary mediastinal large B-cell lymphoma (PMLBCL) and NK/T-cell lymphoma had their greatest proportion in the AYA period (Fig. 4.3). The histological subtype of NHL in AYA with the greatest divergence in race/ethnicity distribution was NK/T-cell lymphoma that occurred more in Hispanics and Asian/Pacific Islanders compared to other ethnic types (Fig. 4.4).

The French-American-British/Lymphoma Malignancy B (FAB/LMB) 96 study, a 5-year prospective international study for the treatment of B-cell lymphoma in children and adolescents, was not a population-based registry, but interestingly some differences were observed between

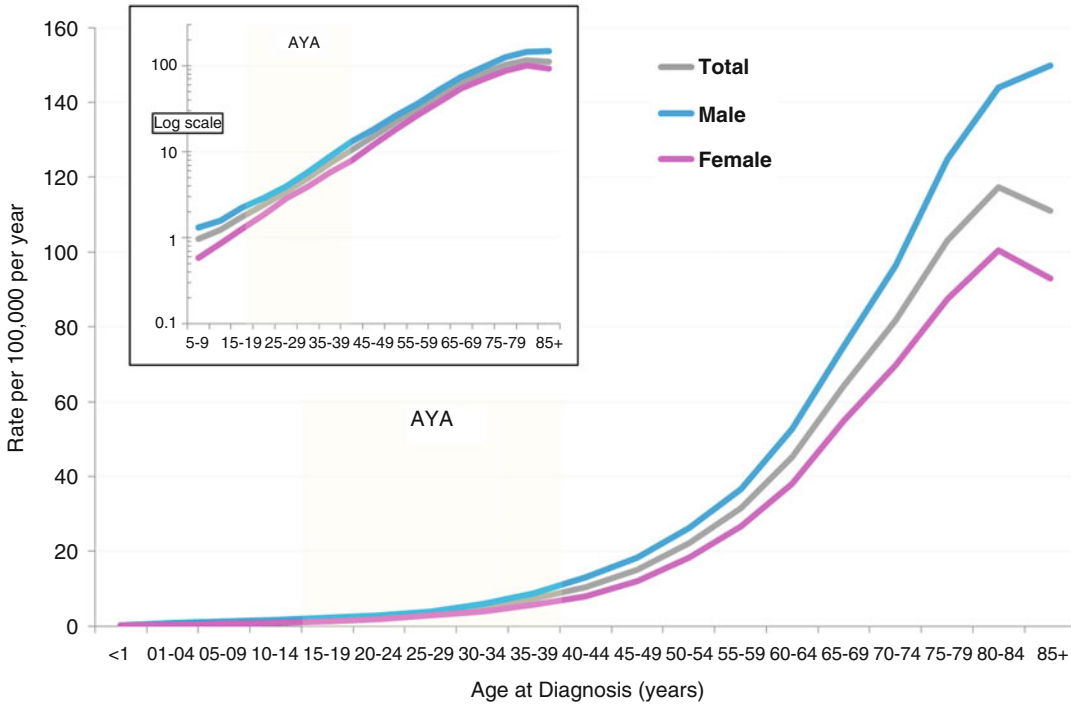

Fig. 4.1 Incidence of NHL by age, United States SEER, 2000–2011

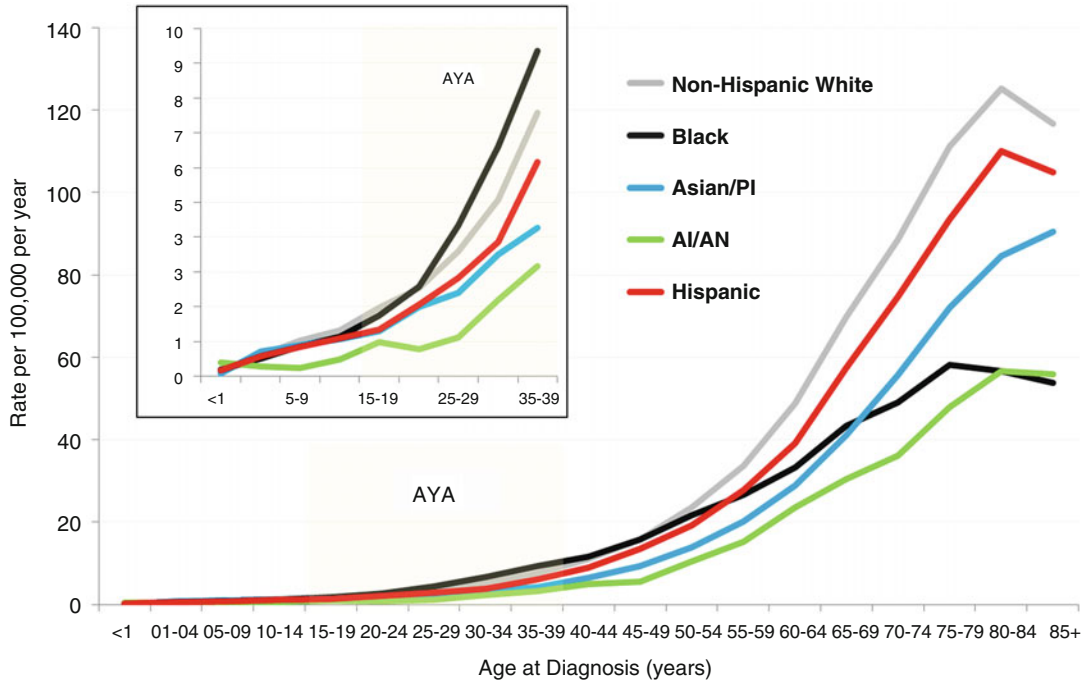

Fig. 4.2 Incidence of NHL by age and race/ethnicity; United States SEER, 2000–2011

Table 4.1 Incidence of non-Hodgkin lymphoma in persons younger than 30 years of age, United States, 1975–2000

Age at diagnosis (years)	<5	5–9	10–14	15–19	20–24	25–29
United States population, year 2000 census (in millions)	19,176	20,550	20,528	20,220	18,964	19,381
Non-Hodgkin lymphoma, iCCC ii(b)						
Average incidence per million, 1975–2000, SEER	3.4	5.4	7.1	11.7	16.5	27.3
Average annual % change in incidence, 1975–2000, SEER	na	0.2 %	2.2 %	2.3 %	3.6 %	6.2 %
Estimated incidence per million, year 2000, United States	2.8	5.5	8.8	14.3	21.8	39.3
Estimated number of persons diagnosed, year 2000, United States	66	110	147	290	413	762
Burkitt and other non-Hodgkin lymphomas, iCCC ii(c), ii(d), and ii(e)						
Average incidence per million, 1975–2000, SEER	2.8	3.7	3.9	3.1	3.6	7.5
Average annual % change in incidence, 1975–2000, SEER	na	−1.0 %	−0.7 %	1.6 %	9.8 %	18.5 %
Estimated incidence per million, year 2000, United States	1.9	3.2	3.6	3.5	5.6	12.5
Estimated number of persons diagnosed, year 2000, United States	54	76	81	72	108	243

na not available, *ICCC* International Classification of Childhood Cancer, *SEER* Surveillance, Epidemiology and End Results

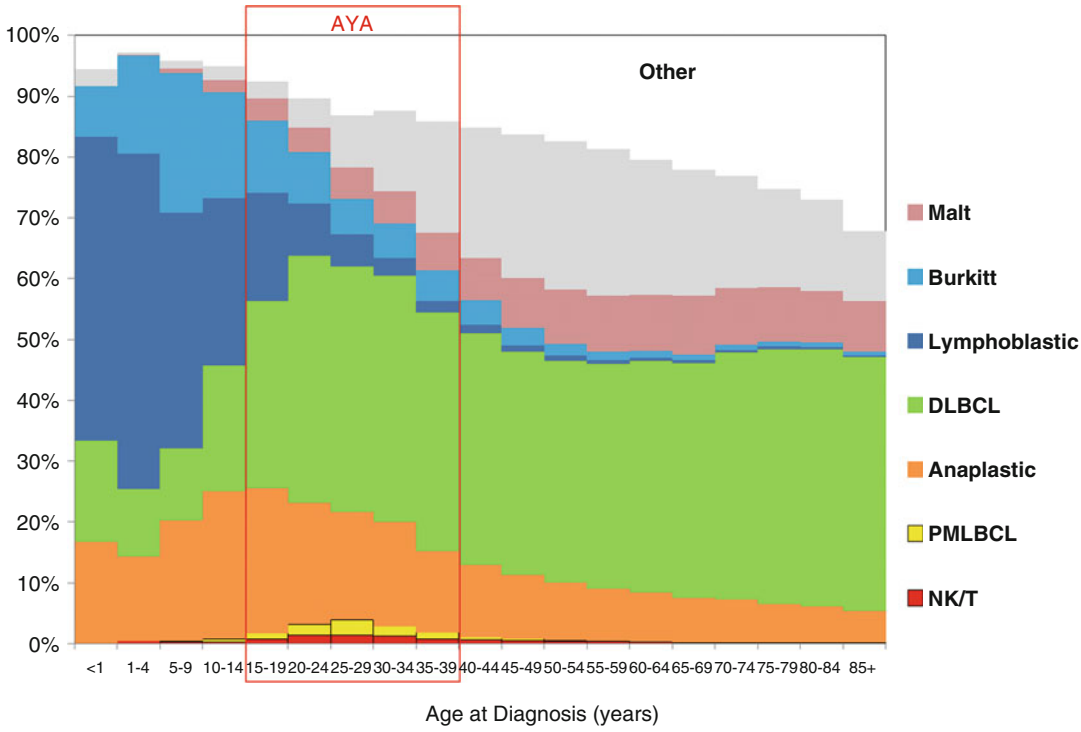

Fig. 4.3 NHL distribution of histologic types by age, United States SEER 2000–2011

the three countries in terms of repartition of the two subgroups of B-cell NHL. After adjusting for age, DLBCL was more frequent in the United States than in the European countries, especially in France [2, 3].

4.3 Etiology/Risk Factors

Whatever the age, it is known that a few patients are at increased risk of developing NHL: those with congenital or acquired immunodeficiency

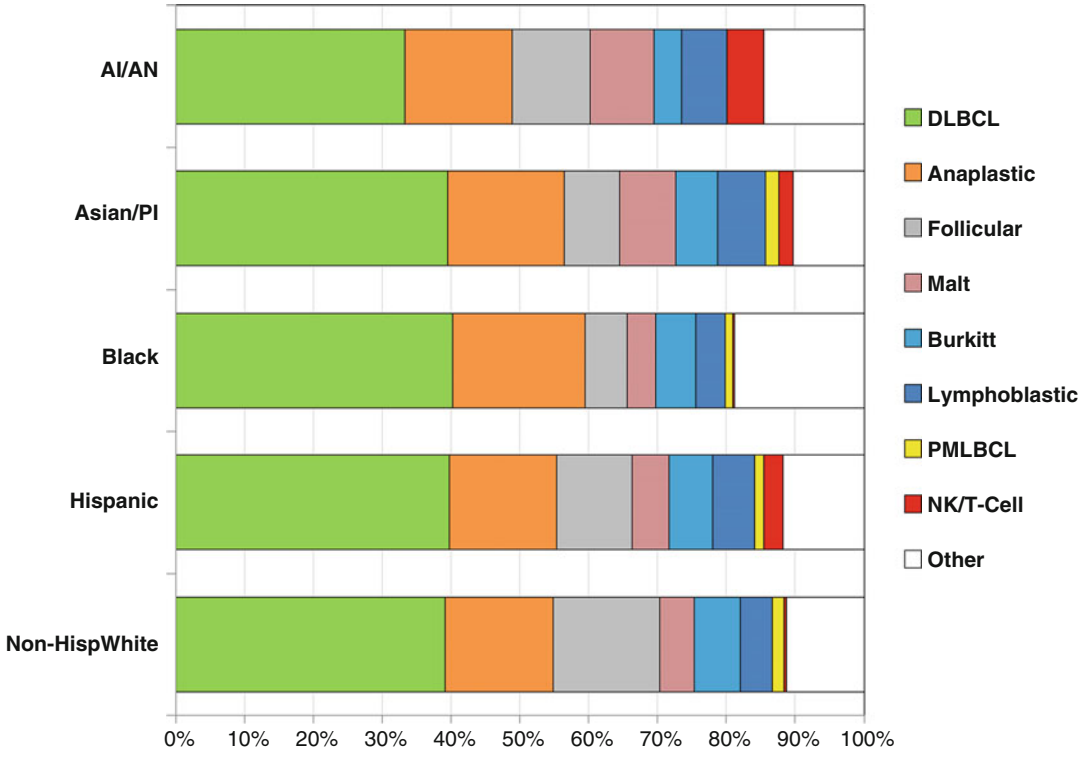

Fig. 4.4 NHL distribution of histologic types by race/ethnicity, ages 15–39, United States SEER 2000–2011

and those receiving immunosuppressive therapy (such as after organ transplantation). The incidence is significantly higher in males than in females and is higher in whites than African American/blacks, as reviewed earlier. Specific geographical areas are also recognized for particular types of lymphoma, such as the "endemic" (African) BL. Other risk factors include Epstein-Barr virus (EBV) or *Helicobacter pylori* infection, tobacco, and chemical or other environmental exposures. In underdeveloped countries, there is a documented link between EBV and BL, while in the developed world, EBV is also associated with other subtypes of NHL. Secondary neoplasms are well-documented sequelae of HIV infection and account for an increase in NHL incidence, particularly in males. The HIV/acquired immune deficiency syndrome (AIDS) epidemic increased the incidence of NHL in young men 25–49 years of age. The effect of HIV/AIDS on NHL peaked in 1995 and subsided in 1999, since which the incidence of NHL has been relatively stable in both male and female AYA (Fig. 4.5). A few familial cases of lymphoid malignancies have been observed, without apparent recognized genetic abnormalities.

4.4 Histology/Cytogenetics

Classification of NHL has changed many times over the years and became more distinct with the increased understanding of lymphomagenesis and the development of new diagnostic tools (immunophenotyping, cytogenetics, molecular biology, and now gene profiling). The current World Health Organization (WHO) classification [4], preceded by the Revised American European Lymphoma (REAL) classification [5], is now widely used. Microarray technologies, by studying the expression of many genes at once, are very promising [6], but their implication for diagnosis and prognosis and their further utility in clinical practice, especially in AYA, require further investigation. The characteristics of the four categories of lymphoma most frequently encoun-

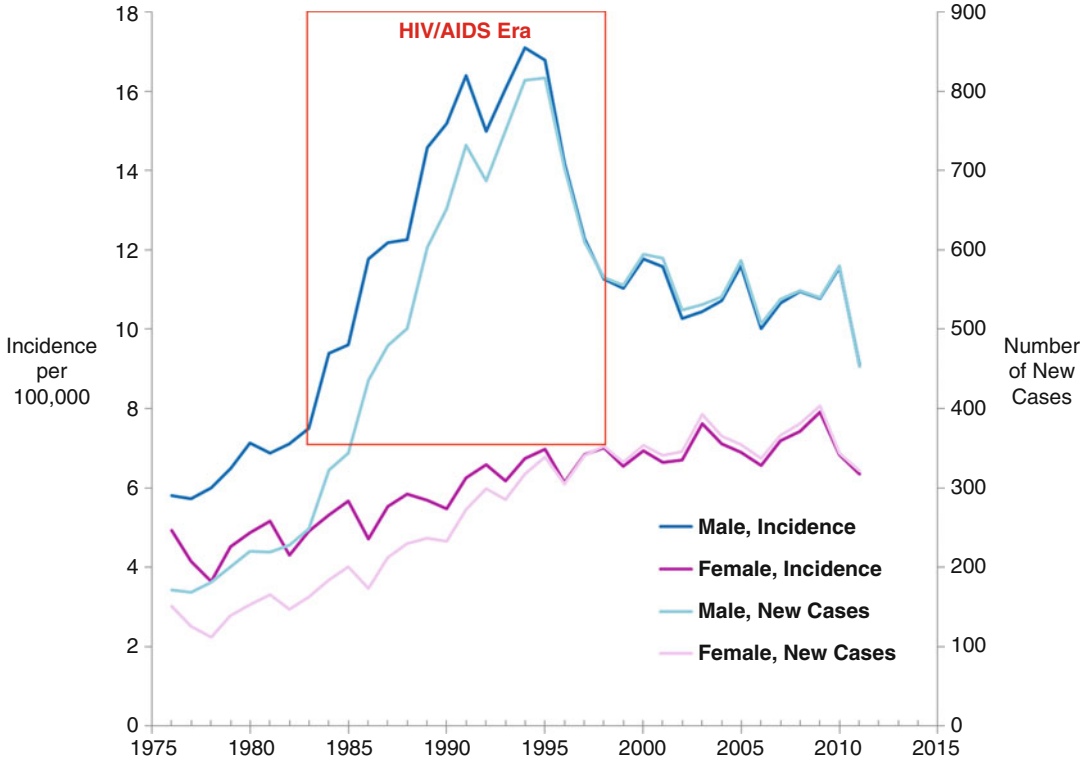

Fig. 4.5 Annual incidence of NHL by sex, ages 25–49, 1976–2011, SEER 9, United States SEER data

tered in AYA (BL, LL, DLBLC, and ALCL) are demonstrated in Table 4.2.

4.5 Clinical Features

The clinical presentation of NHL in AYA, as in other age classes, varies and depends on the primary site of the disease, the histological subtype, and the extent of the disease. BL generally arises in the abdomen (digestive track) and in the Waldeyer ring, while LL generally arises from the thymus. Burkitt abdominal lymphoma generally presents as a large and rapidly growing abdominal mass that is often associated with ascites and other intra- or extra-abdominal involvements. Intussusception leading to the discovery of a small excisable abdominal tumor is a rare presentation that is related to BL or DLBCL. Extensive abdominal surgery should be avoided. The diagnosis can be made on surgical biopsy but also on cytological examination of a serious effusion or on percutaneous needle biopsy of the tumor.

Lymphoblastic mediastinal lymphoma leads to mediastinal compression, which may be life threatening (general anesthesia should be avoided if possible) and is often associated with a concomitant pleural effusion. Therefore, the diagnosis should be made using cytological examination of effusions or bone marrow smears. If a tumor biopsy is needed, then this should be done by percutaneous needle biopsy or by mediastinoscopy. Another lymphoma arising in the thymus is the primary mediastinal B-cell lymphoma of thymus origin, which may present with pericarditis, pulmonary nodules, and/or subdiaphragmatic involvement such as the kidney and pancreas.

Head and neck primary sites including Waldeyer's ring and the facial bones are more often seen in BL. In the less frequent sites such as the superficial lymph nodes, bone, skin, thyroid, orbit, eyelid, kidney, and epidural space, any subtype of lymphoma can be seen, emphasizing the

Table 4.2 Different subtypes of non-Hodgkin lymphoma in adolescents and young adults and their clinical and biologic characteristics

	Burkitt	Lymphoblastic	Large B-cell	Anaplastic large cell
Preferential tumor site	Abdomen head and neck	Mediastinum (T cell) Bone, (sub)cutaneous (B cell)	Abdomen, thymus, bone	Node, skin
Histology				
Cell size	Medium	Medium	Large	Voluminous
Cytoplasm nucleus nucleoli	Narrow Basophilic, with vacuoles round	Narrow, pale Convoluted or not	Cleaved or not, vesicular	Abundant and clear erythrophagocytosis irregular, clear
Chromatin	Several nucleoli Coarse and irregular	Poorly discernable nucleoli Finely stippled	Distinct, often adherent to nucleus membrane	Voluminous
FaB equivalent	L3	L1, L2	NA	NA
Immunophenotyping	CD20+ CD79a + SIg + Ki 67 + >95%	TdT+ B lineage T lineage CD19+, CD7+ CD 79a+, CD2+ S Ig−, CD3c+ cMu ∓	CD20+ CD79a+ SIg ± bcl6 ± Ki 67: 60–90%	CD30+ EMA+ ALK+ (T or "null" markers)
Cytogenetics	t (8;14)(q24;q32) or variant t(2;8) (p11;q24) t(8;22) (q24;q11)	No specific abnormalities, sometimes involvement of T-cell antigene receptor genes (TCR) on chromosome 7(q34) or 14(q11)	Sometimes t(8;14)(q24;q32) der (3)(q27) (bcl6)	t(2;5) (p23;q35) or variant
Result	Transcriptional deregulation of c-MYC		Transcriptional deregulation of bcl6	NPM/ALK-fusion protein; ALK is a tyrosine kinase receptor located on 2p23

FAB French-American-British, *NPM* nucleophosmin, *ALK* anaplastic lymphoma kinase, *EMA* epithelial membrane antigen, *NA* not applicable

necessity of a good-quality sample of histology and immunophenotyping.

ALCL present with more unique features: usually nodal involvement, sometimes painful, which is characteristic of this disease; frequent skin involvement with inflammatory symptoms of the involved nodes, distant macular lesions, or general skin modification resembling ichthyosis; frequent general symptoms with widely fluctuating fever; and "wax and wane" evolution in few cases with previous episode(s) of spontaneous regression.

4.6 Initial Workup and Staging

Diagnosis can be obtained utilizing biopsy material including tumor-touch preparations but also cytological examination of effusion fluids or bone marrow smears, so surgical procedures can be avoided in diffuse BL and lymphoblastic lymphoma (LL) diseases. Also strongly recommended are the immunological and cytogenetic or molecular biology studies.

Staging classifications are different in children compared to adults. Historically, the St Jude (Murphy classification) [7] was used for children but has recently been updated to the new International Pediatric NHL Staging System (IPNHLSS) (Tables 4.3, 4.4, and 4.5) [8]. Once the diagnosis of NHL has been made, a speedy assessment of diagnosis, staging, and general evaluation must be done to commence appropriate treatment as soon as possible. This is particularly important in BL and LL, which have a great propensity to spread rapidly both regionally and systemically, especially in the bone marrow and CNS. Staging classifications are different in children, where the St Jude (also called Murphy) classification [7] is used because of the predominance of extranodal primaries, and in adults where the Ann Arbor classification, more adapted to nodal disease, is used (Table 4.6). These two different staging systems between children and adults make comparisons between pediatric and adult studies difficult, particularly in the adolescent and young adult age range. Also utilized for

Table 4.3 Murphy staging system [7]

Stage I
A single tumor (extranodal) or single anatomical area (nodal), with the exclusion of mediastinum or abdomen
Stage II
A single tumor (extranodal) with regional node involvement
Two or more nodal areas on the same side of the diaphragm
Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm
A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only[a]
Stage III
Two single tumors (extranodal) on opposite sides of the diaphragm
Two or more nodal areas above and below the diaphragm
All the primary intrathoracic tumor (mediastinal, pleural, thymic)
All extensive primary intra-abdominal disease[a]
All paraspinal or epidural tumors, regardless of other tumor sites
Stage IV
Any of the above with initial involvement of the CNS and/or bone marrow (BM) involvement[b]

From Murphy [7]

[a]A distinction is made between apparently localized GI tract lymphoma versus more extensive intra-abdominal disease because of their quite different pattern of survival after appropriate therapy. Stage II disease typically is limited to a segment of the gut plus or minus the associated mesenteric nodes only, and the primary tumor can be completely removed grossly by segmental excision. Stage III disease typically exhibits spread via the lymphatics to the para-aortic and retroperitoneal nodes, via intraperitoneal dissemination to form implants and plaques along the mesentery or peritoneum, or by direct infiltration of structures adjacent to the primary tumor. Ascites may be present, and complete resection of all gross tumor is not possible

[b]If marrow involvement is present initially, the number of abnormal cells must be 25% or less in an *otherwise* normal marrow aspirate with a normal peripheral blood picture

Table 4.4 International pediatric non-Hodgkin lymphoma staging system (IPNHLSS)

Stage I
A single tumor with the exclusion of the mediastinum and abdomen (N, nodal; EN, extra-nodal; bone (B) or skin (S), EN-B, EN-S)
Stage II
A single extranodal tumor with regional node involvement
Two or more nodal areas on the same side of the diaphragm
A primary gastrointestinal tract tumor (usually in the ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable (if malignant ascites or extension of the tumor to adjacent organs, it should be regarded as stage III)
Stage III
Two or more extranodal tumors (including bone or skin: EN-B, EN-S) above and/or below the diaphragm.
Two or more nodal areas above and below the diaphragm
Any intrathoracic tumor (mediastinal, hilar, pulmonary, pleural, or thymic)
Intra-abdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection (except a primary gastrointestinal tract tumor [usually in the ileocecal region] with or without involvement of associated mesenteric nodes, which is completely resectable)
Any paraspinal or epidural tumor, whether or not other sites are involved
Single bone lesion with concomitant involvement of extra-nodal and/or non-regional nodal sites
Stage IV
Any of the above findings with initial involvement of the central nervous system (stage IV CNS), bone marrow (stage IV BM), or both (stage IV combined) based on conventional methods; see Table 4.3
For each stage, type of examination and degree of BM and CNS involvement should be specified, using the abbreviations below to identify involvement; see Table 4.3

Rosolen et al. [8]. Reprinted with permission. © (2015) American Society of Clinical Oncology. All rights reserved
[a]Based on the classification proposed by Murphy [7]

Table 4.5 Additional staging information

Bone marrow (BM) involvement
Stage IV disease, due to BM involvement, is currently defined by morphological evidence of ≥5 % blasts or lymphoma cells by bone marrow aspiration. This applies to any histological subtype and will be maintained in the *IPNHLSS*
However, for each stage, type and degree of BM involvement (by bone marrow aspiration) should be specified, using the abbreviations below to identify involvement:
BMm = BM positive by morphology (specify % lymphoma cells)
BMi = BM positive by immunophenotypic methods (immunohistochemical/flow-cytometric analysis) (specify % lymphoma cells)
BMc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells)
BMmol = BM positive by molecular techniques (PCR-based) (specify level of involvement)
Same approach should be used for peripheral blood (PB) involvement (i.e., PBm; PBi, PBc, PBmol)
Note: definition of BM involvement should be obtained from analysis of bilateral BM aspirates and BM biopsy
Central nervous system (CNS) involvement
CNS is considered involved in case of:
1. Any CNS tumor mass (identified by imaging techniques, i.e., CT, MRI)
2. In case of cranial nerve palsy that cannot be explained by extradural lesions
3. In case of blasts morphologically identified in the CSF
Condition that defines CNS positivity should be specified: CNS positive/mass, CNS positive/palsy, CNS positive/blasts
CSF status: CSF positivity is based on morphological evidence of lymphoma cells
CSF should be considered positive when any number of blasts is detected
CSF unknown (not performed, technical difficulties, etc.)

(continued)

Table 4.5 (continued)

Similarly to BM, type of CSF involvement should be described whenever possible
CSFm = CSF positive by morphology (specify the number of blasts/μL)
CSFi = CSF positive by immunophenotype methods (immunohistochemical/flow-cytometric analysis) (specify % lymphoma cells)
CSFc = CSF positive by cytogenetic/FISH analysis (specify % lymphoma cells)
CSFmol = CSF positive by molecular techniques (PCR-based) (specify level of involvement)
Note: until sufficient data are available, positron emission tomography (PET) should be used with caution for staging and PET results should be compared and discussed in light of other more consolidated imaging approaches

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Table 4.6 Adult non-Hodgkin staging systems and prognostic index

Ann Arbor classification used in adult non-Hodgkin lymphoma		
Stage I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (I_E)	
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II), which may be accompanied by a contiguous involvement of an extralymphatic organ or site (II_E)	
Stage III	Involvement of lymph node regions on opposite sides of the diaphragm, which may be accompanied by involvement of the spleen (III_S) or by a localized involvement of an extralymphatic organ or site (III_E) or both (III_{SE})	
Stage IV	Disseminated involvement of one or more extralymphatic organ or tissues, with or without associated lymph node involvement	
International prognostic index used in adult non-Hodgkin lymphoma (patients <60 year)		
Factors	**Risk classification**	
Performance status >2	Low	0 factor
LDH > normal	Low–intermediate	1 factor
Stages III–IV	High–intermediate	2 factors
	High	3 factors

CNS central nervous system, *LDH* lactate dehydrogenase

therapeutic classification in adults is the International Prognostic Index (IPI) based on stage, serum lactate dehydrogenase (LDH) levels, and performance status (PS) (Table 4.6).

The IPI has been updated twice, firstly by the Vancouver Group who proposed the Revised IPI (R-IPI) after the introduction of rituximab into adult practice [9] (it is fair to observe that this was not universally accepted [10]) and more recently the new NCCN index that has been proposed [11] (again it is not clear yet how widely this will be adopted). The principal modification in the NCCN index is the introduction of three levels of serum LDH to acknowledge very high values likely to represent very bulky tumors and also a similar subdivision in the scoring for age. This new age scoring system is not relevant to the younger patients discussed in this chapter except that it does emphasize the generally favorable outcomes in all patients under 50 years.

PS does not seem appropriate for very fast-growing tumors such as BL and LL and is often not documented in pediatric lymphoma trials. This might make comparisons difficult between childhood and adult studies, especially in large cell lymphoma. PS should be included in future studies that included adolescents. In spite of being an unspecific marker and of different methods of dosage with different "norms," serum LDH level is a very good indicator of tumor burden and generally has prognostic significance.

The traditional boundary between leukemia and lymphoma has been defined arbitrarily be more or less than 25 % blast cells in the bone marrow, but this does not correspond to either clinical or biological differences [8]. CNS involvement is defined by the presence of unequivocal malignant

Table 4.7 International pediatric NHL response criteria (IPNHLRC)

Complete response (*CR*): disappearance of all disease (three designations)
1. *Complete* (*CR*):
(a) CT or MRI reveals no residual disease or new lesions
(b) Resected residual mass that is pathologically (morphologically) negative for disease (detection of disease with more sensitive techniques described as in "supporting data" as in Table 4.2
(c) BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as in "supporting data" as in Table 4.2)
2. *Complete response*, *biopsy negative* (*CRb*):
(a) Residual mass has no morphological evidence of disease from limited or core biopsy (detection of disease with more sensitive techniques described as in "supporting data" as in Table 4.2) with no new lesions by imaging examination
(b) BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as in "supporting data" as in Table 4.2)
(c) No new and/or progressive disease elsewhere
3. *Complete response*, *unconfirmed* (*CRu*):
(a) Residual mass is negative by FDG-PET; no new lesions by imaging examination
(b) BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as in "supporting data" as in Table 4.2)
(c) No new and/or progressive disease elsewhere
Partial response (*PR*): 50 % decrease in the sum of the product of the greatest perpendicular diameters (SPD) on CT or MRI. FDG-PET may be positive (Deauville score of 4 or 5 with reduced lesional uptake compared to baseline). No new and/or PD. Morphological evidence of disease may be present in the BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as in "supporting data" as in Table 4.2); however, there should be a 50 % reduction in the percentage of lymphoma cells
Minor response (*MR*): decrease in SPD is greater than 25 % but less than 50 % on CT or MRI. No new and/or PD. Morphological evidence of disease may be present in the BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as in "supporting data" as in Table 4.2); however, there should be a 25–50 % reduction in the percentage of lymphoma cells
No response (*NR*): for those who do not meet CR, PR, MR, or PD criteria
Progressive disease (*PD*): for those with greater than 25 % increase in the SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with an increase in lesional uptake from baseline, or the development of new morphological evidence of disease in the BM or CSF

Sandlund et al. [17]

cells in a cytocentrifuged specimen of spinal fluid and/or the presence of obvious neurological deficits, such as cranial nerve palsies [8].

Experience with positron emission tomography (PET) in childhood and adolescent NHL is in the early stages of investigation. It is hoped that this diagnostic tool will help to predict the presence of active tumors in a residual mass.

It must be noted that in adult practice by contrast, PET scanning has now been fully established as an essential part of patient management with respect to staging and end of treatment response assessment. This is best illustrated by the revision to the Cheson Response Criteria for Clinical Trials [12, 13] which fully integrates PET/CT scanning into routine research practice and by extension to best routine clinical practice. A much more controversial issue is the use of interim PET scanning to dictate prognosis and therapy. Unlike Hodgkin disease, where this is increasingly well established [14], in DLBLC there is no definite data to support the use of interim PET [15, 16]. Further discussion is beyond the scope of this chapter but in summary there appears to be no improvement in overall outcome when interim PET is used to test whether treatment should be changed during standard therapy. Recently, a new response criterion has been developed for children with NHL entitled "International Pediatric NHL Response Criteria" which incorporates contemporary imaging and laboratory diagnostic testing (Tables 4.7 and 4.8) [17].

Table 4.8 Supporting IPNHLRC data

Bone marrow involvement
BM involvement is currently defined by morphological evidence of lymphoma cells. This applies to any histological subtypes
Type and degree of BM involvement should be specified, using the abbreviations below:
BMm = BM positive by morphology (specify % lymphoma cells)
BMi = BM positive by immunophenotypic methods (histochemical/flow-cytometric analysis) (specify % lymphoma cells)
BMc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells)
BMmol = BM positive by molecular techniques
Same approach should be used for peripheral blood (PB) involvement (i.e., PBm; PBi, PBc, PBmol)
Central nervous system (*CNS*) *involvement*
CSF status: CSF positivity is based on morphological evidence of lymphoma cells
CSF should be considered positive when any number of blasts is detected
CSF unknown
Similarly to BM, type of CSF involvement should be described whenever possible
CSFm = CSF positive by morphology (specify the number of blasts/μL)
CSFi = CSF positive by immunophenotype methods (histochemical/flow-cytometric analysis) (specify % lymphoma cells)
CSFc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells)
CSFmol = CSF positive by molecular techniques
Residual mass (*RM*)
RMm: tumor detected by standard morphological evaluation
RMi: tumor detected by immunophenotype methods (immunohistochemical or flow-cytometric analysis
RMc: tumor detected by cytogenetic/FISH analysis
RMmol: tumor detected by molecular techniques

Patients often have other problems at diagnosis, such as malnutrition, infection, postsurgical complications, and respiratory and metabolic abnormalities; these may be life threatening or compromise the onset of therapy. Tumor lysis syndrome (TLS) may be present at diagnosis or may develop during treatment. Cairo et al. developed a classification and grading system for TLS [18]. In advanced diseases, especially in BL and LL, preventive measures must always be institute: hyperdiuresis and "uricolytic" drugs (allopurinol or urate oxidase). Urate oxidase should be utilized in cases of high tumor burden [19–22]. Urate oxidase converts uric acid allantoin, which is highly soluble in urine. It is an efficient way of promptly reducing serum uric acid levels, thus preventing uric acid nephropathy and preserving renal function, allowing a better excretion of the other cell metabolites such a potassium and phosphorus. Strict clinical and metabolic monitoring of patients during the lysis phase is essential.

4.7 B-Cell Non-Hodgkin Lymphoma

The two main entities of NHL are BL and DLBCL. The other B-cell NHL, such as mantle cell, or mucosa-associated lymphoid tissue lymphomas, are not often encountered in adolescents and young adults and will not be discussed in this chapter.

4.7.1 Burkitt Lymphoma

BL is the most common NHL of childhood, adolescents, and young adults (CAYA) [23, 24]. The incidence, however, decreases with age, being

highest in children <15 years and relatively uncommon in adults >30 years of age. BL is characterized by very distinct epidemiologic differences. Sub-Saharan Africa has an especially unique epidemiology of childhood cancer where endemic BL is the most common pediatric malignancy overall, representing up to one-third to one-half of all pediatric oncologic diagnoses. Sporadic BL, occurring everywhere else in the world, accounts for approximately 40 % of NHL in CAYA outside of sub-Saharan Africa.

BL is characterized on one hand by a high prevalence (around 70 %) of advanced-stage III–IV disease presentation but on the other hand excellent clinical outcomes with event-free survival (EFS) of 85–90 % overall. Most commonly, BL presents with intra-abdominal masses; however masses of the head and neck also occur. The tumor burden in BL is often exceptionally high, with more than half of patients presenting with a significantly elevated lactate dehydrogenase (LDH) level >2 times the upper limit of normal [25]. With this in mind, it is no surprise that BL carries one of the highest risks for the complication of TLS and close monitoring of patients prior to and during induction therapy is vital [18, 19].

The defining characteristic of BL is a translocation of the *C-MYC* oncogene on chromosome 8 with the immunoglobulin genes on chromosome 14, 22, or 2. Histology classically reveals intermediate-sized cells with round nuclei and scant cytoplasm with lipid vacuoles. BL has one of the highest proliferation rates of any malignancy and usually reveals numerous mitotic figures and apoptotic bodies that can be seen engulfed in scattered macrophages portraying the characteristic "starry-sky" appearance on low power histology [25]. Endemic BL occurs in the holoendemic malaria belt of sub-Saharan Africa and is virtually always associated with Epstein-Barr virus (EBV) infection. On the other hand, sporadic BL is associated with EBV in about 30 % of cases [26].

The immunophenotypic signature of BL is characterized by expression of mature B-cell antigens CD20 and CD19, as well as CD10 and BCL6, which are associated with germinal center derivation. BL expresses the proliferation antigen Ki-67 at rates often >99 % and rarely expresses BCL2 [27].

Landmark gene expression profiling (GEP) studies have recently established an extensive biologic definition of B-NHL, producing a molecular definition of BL that extended the spectrum of the WHO criteria [28]. Additionally, Dave/Staudt et al. established that *C-MYC* and its target genes as well as a subgroup of germinal center B-cell genes were more highly expressed in BL versus DLBCL [29]. GEP studies in pediatric B-NHL have highlighted similar findings [30].

The major determinants for risk stratification in BL of CAYA are rooted in the original Murphy stage of the clinical presentation. The previous FAB96 study demonstrated the clinical variables associated with a significantly inferior EFS in pediatric mature B-NHL; those include advanced-stage disease, elevated LDH, primary mediastinal involvement, and combined BM and CNS disease [31]. Additionally, one of the most important prognostic indicators to guide treatment decision is the patient's response to therapy. On the FAB/LMB protocol, failure to achieve at least 20 % reduction in disease burden with the first week of reduction phase chemotherapy is a poor prognostic indicator and requires intensification of the treatment regimen [32]. Additionally, failure to achieve complete remission (CR) by the completion of the first consolidation cycle is also associated with poor long-term survival and is another indication to intensify therapy. Universal guidelines to evaluate treatment response via fludeoxyglucose (FDG)-PET for NHL in CAYA have been published and will serve as the benchmark for further delineating the role of FDG-PET through prospective clinical trials [8, 33].

The prognostic role of BL biology with regard to cytogenetic and minimal-residual disease (MRD) findings is currently being explored. Although specific cytogenetic findings such as deletion 13q, gain of 7q, and complex cytogenetics may be associated with a higher risk for treatment failure, further studies are needed to determine if these patients require and/or benefit from an intensification of the therapeutic approach [34, 35]. Preliminary data on the pres-

ence of MRD in B-cell NHL suggested that the presence of MRD on end-of-therapy (EOT) specimens was associated with disease recurrence [36]. Children/adolescents with intermediate-risk B-NHL, treated with FAB/LMB96 modified chemotherapy plus rituximab, had blood and bone marrow specimens from end of induction (EOI) and EOT assessed for MRD [36]. While recurrence rates were similar between the EOI MRD-positive and MRD-negative patients ($p=0.40$), EOT MRD results demonstrated one relapse in the MRD-positive group and no recurrences in the MRD-negative group ($p=0.077$). More recent data compared the presence of MRD from EOI and end of consolidation, demonstrating that the presence of MRD did not predict relapse and that subsequent therapy actually appeared to eliminate MRD [37]. Further prospective investigations will determine the prognostic role of MRD in BL in CAYA.

Long-term curative outcomes in pediatric BL have dramatically improved over the past three decades, with EFS rates essentially doubling from the late 1970s to the contemporary era (Fig. 4.6) [38]. Since the turn of the century, clinical trials have focused on establishing risk-stratified therapy to diminish acute and long-term toxicities for patients with favorable prognosis and to intensify regimens for those with higher risk for treatment failure [32, 39–41]. International collaboration in large-scale clinical trials has resulted in the modern day FAB/LMB chemotherapy backbone consisting of cyclophosphamide, high-dose methotrexate (HD MTX), cytarabine, vincristine, doxorubicin, and corticosteroids.

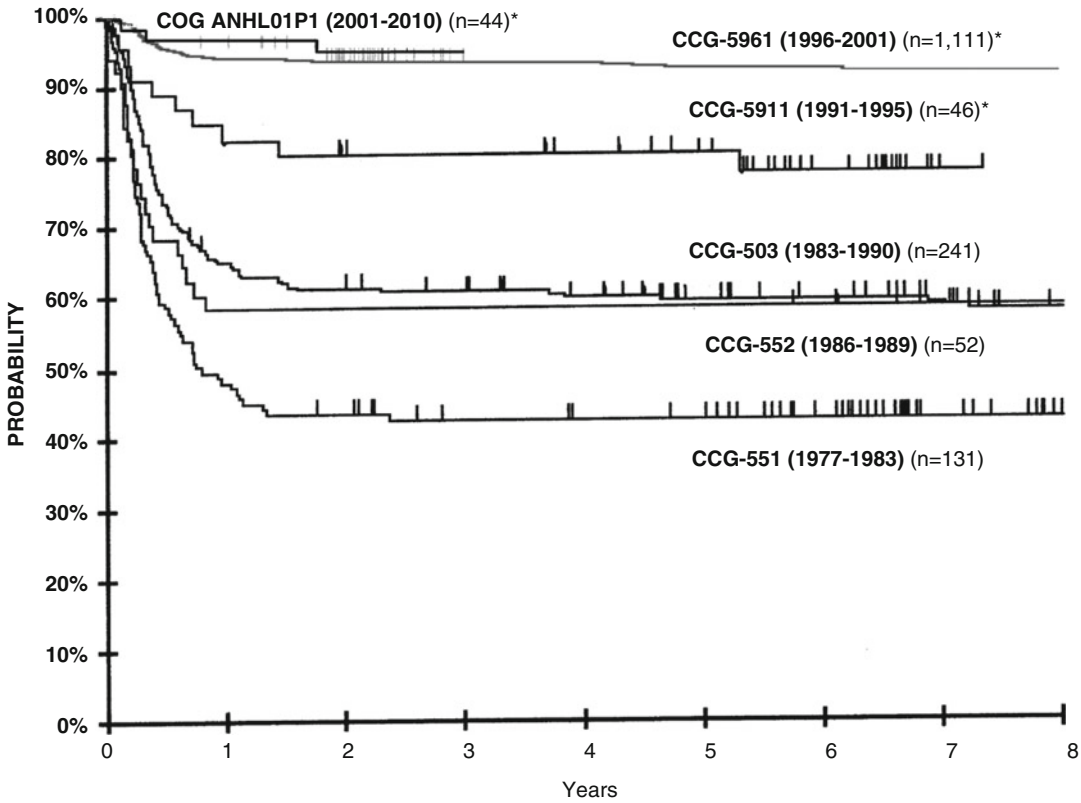


Fig. 4.6 Comparison of EFS by CCG study among stage III/IV and BM/CNS Burkitt and Burkitt-like lymphoma patients from CCG/COG studies: C551, C503, C552, C5911, C5961, and ANHL01P1. *CCG* Children's Cancer Group, *COG* Children's Oncology Group, *EFS* event-free survival (Modified and used with permission from Wiley: Cairo et al. [38], copyright (2003))

FAB/LMB chemotherapy protocols were established based upon three risk-stratification groups. Low-risk group A patients with fully resected stage I or abdominal stage II disease are treated with two cycles of systemic chemotherapy (without intrathecal), with 4-year EFS rates of 98.3 % [42]. FAB group B intermediate-risk regimens demonstrated equivalent EFS rates of 91 % with reduced total doses of cyclophosphamide and deletion of maintenance cycles [32]. Even patients with group C high-risk disease—defined as having central nervous system (CNS) involvement and/or >25 % bone marrow involvement—achieve long-term EFS rates of 79 % with the FAB/LMB backbone chemotherapy bolstered by the addition of HD MTX (8 g/m^2 for CNS-positive patients) during induction and cytarabine (12,250 mg/m^2) plus etoposide for two cycles of intensification followed by four cycles of maintenance chemotherapy [39]. The Berlin-Frankfurt-Munster (BFM) collaborative group uses a very similar risk-stratification system with four groups instead of three; FAB group B is essentially broken down into two groups in the BFM approach. Similarly, their treatment regimen is nearly the same, with slight variations in chemotherapy dosing, number of cycles, and the addition of ifosfamide in the BFM approach accounting for the nuanced differences (see Table 4.9) [25].

Recent large-scale prospective data from the FAB/LMB96 study demonstrated that adolescent age was not associated with a risk of treatment failure in comparison to children with BL [31]. Historically though, there had previously been a general consensus that adolescents with mature B-cell lymphomas experienced inferior outcomes based upon data from the United States, Germany, and France [38, 43, 44]. However, this data may be clouded by multiple factors including derivation from retrospective analyses spanning decades (CCG and BFM data) and analysis of smaller numbers of patients (SFOP data) and that all three studies occurred prior to the discovery of primary mediastinal B-cell lymphoma as a separate B-NHL diagnostic entity requiring different therapy that tends to occur in adolescents and young adults. It is currently accepted that adolescent age is not prognostically significant in BL.

While adults with BL have always experienced much lower curative rates than pediatric patients, this has been attributed to the intrinsically different treatment approaches utilized. More recently, adult BL clinical trials have incorporated pediatric-style chemotherapy regimens with encouraging success [45]. In general, it is well established that pediatric BL protocols achieve significantly higher curative outcomes for the following reasons: (1) dose intensity is incorporated by utilizing 21 rather than 28-day

Table 4.9 Comparison of risk-stratification and treatment regimens between FAB and BFM protocols for CAYA with mature B-NHL

Group	BFM R1	FAB group A	BFM R2	FAB group B	BFM R3	BFM R4	FAB group C
Definition	Resected	Resected	Not resected I, II, III-LDH <500	Not resected I, II, III—CNS negative	III-LDH 500–999 IV+ B-ALL LDH <1000, CNS negative	LDH >1000 and/or CNS positive	B-ALL IV—CNS positive
No of courses	2	3	4	4	5	6	8
MTX g/m^2, infusion	1, 4 h, ×2	–	1, 4, h, ×4	3, 3 h, ×4	5, 24 h, ×4	5, 24 h, ×4	8, 4 h (CNS+; 24 h)
Dox mg/m^2	50	120	100	120	100	100	240
CP g/m^2	1–2	3	2–4	3–3	2–4	2–4	6–8
Ifo g/m^2	4	–	8	–	8	8	0
Eto mg/m2	200	–	400	–	900	1400	2500

BFM Berlin-Frankfurt-Munster, *FAB* French-American-British, *LDH* lactate dehydrogenase, *CNS* central nervous system, *B-ALL* B acute lymphocytic leukemia, *MTX* methotrexate, *Dox* doxorubicin, *CP* cyclophosphamide, *Ifo* ifosfamide, *Eto* etoposide

cycles, (2) HD MTX is uniformly given, and (3) group C patients receive both HD MTX and high-dose cytarabine. Historically, when treated on the same protocol, children and young adults achieve similar outcomes [46, 47]. Figure 4.7 demonstrates survival curves for children and adolescents treated on the FAB/LMB pediatric regimen [31, 45]. Table 4.10 shows a comparison of the most recent survival data for CAYA treated on large-scale prospective clinical trials utilizing FAB/LMB backbone chemotherapy regimens.

The vast majority of BL cases in CAYA express the CD20 antigen, begging the question of whether adding anti-CD20-targeted immunotherapy to standard chemotherapy will improve outcomes [48]. Adding rituximab to BL chemotherapy has been shown to be safe and effective in the largest prospective trial for adults with BL, with particularly excellent outcomes for AYA [45]. The Children's Oncology Group (COG) recently published results on a pilot study for mature B-NHL integrating rituximab into the standard FAB/LMB backbone chemotherapy. The study showed that it was safe to combine rituximab with FAB/LMB chemotherapy, and this chemoimmunotherapeutic approach yielded a 95 % probability of EFS at 3 years for 45 patients with advanced-stage III/IV group B intermediate-risk disease [40]. Meanwhile, rituximab combined with group C regimen produced a 3-year EFS of 90 % in 40 patients [41]. The BFM also evaluated the efficacy of rituximab with 37 of 87 newly diagnosed patients with B-NHL (42 %) demonstrating a significant response to a 1-week window of a single dose of rituximab [49]. Current large-scale clinical trials in pediatric BL are focusing on evaluating the combination of rituximab plus FAB/LMB chemoimmunotherapy regimen in a larger cohort of patients [50].

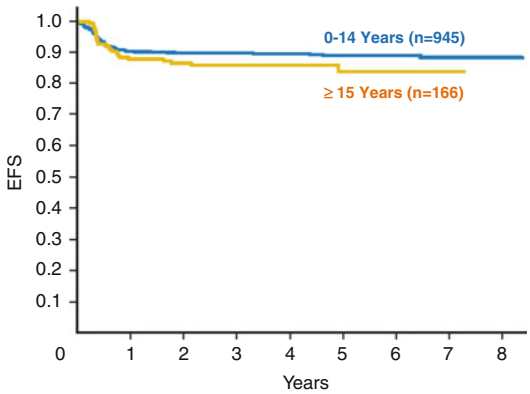


Fig. 4.7 Three-year probability of event-free survival in children (ages 0–14 years) versus adolescents (ages 15–21 years) treated in the French-American-British mature B-cell lymphoma 96 (FAB/LMB 96) study (Reprinted with permission. © (2012) American Society of Clinical Oncology. All rights reserved." Cairo et al. [30])

Although the prognosis for patients with newly diagnosed BL is excellent, CAYA with relapsed and/or refractory BL experience dismal outcomes. With reported long-term survival rates ranging from 12 % to 28 %, it is well established that salvaging those patients with relapsed/refractory BL is inordinately difficult (Fig. 4.8) [38, 39, 51]. A reinduction regimen combining ifosfamide, carboplatin, and etoposide (ICE) with rituximab for children with relapsed/refractory B-NHL produced encouraging results; however maintaining long-term remission can only be established utilizing hematopoietic stem cell transplantation (HSCT) [52, 53]. While the data for HSCT in relapsed/refractory BL is not robust, it has been demonstrated repeatedly that long-term survival utilizing high-dose chemotherapy followed by autologous HSCT is <30 % [54, 55]. The combination of autologous HSCT followed in tandem by reduced-intensity allogeneic HSCT

Table 4.10 Comparison of survival outcomes comparing children, adolescents, young adults, and adults treated on large-scale prospective protocols

	Cairo et al. [31]		Hoelzer et al. [45]		
	0–14 years	15–21 years	15–25 years	26–55 years	>55 years
Number of patients	945	166	69	196	98
EFS/PFS	89 %	84 %	82 %		60 %
Overall survival	91 %	85 %	90 %	84 %	62 %

to maintain long-term remission has shown promise in small numbers of CAYA with relapsed/refractory BL; five of eight patients achieved long-term CR (1.9–8.8 years) utilizing this approach [56]. There seems to be a potential graft-versus-lymphoma (GVL) effect in BL and it is vital to further determine the potential role of allogeneic HSCT in CAYA with relapsed/refractory BL.

Certainly long-term survival in patients with relapsed or refractory BL in the modern era is meager. In the absence of established therapies with curative potential, novel approaches to therapy are desperately needed. Therapeutic strategies that are currently under investigation include agents targeting specific molecular pathways and novel cellular and humoral immunotherapies. Promising targeted cell-signaling pathway inhibitors include ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, and idelalisib, a phosphoinositide-3-kinase inhibitor [57, 58]. Chimeric antigen receptor-based cellular immunotherapies are under evaluation in clinical trials for CAYA based upon exciting results from preclinical data as well as success in treating acute lymphoblastic leukemia (ALL) [59, 60]. Finally, novel humoral immunotherapies targeting both CD19 (blinatumomab and SAR3419) and CD20 (obinutuzumab and ofatumumab) are also being evaluated in clinical trials. As a novel anti-CD20 monoclonal antibody that has demonstrated superior results in comparison with rituximab in both preclinical and clinical trials, obinutuzumab is currently being evaluated in a clinical trial for CAYA with relapsed/refractory mature B-NHL in combination with the reinduction ICE chemotherapy platform (NCT02393157) [61–65]. With a number of novel therapeutic agents on the horizon, there is hope to not only improve the chances for salvaging patient with relapsed/refractory disease but to also improve overall outcomes by incorporating targeted therapies with chemotherapy in up-front regimens.

4.7.2 Diffuse Large B-Cell Lymphoma

Depending on the country in pediatric practice, DLBCL is included either in studies designed for BL (LMB and BFM studies) [44, 66] or in studies designed for large cell NHL in general (Pediatric Oncology Group [POG] studies) [67, 68]. In the LMB89 study, DLBCL represented 10% of all registered patients. As with BL, they are treated according to initial resection and stage. The EFS is similar to that of BL (Fig. 4.9), but it should be noted that the proportion of patients with

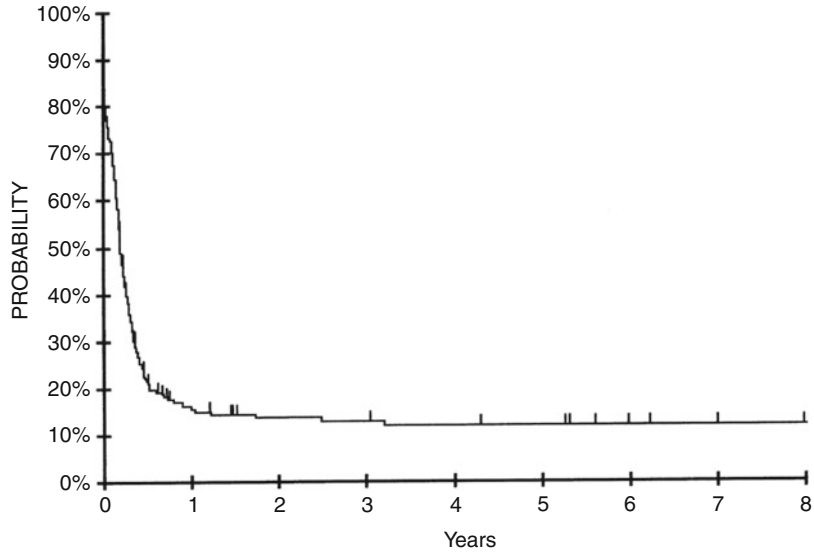


Fig. 4.8 Survival probability after progression/recurrence of mature B-NHL in CAYA. The probability of 4-year survival of patients with persistent, progressive, or recurrent disease, excluding those experiencing toxic deaths or secondary neoplasms. This research was originally published in Blood (Cairo et al. [39]. © by the American Society of Hematology)

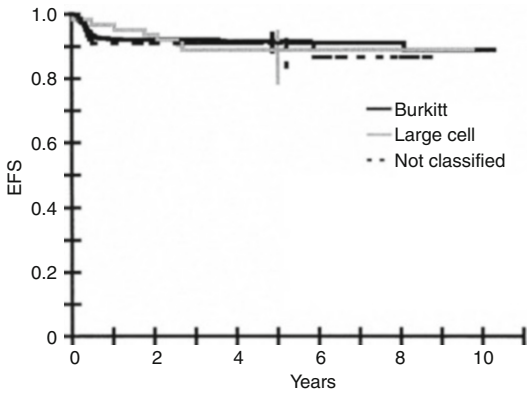


Fig. 4.9 Event-free survival of patients treated in the Societe Francaise d'Oncologie Pediatrique LMB89 protocol according to histology (Burkitt vs. diffuse large B-cell lymphoma). This research was originally published in Blood (Patte et al. [44]. © by the American Society of Hematology)

advanced stages is lower than in BL. However, by stage, EFS is not significantly different [69]. In the BFM90 study, the EFS of DLBCL is also similar to that of BL. The criticism of such an approach is that too much CNS-directed therapy is given in DLBCL, in which the risk of CNS disease is lower than in BL.

In a POG study, all advanced-stage large cell lymphomas, by histology and/or immunophenotype, were treated with an APO (doxorubicin + prednisone + oncovin)-based regimen. The addition of cyclophosphamide (CPM) did not change the outcome [68]. In another study, the addition of HD MTX and ARA-C was randomized. Results indicate a benefit to DLBCL, but not to ALCL [70].

There are important distinctions between adult and pediatric strategies in the management of DLBCL and the analysis of the outcome of regimens used is complicated by the mixing of the issues of chemotherapy schedule and rituximab usage. Pediatric practice generally uses intensive "Burkitt-like" regimens without rituximab. In adult practice CHOP (CPM, doxorubicin, vincristine [VCR], prednisone) or CHOP-like regimens such as ACVBP (doxorubicin, CPM, vindesine, bleomycin, prednisone) [71] are delivered with rituximab in almost all cases. The publication of the seminal paper by Coiffier et al. [72] in patients over 60 years of age demonstrated that the addition of rituximab to CHOP significantly increased the CR rate, EFS, and overall survival (OS) at 3 years (hazard ratio for OS, 0.64). The advantage achieved with the addition of rituximab was then corroborated by two subsequent studies in <60-year-old, good-risk patients and in all patients over the age of 18 years [73, 74]. There is no data concentrating on outcome in the AYA population though the analyses underlying the sequential IPI demonstrate that increasing age behaves as a negative continuous variable prognostic factor [9, 11, 75]. Outcomes in younger good-risk patients in the MiNT trials were extremely good [76] and a further paper reporting on the outcome of patients between 18 and 35 years in six consecutive studies by the German High-Grade Lymphoma study group (DSHNHL) has also reported good outcomes (Fig. 4.10) [77]. A key consideration for younger patients is that the CHOP regimen delivers a relatively high anthracycline dose (300–400 mg/m^2 in six to eight courses) and most young people's physicians do not wish to consider these doses in view of the risk of cardiac damage.

It is not likely that any randomized studies will be done to distinguish between these therapy choices. There is, however, an ongoing European Intergroup study to determine the definitive answer to the question of whether the addition of rituximab to pediatric regimens is of value (NCT 01516580). This is based on the standard pediatric NHL COP (CPM, VCR, prednisone)-COPADM (COP, doxorubicin, MTX)-COPADM-CYM (cytarabine HD MTX)-CYM backbone.

In adult practice a major change in the understanding of the biology of DLBCL has been the advent of GEP. In some ways incorporation of this innovation into routine clinical practice has been slower than might have been expected given that the initial papers appeared in 2000. Adoption into clinical practice was held back by the switch to rituximab-based schedules in adult practice around the time of the original report [72] and this called into question whether the initial observations remained valid following this major change in therapy. This problem was resolved by

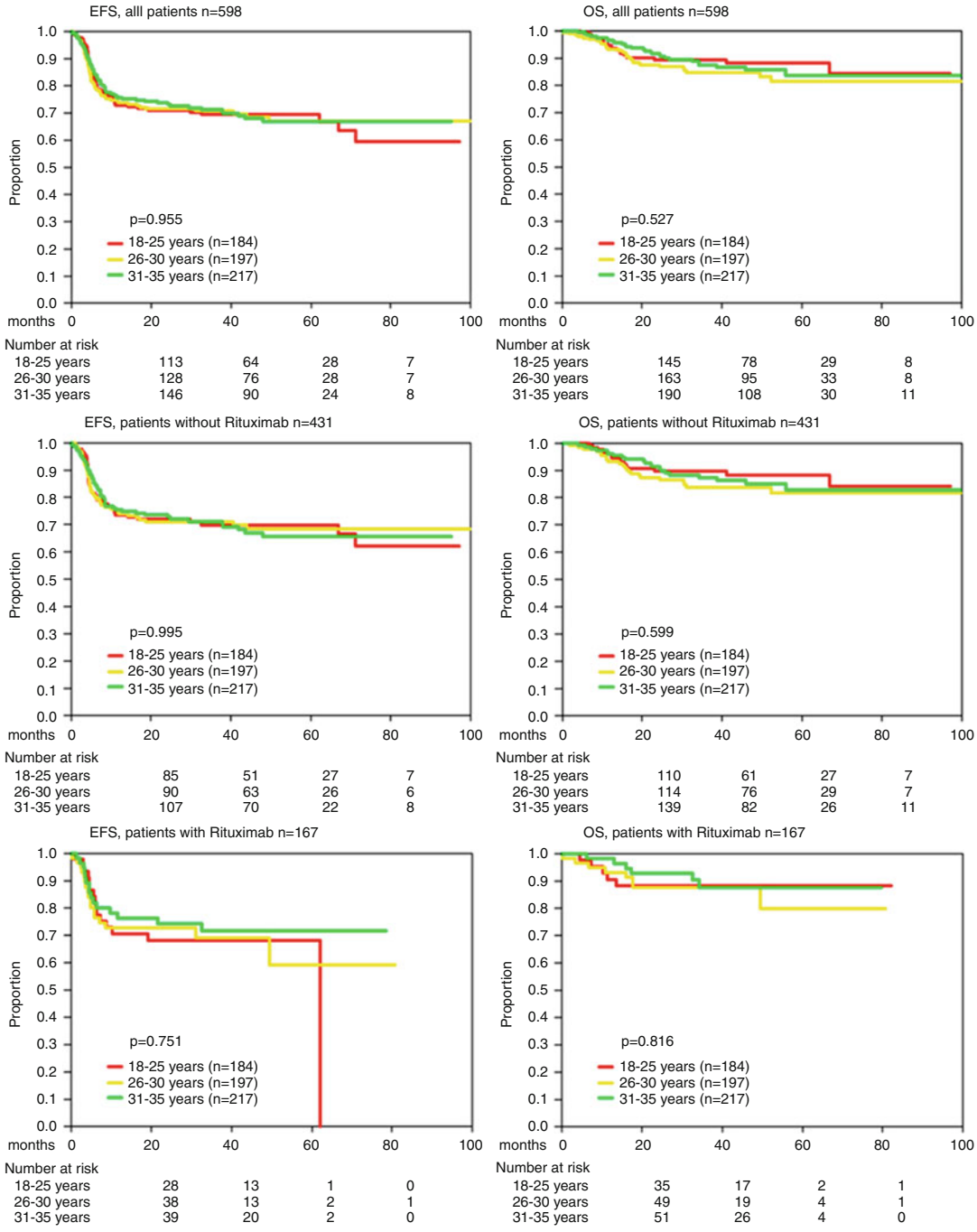


Fig. 4.10 EFS and OS for all patients and patients without and with rituximab (Reprinted by permission from Macmillan Publishers Ltd: Leukemia, 28:2260–2263, copyright (2014))

the Lenz et al. paper in 2008 [78] which updated the observations to a rituximab-treated population and the data is summarized Wilson et al. in Fig. 4.11 [79].

It is now accepted that two principal subtypes of DLBLC can be recognized, namely, germinal center B-cell type (GCB) and activated B-cell type (ABC). These are biologically distinct and it

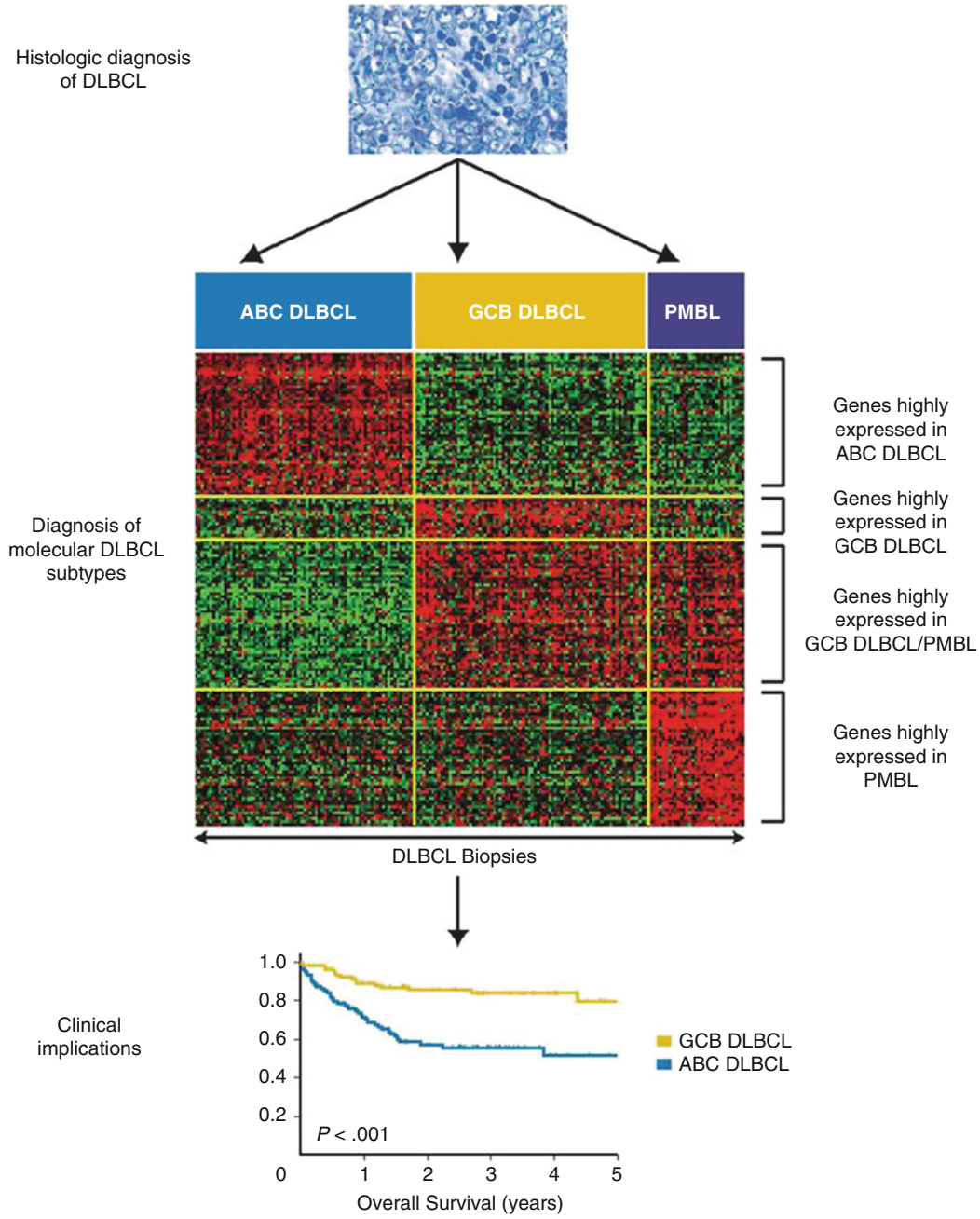


Fig. 4.11 Diagnosis and outcome of DLBCL subtypes by GEP. (**a**) Heat map showing differential expression of genes in GCB, ABC, and PMBL DLBCL subtypes. (**b**) Kaplan-Meier estimates of progression-free and overall survival are shown according to GCB or ABC DLBCL subtype in patients treated with R-CHOP-based therapy. Median follow-up is approximately 2 years (From Wilson [79])

is likely that their recognition will assume greater clinical importance with the advent of novel therapies. The first of these novel therapies to be recognized was the B-cell receptor pathway inhibitor, Ibrutinib, which inhibits BTK and appears to be more active in the ABC subtype. Implementation of this classification was delayed by a desire to try and make this sub-categorization

using immunohistochemistry which is cheaper and more accessible in routine clinical practice. However expert opinion is now that GEP is the best way to achieve this sub-classification [80]. The main distinction to be made is between the GCB and ABC subtypes but some patients are inevitably intermediate (sometimes called type 3) or technically unclassifiable. It is also worth noting that a general tendency toward smaller needle core biopsies rather than formal lymph node excision biopsies has made the pathologist's task in achieving this sub-classification much more difficult.

In adult practice there is considerable debate on how R-CHOP (rituximab + CHOP) as the standard care could be improved upon and this is also clearly relevant to therapy for AYA patients. This is mainly an issue for "poor-risk patients" as defined at diagnosis by IPI since, as previously observed, there is no proven rationale for the alternative PET-based strategy of identifying by interim PET scanning those patients who might require dose intensification. The components of the IPI are age, stage, serum LDH, PS, and extranodal localization. The use of high-dose chemotherapy and HSCT in first remission is controversial and is not widely used. One randomized study [81] showed an apparent advantage but can be criticized on the grounds that it included many patients from the pre-rituximab era while a second, while demonstrating a progression-free survival (PFS) advantage, failed to show an OS difference due to effective salvage in the control (non-transplant) arm at relapse [82]. The French R-ACVBP (rituximab, doxorubicin, CPM, vindesine, bleomycin, prednisone) regimen has yielded some of the best results reported and includes an intensive consolidation phase [71]. Another intensified regimen, R-CHOEP 14 (R-CHOP + etoposide), has been reported from Germany [83] and the Nordic countries [71, 84] in phase 2 studies with good results. In the United Kingdom, the Burkitt regimen R-CODOX-M (rituximab + CPM, doxorubicin, VCR, MTX, cytarabine) and R-IVAC (rituximab + etoposide, cytarabine, ifosfamide) has been tested in a phase 2 study in poor-risk (IPI 3–5) patients [85].

With the advent of GEP and the identification of ABC subtype patients, there are now multiple studies of the addition of novel agents such as bortezomib (randomized evaluation of molecular-guided therapy for diffuse large B-cell lymphoma with bortezomib [ReMOdL-B]—UK National Cancer Research Institute [NCRI]) and ibrutinib (Phoenix International company lead study, NCT 01855750). Another agent, lenalidomide (Celgene), is also under study in multiple trials and also appears to be more active in the ABC subtype [86]. With respect to novel anti-CD20 monoclonal antibodies, the first alternative, ofatumumab (a "type 1" antibody), was not shown to be superior to rituximab in second-line therapy with R-DHAP (rituximab + dexamethasone, cytarabine, cisplatin) versus O-DHAP (ofatumumab + dexamethasone, cytarabine, cisplatin) in the HOVON—ORCHARRD study [87], but there is an ongoing large phase 3 international trial comparing the activity of rituximab with that of obinutuzumab in combination with CHOP in first-line therapy of DLBCL (GALLIUM—Roche Commercial study NCT 01332968). Obinutuzumab is a novel type 2 anti-CD20 antibody claimed to have superior characteristics in vitro [88] and superior outcome reported in another B-cell malignancy, chronic lymphocytic leukemia (CLL) [89]. There has been an unprecedented increase in novel therapies in B lineage DLBCL and other potential novel therapies include the anti-BCL2 inhibitor GDC199 (Abvie) and in common with a range of other malignancies, novel therapies targeting the PDL 1 pathway (e.g., nivolumomab, BMS).

Biologic characteristics may also have prognostic value, such as the presence of so-called "double-hit" lymphomas [90] where molecular abnormities of *c-myc* and Bcl 2 are detectable or even "triple hit" where Bcl6 is also mutated. This adverse outcome is not always illustrated in published trial results when whole populations are screened, for example, in the UK NCRI R-CHOP 14 vs. R-CHOP21 study [73].

Overall therapeutic results in adults are not as satisfactory as in children. This might be due to differences in biology of DLBCL in children, young people, and adults [91] and there

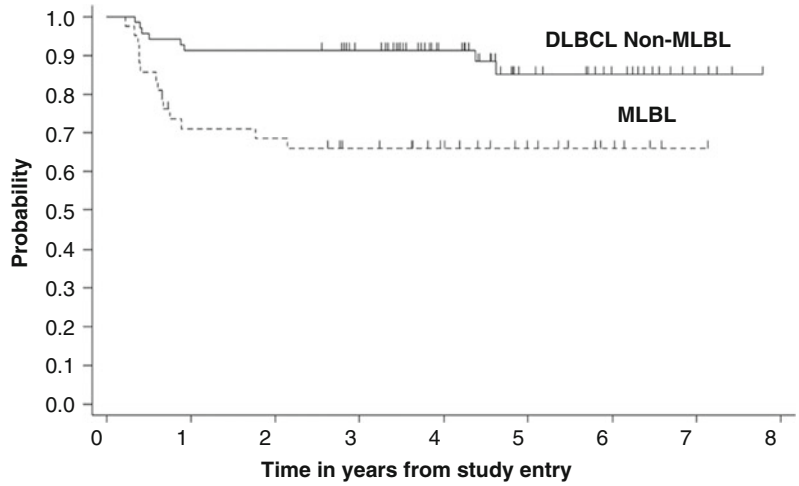


Fig. 4.12 Probability of 5-year EFS calculated using the Kaplan-Meier method for patients with MLBL compared with stage III non-MLBL DLBCL patients treated on group B therapy in the FAB/LMB 96 study. The 5-year EFS for MLBL patients was 66 % (95 % CI, 49–78 %), and for stage III non-MLBL DLBCL patients, it was 85 % (95 % CI, 71–92 %; $P < 0.001$). This research was originally published in Blood (Gerrard et al. [92]. © by the American Society of Hematology)

may be an analogy with ALL where there are varying patterns of cytogenetic abnormalities with age.

4.7.2.1 Primary Mediastinal B-Cell Lymphoma

One particular subtype of DLBCL is PMLBCL, which has a different biology and has also now been shown to have a distinct GEP (Fig. 4.12) [93].

In the pediatric BFM and FAB/LMB 96 series, PMLBCL had a worse prognosis than other DLBCL, with an EFS of approximately 65–75 % [77, 78]. Conversely, the Children's Cancer Group (CCG) claimed that the outcome of these lymphomas was better than for other DLBCL [40]. In fact, the number of patients is small and there is a need to combine these data to find prognostic factors and to adapt therapy.

In adult practice there is a divergence between two strategies; firstly, there are those using R-chemo DLBCL regimens (usually R-CHOP) in which case radiotherapy consolidation is usual. This use of radiotherapy, though, is now being examined by an International Extranodal Lymphoma Study Group (IELSG) randomizing to radiotherapy or no radiotherapy in patients who are PET negative at the end of standard chemotherapy. The second approach following recent NEJM publication is to use the DA-EPOCH-R regimen and in this case radiotherapy is minimized [94]. In this same way as with the BL data using the same regimen, this data is controversial as it is numerically modest and reported from only two centers and recruited over a long period of time; nevertheless the results are compelling (Fig. 4.13).

It would appear reasonable to require further confirmation (phase 3) data that will be needed before DA-EPOCH-R should be adopted as standard of care. However, the probable lower risk of cardiotoxicity of an infusional regimen makes it appealing to use in pediatric and AYA, and in Europe there is an ongoing open, single-arm phase 2 study of the use of this regimen up to the age of 18 years which should, it is hoped, address the issue of the previous disappointing outcome in this histological subgroup. Following the Dunleavy et al. publication, a letter was published in response detailing the regimen was adopted by the BFM group for children and adolescents with PMBCL as the best available in clinical practice [95], and this treatment was

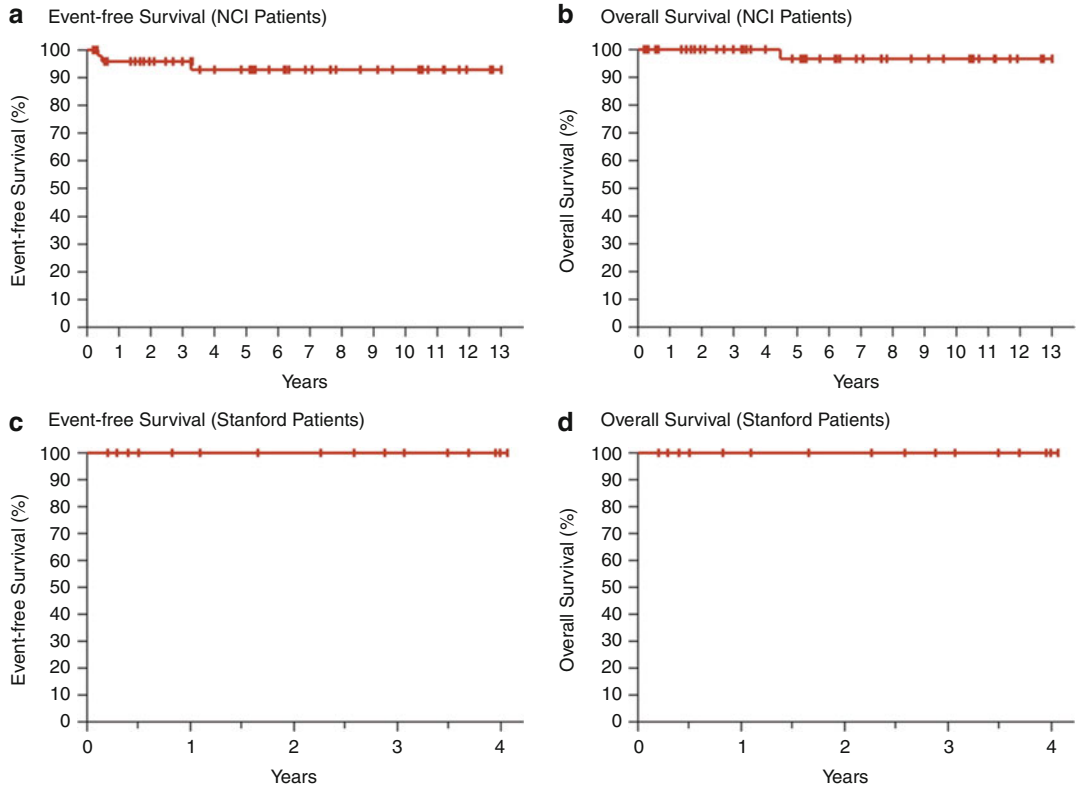


Fig. 4.13 Kaplan-Meier estimates of event-free and overall survival of patients with primary mediastinal B-cell lymphoma receiving DA-EPOCH-R, according to study group. DA-EPOCH-R was administered to 51 patients in a prospective trial at the National Cancer Institute (*NCI*) and to 16 patients in a retrospective trial at Stanford University. In the prospective NCI cohort, the event-free survival rate was 93 % (Panel **a**) and the overall survival rate was 97 % (Panel **b**) at a median follow-up of 63 months. In the retrospective Stanford cohort, the event-free and overall survival rates were both 100 % (Panel **c** and **d**, respectively) at a median follow-up of 37 months (From Dunleavy et al. [94]. Copyright © (2013) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society)

adopted for patients in the B-cell NHL-BFM04 study in 2010. They reported that some changes were made from the original study protocol including the addition of intrathecal prophylaxis and limitations of the cumulative doxorubicin dose to 360 mg/m^2. At the time of this letter in 2013, they had treated 15 patients between 11 and 17 years with an EFS and OS of 92 ± 8 %. Interestingly, they also observed a high rate of PET positivity (9 out of 15), none of which demonstrated positive histology; when biopsied (7 out 9 were resected), there was one case of CNS relapse. These results, though again preliminary, look highly encouraging.

4.7.3 Anaplastic Large Cell Lymphoma

ALCL is the least common form of AYA NHL and consists of three major subtypes: primary systemic anaplastic lymphoma kinase (ALK)-positive ALCL, primary systemic ALK-negative ALCL, and primary cutaneous ALCL (C-ALCL). ALK-positive ALCL, by definition, overexpresses an ALK-fusion gene resulting from a translocation involving ALK (ALK gene).

In the last WHO classification of NHL (Table 4.11) [24], ALK-positive ALCL is recognized as a distinct disease entity within the spec-

Table 4.11 WHO 2008 classification of precursor and mature T/NK-cell neoplasms

Leukemic or disseminated
T-lymphoblastic leukemia/lymphoma
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorders of NK cells
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia (HTLV1-positive)
Systemic Epstein-Barr virus (EBV)-positive T-cell lymphoproliferative disorders of childhood
Extranodal
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Extranodal-cutaneous
Mycosis fungoides
Sezary syndrome
Primary cutaneous CD30+ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous aggressive epidermotropic CD8+ cytotoxic lymphoma
Nodal
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK-positive
Anaplastic large cell lymphoma, ALK-negative
Primary cutaneous small/medium CD4+ T-cell lymphoma

Swerdlow et al. [96]
ALK anaplastic lymphoma kinase, *EBV* Epstein-Barr virus; *HTLV1* human T-cell lymphotropic virus-1, *NK* natural killer, *NOS* not otherwise specified, *WHO* World Health Organization

trum of mature T-cell lymphomas and is distinct from ALK-negative ALCL, which is now classified as a provisional entity. There is still controversy in the literature about the existence of this entity which may be classified in the future within the group of peripheral T-cell lymphomas without other specifications. Most C-ALCL are not associated with ALK rearrangement and are classified in the WHO classification in the group of primary cutaneous CD30+ T-lymphoproliferative disorders [97].

The median age of presentation of ALCL ranges between 17 and 50 years, with a bimodal age of distribution with a larger peak in the 20- to 30-year-old range and a smaller peak in the sixth and seventh decades of life (SEER data) (Fig. 4.3). ALK-positive ALCL tends to occur in the AYA age range, whereas ALK-negative cases tend to occur in an older age group. C-ALCL rarely occurs in the AYA age group and is usually manifested in the sixth and seventh decades of life.

There is a male predominance (6–7:1) in ALCL in the AYA age group. Systemic ALCL is characterized by peripheral, mediastinal, or intra-abdominal lymph node involvement, frequently associated with B-symptoms and extra-nodal involvement. Less than 15 % of patients exhibit cytologically detectable bone marrow disease, whereas reverse transcription-polymerase chain reaction (RT-PCR) for nucleophosmin (NPM)-ALK can detect minimal disseminated disease (MDD) in blood or bone marrow in around 50 % of the patients at diagnosis [98]. CNS involvement is detected in less than 5 % of the patients. C-ALCL usually presents as a solitary skin nodule or papule confined to the skin.

4.7.3.1 Biology/Pathology

ALCL is defined by large, pleomorphic, multinucleated cells or cells with eccentric horseshoe-shaped nuclei and abundant clear to basophilic cytoplasm with an area of eosinophilia near the nucleus (termed "hallmark cells"). These hallmark cells commonly resemble Reed-Sternberg cells (characteristic of Hodgkin lymphoma), although they tend to have less conspicuous nucleoli. Neoplastic cells tend to infiltrate in a sinusoidal pattern in regional lymph nodes, mimicking metastatic disease, although diffuse effacement of nodes may also be demonstrated. There is a high propensity of systemic ALCL (S-ALCL) to spread to extranodal tissues (skin, bone, soft tissues) either as the only sites of disease or, more commonly, in association with nodal disease [99].

Five morphologic variants of ALCL have been identified in the 4th edition of the WHO classification. These variants include the common variant (70 %), which is composed primarily of hallmark cells, the lymphohistiocytic variant

(10 %), which has a large number of benign histiocytes admixed with neoplastic cells, and the small-cell variant (10 %), which is composed of small neoplastic cells and only scattered hallmark cells, Hodgkin-like variant (1–3 %), and ALCL with composite pattern (10–20 %) defined as having features of more than one pattern in a single lymph node biopsy.

C-ALCL is a peripheral T-cell lymphoma of large, anaplastic, CD30-positive cells that is limited to the skin. It usually presents as a solitary tumor, nodule, or papule that is composed of larger, pleomorphic cells that infiltrate the upper and deep dermis and extend into the subcutaneous tissues. Epidermal invasion is uncommon and surrounding inflammation is usually present.

The majority of ALCL has been shown to be of the T-cell phenotype but the phenotype is often aberrant with a lack of expression of one or several the T-cell antigens such as CD2, CD3, CD4, CD5, or CD8 [100]. Expression of epithelial membrane antigen (EMA) and of cytotoxic antigens, such as TIA-1 or granzyme, and perforin, is observed in most cases. Most cases of S-ALCL and C-ALCL demonstrate T- cell receptor gene rearrangements, even when immunophenotypic analysis fails to demonstrate expression of T-cell antigens [101].

Most cases in CAYA are associated with a characteristic genetic alteration involving the ALK locus on chromosome 2. Classically this is manifested as the t(2;5) (p23;q35) translocation, which includes a rearrangement of a nucleolar phosphoprotein gene (NPM1) adjacent to the ALK tyrosine kinase gene [102]. Less common translocations include translocation of ALK to partner genes on chromosomes 1, 2, 3, and 17, which also results in upregulation of ALK expression [103]. All translocations involving ALK produce fusion proteins with constitutive tyrosine kinase activity that in most cases derives from spontaneous dimerization induced by the different fusion partners. Constitutive ALK activation results in the activation of multiple downstream pathways such RAS/ERK, SHH/GLI1, JAK/STAT3, and AKT/PI3K, leading to growth-factor-independent cell proliferation and inhibition of apoptosis [104, 105].

The pattern of ALK staining is usually nuclear with or without cytoplasmic staining for t(2;5) and is only in the cytoplasm for many of the alternative translocations [103]. Greater than 90 % of advanced AYA cases of S-ALCL are associated with ALK translocations, which are commonly absent in C-ALCL and seen with lower frequency in adults with S-ALCL. The presence of an ALK translocation or ALK protein expression, however, appears to be associated with a better prognosis in adults [101, 106]. ALK staining is absent most in C-ALCL; however authentic ALK-positive C-ALCL have been described [107].

Since ALK is not expressed in normal cells except in the CNS and testis, its abnormal expression in tumor cells may induce immune response [108]. Indeed, accumulating evidence indicates that the immune system plays a major role in both the pathogenesis and final control of ALK-positive ALCL [109]. Antibodies against ALK and cytotoxic T-cell and CD4 T-helper responses to ALK have been detected in patients with ALK-positive ALCL both at diagnosis and during remission with a significant inverse correlation between ALK-antibody titers and the incidence of relapses [110]. A high incidence of germline monoallelic variants of the perforin gene has also been shown in patients with ALCL (27 %) as compared to its incidence in the general population (10 %) suggesting that impairment of cytotoxic lymphocyte function may predispose to ALCL [111].

4.7.3.2 Management of S-ALCL

In recent trials with very diverse first-line chemotherapy regimens in terms of the duration of treatment and the number and cumulative doses of drugs, similar EFS rates of about 65–75 % have been achieved in children, adolescents, and adults (Table 4.12).

In adults, no large comparative studies of adults have been published. Patients are generally treated according to protocols designed for diffuse large cell lymphoma mostly with anthracycline-containing regimens (CHOP, CHOEP, or ACVBP [99, 106, 117–119]. Most investigators report high response rates ranging from 60 % to 90 % and 5-year EFS and OS, respectively, around 65–75 % and 70–93 % in

Table 4.12 Main series of ALCL in children and adults

Author	Protocol	Period	Number of patients		DFS (%)	OS (%)
			Total number	Percentage ALK + (%)		
Laver [112]	APO ± MTX/ara-C	1994–2000	86	89	72	88
Lowe [113]	Compressed T-NHL protocol	1996–2001	86	90	68	80
Brugieres [114]	ALCL99 + randomization for vinblastine	1999–2006	375	96	74	92
Alexander [115]	APO with maintenance randomized VBL weekly vs. VCR/3 weeks	2004–2008	125	90	76	85
Falini [106]	Doxorubicin-based chemotherapy	NA	96	60	82[a]	71[a]
Gascoyne [116]	Doxorubicin-based chemotherapy	NA	70	51	82[a]	79[a]
Suzuki [117]	Doxorubicin-based chemotherapy	NA	143	58	NA	72[a]
Savage [99]	Anthracycline-based chemotherapy	1990–2002	159	55	60[a]	70[a]
Schmitz [118]	CHO(E)P or high-dose CHOEP	1993–2007	191	40	76[a]	90[a]
Sibon [119]	Doxorubicin-based chemotherapy	1987–2003	138	46	72[a]	82[a]

[a]Only for ALCL ALK+

ALCL ALK-positive patients, whereas the OS of ALCL ALK-negative patients does not reach 50 % in most studies. Systematic intensification of chemotherapy with the use of autologous stem cell support has been investigated in some institutions as part of a program designed for aggressive lymphoma [120].

In children, two main approaches have been used in S-ALCL: short-pulse regimens, based on regimens used in aggressive B-cell NHL in Europe, and semi-intensive more prolonged chemotherapy in North America [112, 113, 115, 121–127]. In the ALCL99 randomized trial organized by the European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) a 5-year EFS of 73 % could be obtained in a series of 352 patients with a polychemotherapy based on the BFM90 backbone (six alternating courses of dexamethasone, MTX, and CPM/etoposide/cytarabine in course A and CPM/doxorubicin in course B). This trial could demonstrate that the MTX schedule of the BFM protocol including intrathecal (IT) therapy can be safely replaced by a less toxic schedule, MTX 3 g/m^2 in a 3 h infusion without IT therapy [114], and that adding vinblastine to each course and as maintenance for a total treatment duration of 12 months significantly delayed the occurrence of relapses, but did not reduce the absolute risk [128].

The POG study using an APO regimen in children with advanced S-ALCL has demonstrated a 65–75 % 3- to 5-year EFS and showed that the results were not improved by the addition of MTX and cytarabine [112]. A T-cell lymphoblastic protocol was tested in a pilot study for advanced ALCL (CCG-5941) [113]. Patients were treated for 48 weeks with a regimen combining an induction therapy consisting of VCR, prednisone, daunomycin, CPM, and L-asparaginase followed by an intensification phase with VCR, cytarabine, etoposide, HDMTX, 6-thioguanine (6TG), and L-asparaginase and a maintenance therapy consisting of alternating pulses of CPM/6TG, (2) VCR/prednisone/doxorubicin, VCR/HD MTX, and cytarabine/etoposide. The 3-year EFS and OS were 73 ± 6 % and 83 ± 5 %, respectively, in a series of 86 patients.

The effects of the addition of vinblastine in the maintenance treatment were also studied in the ANHL0131 trial; 125 patients were randomized to receive either a maintenance regimen including weekly vinblastine or the standard APO with three weekly VCR regimens. There was no difference between the patients randomized to the APO versus APV (doxorubicin, prednisone, vinblastine) arms in either EFS or OS (3-year EFS 74 % vs. 79 %, $P = 0.68$, 3-year OS of 84 % vs. 86 %, $P = 0.87$) [115].

Optimal therapeutic approaches for limited S-ALCL have not been well defined. Several reports concerning a very limited number of patients suggest that localized (stage I resected),

ALCL can be safely treated with 2 months of chemotherapy including dexamethasone, ifosfamide, MTX, cytarabine, etoposide, and prophylactic IT therapy [126, 129]. A 75 % EFS has been reported in a small number of children and adolescents with localized CD30-positive large cell lymphoma, presumably S-ALCL, who were treated at St. Jude Children's Research Hospital with three courses of CHOP, either with or without maintenance with 6-mercaptopurine and MTX [130].

4.7.3.3 Management of C-ALCL

The outcome of C-ALCL is usually excellent with survival rates over 90 % but a proportion of patients experience multiple relapses. Treatment is usually limited to complete excision whenever possible for patients with solitary lesions, whereas MTX is the preferred treatment for those with multifocal lesions [131]. Brentuximab has also been tested with success recently especially in relapse.

4.7.3.4 Prognostic Factors

Several prognostic factors have been indentified in ALCL. Main prognostic factors identified in patients treated according to adult protocols are the IPI score and the ALK status with better outcome of ALK-positive ALCL as compared to ALK-negative ALCL [106, 116, 132]. However the prognostic impact of ALK positivity seems to be restricted to patients older than 40, both in the International Peripheral T-Cell Lymphoma Project study and in the retrospective study from the GELA group (Groupe d'Etude des Lymphomes de l'Adult) in which outcomes did not differ according to ALK status when the analysis is limited to patients ≤40 at diagnosis [116, 119]. The prognostic impact of IPI has not been validated in pediatric studies including children and adolescents.

A pooled analysis of patients included the pediatric BFM, UK, and French prospective trials demonstrated an increased risk of failure brought to light three prognostic factors: (a) mediastinal involvement; (b) visceral involvement defined as spleen, lung, or liver involvement; and (c) skin lesions. For the good-prognosis group with no factors, the 5-year EFS was 89 %; for the poor-risk group with at least two factors, the expected 5-year OS was 61 % in patients with mediastinal or visceral involvement and skin lesions [133]. In a large series of 375 patients included in the ALCL99 trial and centrally reviewed, the presence of a histologic lymphohistiocytic and small-cell component has also been shown to be associated with a higher risk of relapse [100]. Several new parameters predicting the risk of relapse have also been identified such as the detection of MDD in bone marrow and blood by RT-PCR which is associated with a risk of relapse of 50 % [134], the persistence of minimal-residual disease (MRD) after the beginning of treatment [135], and a low production of anti-ALK-antibody titers [136]. Using MDD and antibody titer results in a series of 128 patients allowed the classification of patients into three biological risk groups with different prognosis: high-risk group, MDD-positive and low antibody titer (20 % of the patients with a 5-year PFS of 28 %); low-risk group, MDD-negative and high antibody titer (31 % of patients with a 5-year PFS of 93 %); and intermediate-risk group, all remaining patients (48 %) with a 5-year PFS of 68 % [137].

4.7.3.5 Treatment of Relapses

There is currently no gold standard for the treatment of relapses. Several strategies including reinduction chemotherapy followed by autologous or allogeneic HSCT or weekly vinblastine can be successful [54, 138–144]. One of the unique features of ALCL compared to other pediatric NHL is its sensitivity to chemotherapy after recurrence leading to a survival rate of more than 85 % in most series [139, 141, 144]. The efficacy of vinblastine, initially shown by the French group a small series of patients with multiple relapses [138], was confirmed in the intermediate analysis of the European ALCL relapse study with an 87 % 2-year EFS rate in a small series of patients with a late relapse (median follow-up 34 months) [145]. The main prognostic factor after relapse is the time interval between initial diagnosis and relapse with a worse outcome for patients with early relapses as compared

for those patients whose relapse occurs more than 1 year after initial diagnosis [139, 141, 144].

Several new drugs are now available for the treatment of relapsed ALCL. The antibody drug conjugate brentuximab vedotin, an anti-CD30 monoclonal antibody conjugated to the antimicrotubule cytotoxic monomethyl auristatin-E, is associated with a high response rate (86 %) and durable remissions in relapsed/refractory ALCL and is under investigation in the up-front setting [146, 147]. It has been approved by the Food and Drug Administration (FDA) and European Medical Agency (EMA) for the treatment of systemic ALCL after failure of at least one chemotherapy regimen in adults.

ALK inhibitors such as crizotinib, an ALK/MET inhibitor, are also promising drugs. Crizotinib is now approved by the FDA and EMA for the treatment of ALK-positive lung cancers. An excellent response rate was obtained in ALCL in children (seven out of nine CR in patients with relapsed/refractory ALCL included in a pediatric phase 1 trial of crizotinib) [148]. The same results were obtained with a response rate of 91 % in 11 patients with ALK+ resistant/refractory adult lymphoma [149]. Despite the presence of mutations in the ALK catalytic domain of rare ALCL patients at diagnosis [150], resistance to crizotinib in ALCL seems to be a rare event in children and adolescents whereas relapses have been described within 2 months following the beginning of the treatment in four out of nine adult patients described by Gambacorti-Passerini et al. [149]. Several new anti-ALK agents have been developed and still have to be evaluated in this disease [104].

The role of crizotinib in the treatment of ALCL still has to be defined. It is remarkably effective to induce CR in patients with a relapse or a primary resistant disease but we still do not know whether crizotinib alone can be a curative treatment, if it has to be combined with chemotherapy to induce durable remission or if it should be considered as a bridge to allogeneic transplantation in patients with very high-risk disease.

The role of brentuximab and crizotinib added to front line treatment of ALCL is currently being evaluated in prospective trials by the COG in children and adolescents (NCT01979536).

4.8 Lymphoblastic Lymphoma

Lymphoblastic lymphoma (LL) is one of the most common NHL in the AYA group. Initially described as a distinct pathological entity by Sternberg in 1916, it was in 1975 when Barcos and Lukes defined this pathological entity as "lymphoblastic lymphoma" because of its close morphologic similarity to blasts of acute lymphoblastic leukemia [151]. LL is considered an aggressive form of NHL by the REAL and WHO classifications. The majority of LL cases (≥75 %) express a T-cell lineage and the remainder express a pre-B or B-cell immunophenotype. The most typical cytogenetic abnormalities, especially of the T-cell immunophenotype, commonly include T-cell receptor (TCR) gene rearrangements, including TCRα/β (14q11-13), TCRβ (7q32-36), and TCRγ (7p15). Other commonly abnormal rearranged genes that have been described include *TAL-1*, *TAL-2*, *TCL-1*, *TCL-2*, *TCL-3*, *HOX-11*, *RHOM-1*, *RHOM-2*, *LYL-1*, *TAN-1*, *LCK*, *PBX-1*, and *E2A* among others. There is a high incidence of LL in children with a median age of onset at around 9 years [152–155], with a peak incidence in the AYA group (15–30 years) and a median onset of approximately 25 years of age [156, 157]. There is a predominant male to female ratio ranging in different studies from 2:1 to 3:1. LL tends to present most commonly as a mediastinal mass or lymph node in the AYA age group (≥90 %), may involve the bone marrow at diagnosis (25 %), tends to present with advanced-stage disease (≥III; 75 %), and less often involves the CNS (5 %) (Fig. 9.14) [33, 159].

4.8.1 Biology/Pathology

LL has been well described in both the REAL and WHO classifications, including precursor T (and B) LL. Precursor B-cell disease predominates in ALL compared to most of the LLs that are of precursor T-cell origin (80–90 % T cell vs.

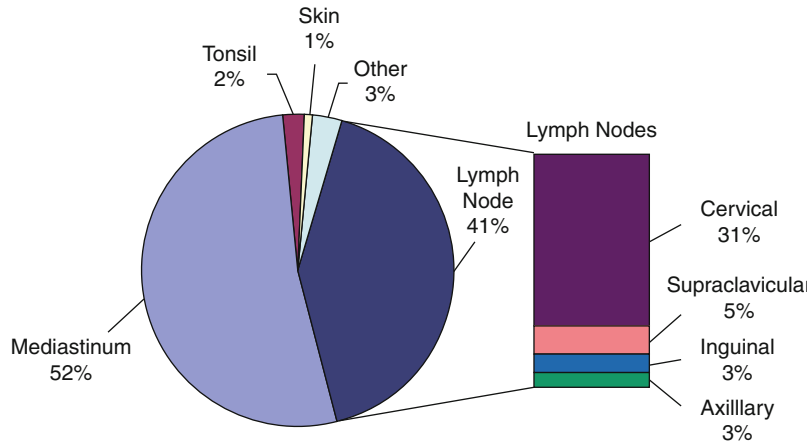


Fig. 4.14 T-lymphoblastic lymphoma sites of diagnostic biopsy (Used with permission from Wiley: Patel et al. [158], copyright (2012))

10–20 % B cell). Precursor T-cell LL tends to present as mediastinal or upper torso nodal masses, whereas precursor B-cell LL is more likely to present in the skin, soft tissue, bone, tonsil, and peripheral lymph nodes [160].

The morphologic features of LL include diffuse or partial effacement of lymph nodes that usually infiltrate interfollicular zones with sparing of benign, reactive follicles. A starry-sky pattern derived from the presence of macrophages ingesting apoptotic debris occurs commonly. Cytologically, the neoplastic cells are indistinguishable from those seen in precursor B-cell or T-cell ALL. The cells have an immature, blastlike appearance with fine chromatin, inconspicuous or absent nucleoli, and scanty cytoplasm that ranges from pale to slightly basophilic in color, and most LL have a high proliferative rate [160].

Immature B- or T-lymphoid blasts express terminal deoxynucleotidyl transferase (TdT). T-LL commonly expresses CD1, CD2, CD5, and CD7 along with co-expression of CD4 and/or CD8. The frequency of CD4/CD8 double-positive cases supports the notion that T-LL is derived in most cases from a more mature thymocyte counterpart relative to T-ALL [158]. Occasionally, both CD4 and CD8 may be absent. CD10 is expressed in 15–40 % of cases, and occasionally natural killer antigens such as CD57 or CD16 may be seen [160]. A recent analysis of T-LL in children showed a cohort of early T-cell and suspicious early T-cell phenotype totaling approximately 14 % of cases including a smaller cohort that are also TdT negative [158]. This same analysis suggested a trend toward decreased EFS and OS in these patients which is similar to various reports showing poorer prognosis in T-ALL cohorts [161, 162]. However, the most recent COG reports do not support this conclusion and it remains to be seen what the exact prognostic significance of early T-cell phenotype will be. Precursor B-cell LL most often displays the immunophenotype of early pre-B or pre-B phenotypes (CD19, CD10, and TdT with variable CD20, CD22, HLA-Dr, and cytoplasmic immunoglobulin) [160].

T-LL will commonly display early T-cell gene rearrangements (TCRδ, TCRγ, TCRα, and/or TCRβ) [157, 163]. Precursor B-LL commonly demonstrates clonal immunoglobulin gene rearrangements and lacks evidence of somatic hypermutation [164]. Cytogenetic abnormalities are common (50–80 %) in both B- and T-LL [157]. T-LL chromosomal breakpoints have included TCR genes or specific oncogenes TCRα/δ (14q11), TCRβ (7q32-36), and TCRγ (7p15). Often the TCR enhancer or promoter elements are translocated and juxtaposed to putative transcription factors [157, 163]. Specific oncogenes associated with T-LL include TCL-1 (14q32), which is involved in t(7;14)(q35;q32) or t(14;14)(q11;q32); TCL-2 (11p13), which is involved in t(11;13)(p13;q11); TCL-3 (10q24), which is seen in t(8;14)(q24;q11); and TAL-1 (1p32), which is involved in t(1;14)(q32;q11). Despite significant similarities between the malignant precursors of

T-ALL and T-LL, recent gene profiling of patient samples has demonstrated clear differences between the two including key differences in NOTCH pathway mutations [165, 166]. This suggests that LL may not just be part of a spectrum and may in fact have separate oncogenic mechanisms, thus requiring a unique therapeutic approach.

4.8.2 Treatment and Management

The history of the treatment for LL over the past three decades has seen a progression from conventional lymphoma-based treatment to ALL-based treatment. With current therapies, the majority of patients, including those with advanced-stage disease, can expect a likelihood of 80–85 % EFS utilizing modified ALL regimens [33, 152, 154]. Children with limited-disease LL, Murphy stages I and II, have a favorable prognosis with a long-term OS of 85–90 % but disease-free survival (DFS) rates of only 63–73 %.

Over the past 20 years, successful therapeutic approaches in patients with LL have varied and have included CHOP with mercaptopurine and MTX maintenance (POG) [167], LSA2L2 (CPM, vincristine, MTX, daunomycin, prednisone, cytarabine, thioguanine, asparaginase, BCNU, hydroxyurea; Memorial Sloan-Kettering Cancer Center [MSKCC]) [153], COMP (CPM + oncovin + MTX + prednisone; CCG) [168], and modified LSA2L2 with the addition of HD MTX [169]. The need for local radiotherapy, especially to the mediastinum, has been virtually eliminated. The addition of CNS prophylaxis with HD MTX for either 7 or 12 doses depending on CNS status, reserving cranial radiation only for those who are CNS positive, was shown to be equally, if not more, effective, thus avoiding the need for cranial irradiation in CNS-negative patients [154, 170, 171].

The treatment for limited-stage disease (I/II) LL in the AYA group has been quite varied. Most AYA patients, both limited stage and advanced stage (III/IV), have received similar treatment regardless of initial staging. The probability of OS of limited-stage LL in the AYA group varies from 40 % to 60 % [157]. Hoelzer et al. reported a 5-year OS rate for stage I/II LL in AYA of 56 ± 24 % in the German ALL studies (GMALL) [172]. Few studies of LL in the AYA age group have utilized involved-field radiotherapy, and most studies have utilized either CHOP, BFM, LSA2L2, BACOP (bleomycin + epidoxorubicin + CPM + VCR + prednisone), or M-BACOD (MTX + bleomycin + doxorubicin + CPM + VCR + dexamethasone)-type multiagent chemotherapy regimens.

The prognosis for children with advanced LL has improved significantly since the introduction of the ten-drug LSA2L2 regimen by Wollner et al. at MSKCC [173]. The CCG subsequently compared LSA2L2 with COMP in advanced LL in children [174]. The 5-year EFS for children with advanced-disease LL treated with LSA2L2 in comparison with COMP was significantly better (64 % vs. 34 %, $p < 0.001$ [174]. Recent excellent results have also been demonstrated without the requirement of involved-field radiotherapy [154]. Treatment approaches for childhood advanced LL have varied, with many pediatric cooperative groups investigating ALL-based therapeutic regimens. An OS of 60–90 % has been demonstrated using a variety of multiagent chemotherapy regimens ranging from 12 to 32 months of therapy (Table 4.13) [152–155, 169, 174–180]. More recently, excellent results (including a 90 % EFS) have been demonstrated with the BFM NHL90 protocol, which utilizes HD MTX, dexamethasone, moderate doses of anthracyclines, and CPM, as well as prophylactic cranial radiation, with a treatment stratification based upon tumor response to induction therapy [154]. The treatment for advanced-stage (III/IV) LL in the AYA group has also been varied. The probability of DFS in advanced-stage (III/IV) LL in the AYA group has ranged from 30 % to 60 % [157]. Initial results with an LSA2L2-like regimen by Coleman et al. [181] and the Stanford group in 44 patients with LL yielded a 56 % 3-year DFS. Morel et al. in a French cooperative series of studies utilizing CHOP, LNH84, FRALLE, and LALA demonstrated a 33–53 % DFS in adolescent and young

Table 4.13 Outcome results in adolescents/young adults with advanced lymphoblastic lymphoma

	German (Hoelzer et al.)	ECOG (Colgan et al.)	Stanford (Coleman et al.)	France (Morel et al.)	Italian (Zinzani et al.)
# patients	45	39	44	80	106
Protocol	GMALL89	CHOP/LAS	LSA_2L_2	CHOP, LNH84, FRALLE, LALA	L17, L0288
Duration (mos)	12	15	12	12–15	12–15
DFS	57 %	49 %	56 %	33–53 %	56 %

DFS disease-free survival, *ECOG* Eastern Cooperative Oncology Group, *CHOP* cyclophosphamide + doxorubicin + vincristine + prednisone, *LASP* l-asparaginase)

adult patients with advanced LL [182]. Zinzani et al. reported for the Italian cooperative studies an overall 56 % 10-year DFS in patients with advanced LL treated on successive Italian studies (L17, L0288, L20) [183]. More recently, Hoelzer et al. utilizing two German ALL protocols (GMALL89 and GMALL93) reported a 57 % 3-year DFS in AYA patients with advanced LL (Table 4.13) [172]. Finally, Thomas et al. at the MD Anderson Cancer Center has piloted the use of hyperfractionated-CVAD (CPM + doxorubicin + VCR + dexamethasone) in AYA with advanced LL and demonstrated in early results a 3-year DFS of 72 % [157]. In comparison with the results with treatment for advanced LL in children vs. AYA, the outcome appears to be superior in children with the use of pediatric-designed treatment protocols (Table 4.13).

Additional approaches for advanced LL in the AYA group have been the use of high-dose therapy and autologous or allogeneic HSCT. Bouabdallah et al. reported the results of allogeneic HSCT ($n=12$; 11 underwent the procedure during their first complete remission (CR1) and autologous HSCT ($n=18$; 16 = CR1) in AYA patients with advanced LL [184]. The overall 5-year EFS for all transplant patients was 66 % compared to 33 % in a similar group of patients not transplanted ($p<0.01$) [184]. The allogeneic subgroup had an OS of 78 %, compared to 50 % in the autologous transplant group ($p<0.06$) [184]. Sweetenham et al. randomized AYA patients (median age = 26 years) with advanced LL in CR1 to high-dose therapy and autologous peripheral blood stem cell transplantation (PBSCT) vs. continued chemotherapy [185]. The relapse-free survival was 55 %, in the autologous PBSCT group compared with 24 % in the chemotherapy group. In a retrospective analysis of autologous PBSCT vs. allogeneic HSCT in patients with LL reported to the International Bone Marrow Transplant Registry and Autologous Blood and Marrow Transplant Registry, Levine et al. demonstrated that the relapse rate was significantly lower in allogeneic HSCT recipients at 1 and 5 years (32 % vs. 46 %, $P=0.05$, and 34 % vs. 56 %, $P=0.004$, respectively; Fig. 4.15) [186]. These results suggest that there may be an allogeneic graft vs. lymphoma effect in AYA patients with advanced LL.

Despite significant advances in both limited as well as advanced disease, patients with relapsed T-LL have a dismal prognosis with reported 3-year EFS rates of <15 % [187]. Thus, current strategies for the treatment of LL involve modifications of currently successful ALL-type protocols to incorporate newer targeted agents up front in order to improve the OS of the 15–20 % of patients that are refractory or relapsed. Nelarabine has been a particularly promising agent for T-cell malignancies. Nelarabine is a water-soluble prodrug of araG that is resistant to cleavage by endogenous purine nucleoside phosphorylase, thus accumulating in T-cells more so than B-cells making it very cytotoxic to T-lymphoblasts at low concentrations. COG reported on a phase 2 trial using single agent nelarabine in relapsed T-cell malignancy and found a >50 % response rate [188]. In addition, as part of the NECTAR (nelarabine, etoposide, and cyclophosphamide) combination for relapsed T-LL, it was found to be effective with an overall response rate of 25 % in T-LL and well tolerated with few unexpected toxicities [189]. More data and larger cohorts are

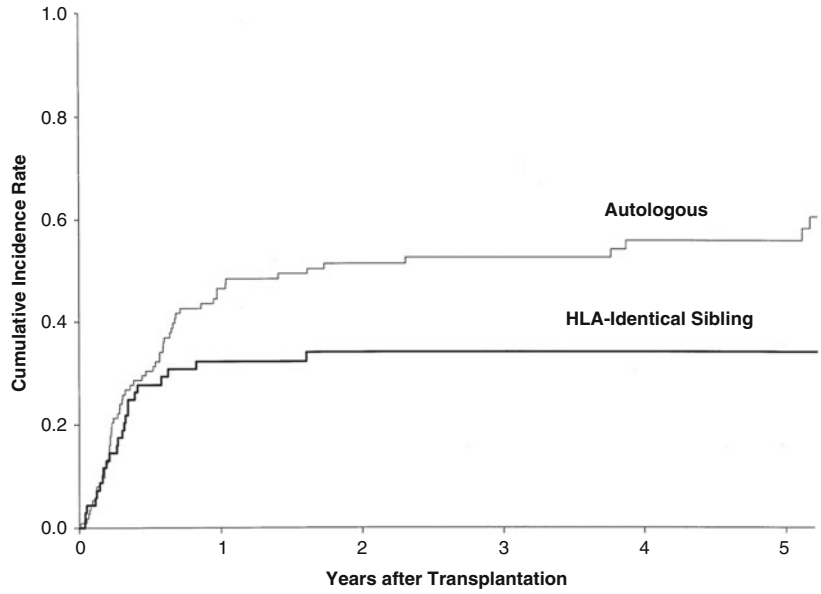


Fig. 4.15 A comparison of probability of relapse in patients with lymphoblastic lymphoma treated with HLA-identical sibling allogeneic transplantation vs. autologous transplantation. This research was originally published in Blood (Levine et al. [186]. © by the American Society of Hematology)

needed to better define activity of this drug both in relapsed and up-front regimens, such as the recently completed COG T-ALL/T-LL trial. In addition to nelarabine, there is also some data to support the early use of the proteasome inhibitor bortezomib based on preclinical data and clinical trials in both children and adults. Bortezomib has been used both in relapse and up-front settings either alone or in combination with standard combination chemotherapy in T-cell as well as other NHL with an ORR around 75 % in most clinical trials and 3-year OS ranging from 40 % to 60 % [190–194]. Developments of preclinical models to study T-cell malignancies using mutant zebra fish will continue to provide more thoughtful new targets in the treatment of T-LL [195]. Overall, while promising, we are at the early stages of determining how best to use these newer agents and what the ultimate impact on OS and EFS will be in higher risk AYA patients.

In summary, AYA patients with advanced LL have benefited from the use of pediatric ALL-type chemotherapy regimens, long-term maintenance chemotherapy (12–24 months), aggressive intrathecal CNS prophylaxis, and high-dose therapy with HSCT in selected patients in CR1 and responders in their first partial remission or in their second complete remission. Additional research is required to determine the molecular basis of AYA LL, its relationship to pediatric LL, comparison to AYA T-ALL, mechanisms of drug resistance, and the development of novel targeted therapeutic approaches.

4.9 Rare Non-Hodgkin Lymphomas in Adolescents and Young Adults

Non-anaplastic peripheral T/NK-cell lymphomas and follicular lymphomas comprise approximately 5–15 % of all NHL that occur in AYA from ages 15 to 39 years of age with an increasing frequency of follicular lymphoma occurring between ages 25 and 39 years of age (Fig. 4.3).

Pediatric follicular lymphoma was recognized as a distinct novel variant of follicular lymphoma in the 2008 WHO classification [196]. The classical t(14;18)(q32;q21) translocation demonstrated in adult follicular lymphoma is generally absent in the pediatric follicular lymphoma variant similar to the rarity of BCL2 aberrations found in pediatric follicular lymphoma [27, 197]. True pediatric follicular lymphomas represent less than 2 % of NHL in children less than 15 years of age. Despite the majority of pediatric follicular lymphomas displaying a predominant grade 3 histological pattern (Fig. 4.16), patients with a

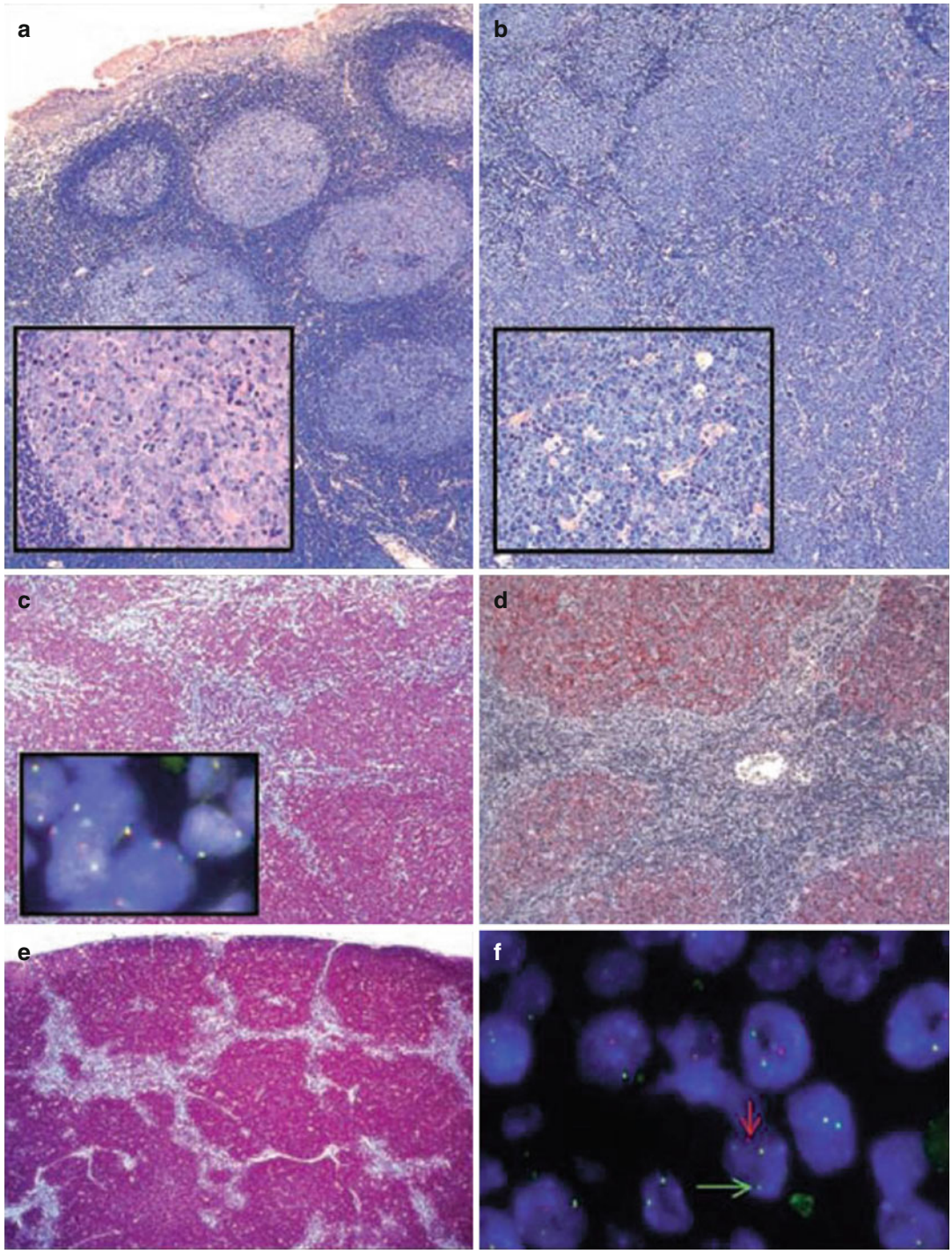


Fig. 4.16 Follicular lymphoma grade 3a involving the tonsil (**a**) with a simultaneous DLBCL component in deeper parts of the tumor (**b**) with higher magnification. In the inserts (**a** + **b** Giemsa stain). Strong expression of BCL2 (**c**) in the absence of *BCL2* breaks (insert in **c**) and dense networks of follicular dendritic cells positive for CD23 (**d**). A floral follicular growth pattern highlighted by staining for CD10 (**e**). Breaks in the *IGH* gene (**f**, *arrows* indicate the split signal) (From et al. [198]. Obtained from the Haematologica Journal website http://www.haematologica.org)

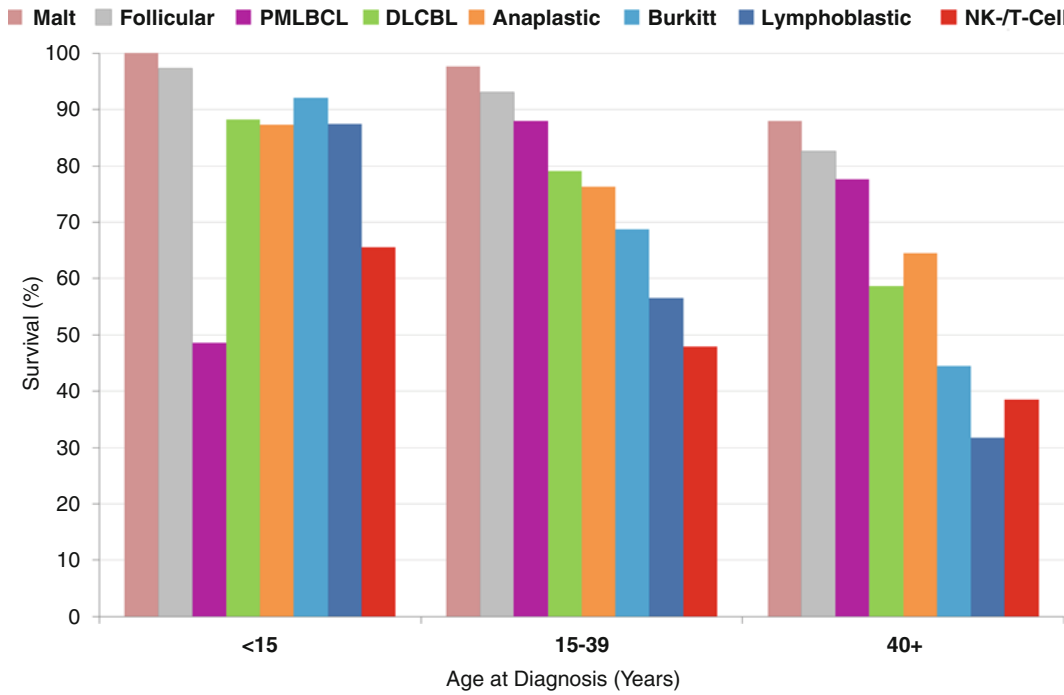


Fig. 4.17 NHL 5-year lymphoma-specific survival by histologic type and age, 2000–2011; United States SEER data

pediatric follicular lymphoma have an outstanding prognosis with an estimated 5-year EFS of 96 ± 4 % [198].

However, in the older age of the AYA group, the pediatric follicular lymphoma variant begins to disappear and the more classical adult follicular lymphoma begins to emerge displaying the classical t(14;18)(q32;q21) translocation juxtaposing BCL2 next to the immunoglobulin heavy chain (IGH). In this more common adult form, the majority of the follicular lymphomas are indolent, low-grade lymphomas of either grade 1 or grade 2 classification and rarely transform to a high-grade lymphoma, such as diffuse large B-cell lymphoma (DLBCL) [199, 200]. In general, the low-grade adult-type follicular lymphomas that occur in the 15–39 years age range have an excellent overall survival (OS) (≥85 % OS) (Fig. 4.17).

Non-anaplastic peripheral T/NK-cell lymphoma in AYA is extremely rare with an incidence of under 2 % (Fig. 4.3). If one excludes the most common forms of T-cell lymphoma in CAYA (T-lymphoblastic lymphoma and T-anaplastic large cell lymphoma), the next most common histological subtypes are peripheral T-cell lymphoma (PTCL) (not otherwise specified [NOS]), hepatosplenic γ/δT-cell NHL, subcutaneous panniculitis-like T-cell lymphoma (SPTCL), primary cutaneous γ/δ T-cell NHL, EBV^+ T-cell lymphoproliferative disease (LPD), extranodal NK-cell NHL, and angioimmunoblastic T-cell NHL (Fig. 4.18) [201]. However, there are many other even rarer subtypes of T/NK lymphomas that can occur with AYA range as defined by the WHO 2008 classification (Table 4.11) [196].

The prognosis of children and adolescents with non-anaplastic peripheral T/NK-cell lymphoma, especially PTCL NOS, has generally been better than what has been reported in adults [201–205]. In general, children and adolescents with PTCL NOS have an approximately 50–60 % 5-year EFS; however, those with either NK/T or hepatosplenic TCL have a dismal prognosis (≤20 % 5-year EFS) (Fig. 4.19) [204]. In contrast, young adults and older adults with peripheral T/NK-cell NHL (excluding ALCL) have a very dismal prognosis with 10-year EFS of ≤20–30 % (Fig. 4.20) [205].

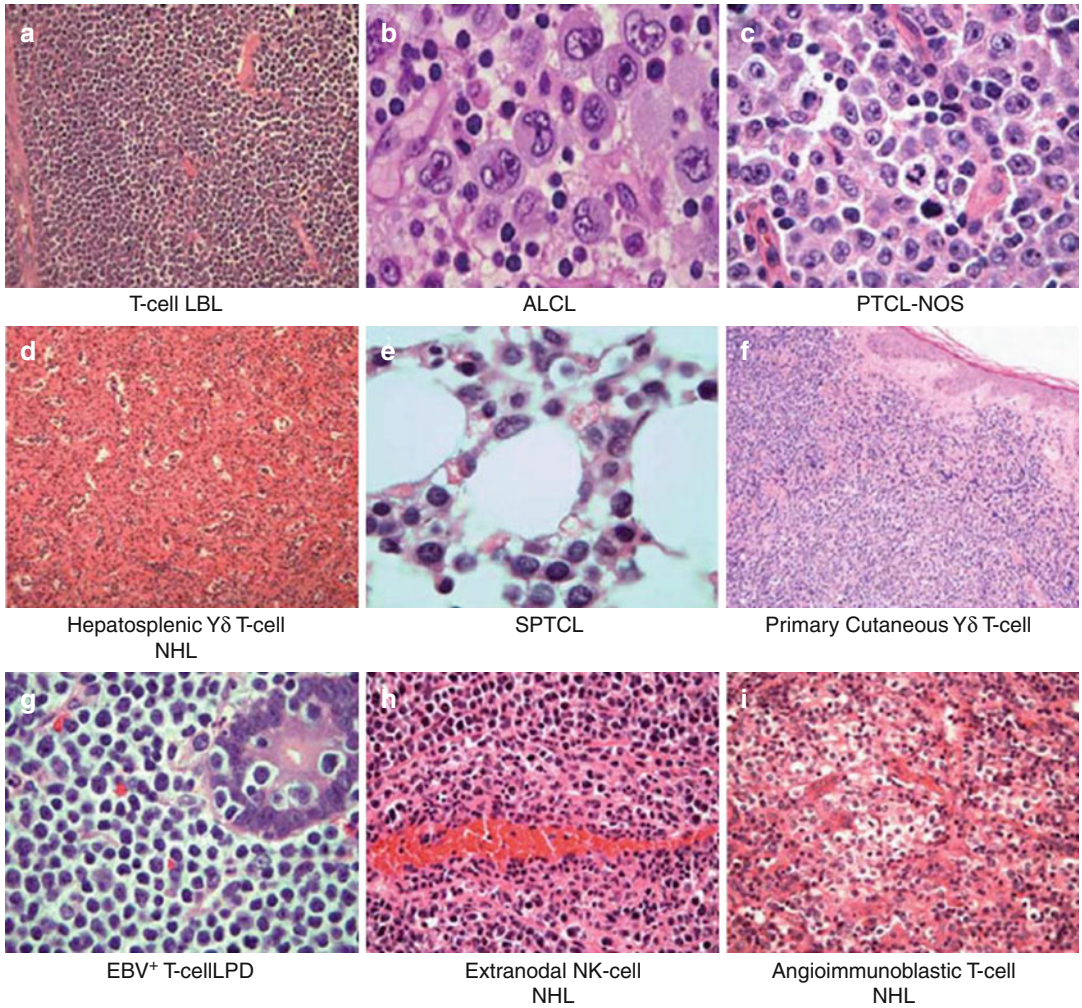


Fig. 4.18 Montage of pathology images for several different T- and NK-cell lymphomas in children and adolescents. (**a**) T-lymphoblastic lymphoma (T-LBL) showing diffuse infiltration of T-lymphoblasts with fine nuclear chromatin and scarce cytoplasm. Blasts have inconspicuous nucleoli and irregular nuclear contours. 200× magnification, H&E stain. (**b**) Anaplastic large cell lymphoma (*ALCL*), *ALK*$^+$, showing large neoplastic cells with marked pleomorphism and abundant cytoplasm. Characteristic horseshoe-shaped cells are seen. Cells stained strongly with CD30 and ALK antibodies demonstrate a mature T-cell immunophenotype. 400× magnification, H&E. (**c**) Peripheral T-cell lymphoma (*PTCL*), NOS with predominantly large cell morphology. Neoplastic cells are large with abundant cytoplasm and variably prominent nucleoli. Immunophenotyping reveals a mature T-cell phenotype, but cells lack expression of CD30 or ALK. 400× magnification, H&E. (**d**) Hepatosplenic gamma/delta T-cell lymphoma. Small-to-intermediate neoplastic cells have infiltrated liver sinusoids. These cells show round nuclear contours, clumped chromatin without prominent nucleoli, and abundant clear cytoplasm. 100× magnification, H&E. (**e**) Subcutaneous panniculitis-like T-cell lymphoma (*SPTCL*) demonstrating invasion of malignant cells into fat. Small-to-intermediate-size neoplastic cells with moderate cytologic atypia and irregular nuclear contours surround fat lobules. 400× magnification, H&E. (**f**) Primary cutaneous gamma/delta T-cell lymphoma that presented with skin nodules and plaques with extensive dermal involvement and extension into panniculitic fat. Medium-to-large neoplastic cells have occasional prominent nucleoli. Neoplastic cells lacked CD4 and CD8 expression and were EBV negative. 200× magnification, H&E. (**g**) T-cell posttransplant lymphoproliferative disorder in a patient with liver transplant 2 years prior. Clonal T-cells have invaded the intestine and are EBV positive. (**h**) Extranodal T/NK-cell lymphoma of the nasal cavity showing angiocentric pattern with vascular invasion. Neoplastic cells are small-to-intermediate in size with abundant cytoplasm. Irregular nuclei show clumped hyperchromatic chromatin. Cells are CD8 and EBV positive. 400× magnification, H&E. (**i**) Angioimmunoblastic T-cell lymphoma (*AITL*) with diffuse nodal effacement and prominent arborizing vessels. Neoplastic cells are intermediate size and show variable clear cytoplasm. 200× magnification, H&E (From El-Mallawany et al. [201])

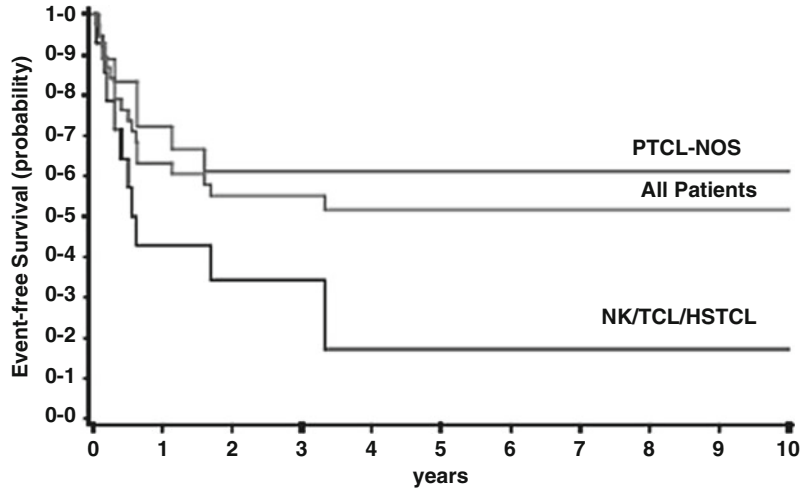


Fig. 4.19 Kaplan-Meier estimates of event-free survival (*EFS*) for all patients and the subgroups of PTCL NOS and combined group of natural killer (*NK*)/T-cell lymphoma (*TCL*) and hepatosplenic T-cell lymphoma (*HSTCL*). The 5-year EFS was 52 %, 61 %, and 17 % (Used with permission from Wiley: Kontny et al. [204], copyright (2015))

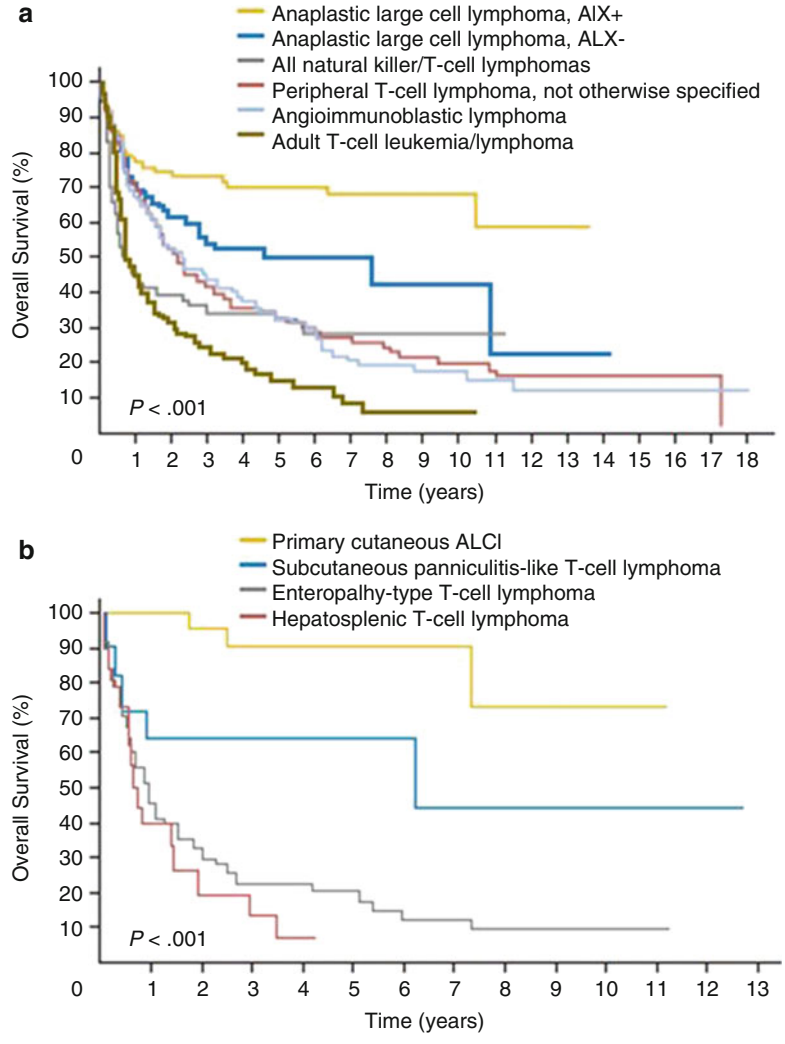
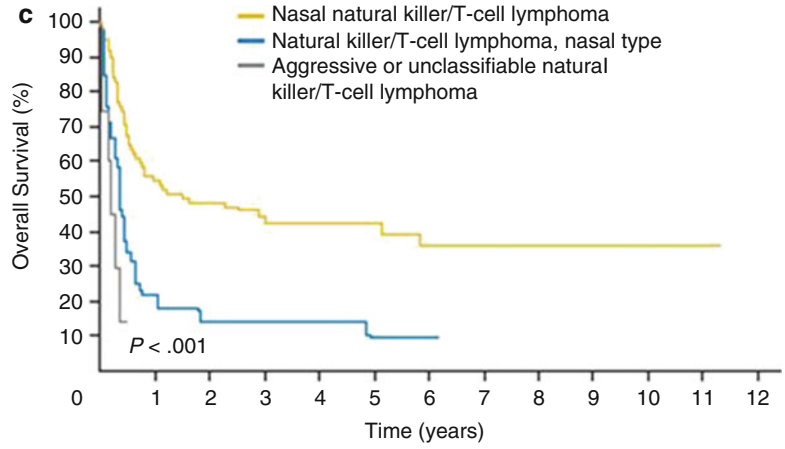


Fig. 4.20 (**a**) Overall survival of patients with common subtypes of peripheral T-cell lymphoma (*PTCL*). (**b**) Overall survival of patients with less common subtypes of PTCL. (**c**) Overall survival of patients with natural killer T-cell lymphoma (Vose et al. [205]. Reprinted with permission. © (2008) American Society of Clinical Oncology. All rights reserved)

Fig. 4.20 (continued)



New advances in the treatment of peripheral T/NK-cell lymphomas include the use of targeted antibodies, small molecular-targeted inhibitors and the use of stem cell transplantation. The recent use of L-asparaginase in a reinduction regimen known as "SMILE" (steroid [dexamethasone], methotrexate, ifosfamide, L-asparaginase and etoposide) has resulted in significant overall responses in patients with relapsed/refractory and now newly diagnosed extranodal NK/T-cell lymphoma [206]. Pralatrexate has recently been approved for patients with relapsed/refractory PTCL NOS [207]. Two monoclonal antibodies have also recently been tested in peripheral T/NK-cell NHL, i.e., the anti-CD30 antibody, brentuximab vedotin, and the anti-CCR4 antibody, mogamulizumab, and both have been shown to be safe and with significant efficacy [208–210]. More recently, both autologous and allogeneic stem cell transplantations have also been demonstrated to play an important role in improving EFS in peripheral T/NK-cell NHL especially in the rarer subtypes with a uniformly bad prognosis and also as consolidation therapy in better risk patients (Figs. 4.21 and 4.22) [211, 212].

4.10 Overall Survival

Overall 5-year survival rates of patients with all types of NHL by era during the past 35 years are shown in Fig. 4.23 as a function of diagnosis. Progress was most significant in children and young adolescents, with an increase from about 50 % to over 89 %. Similarly, among 15- to 39-year-olds, little progress was achieved until the 1990s, when the 5-year survival rate increased from about 50 % to 85 % in 2010 (Fig. 4.23).

For specific histologies of NHL in AYA, the current 5-year survival rates are approximately 98 % for MALT, 92 % for follicular, 88 % for PMLBCL, 78 % for DLBCL, 75 % for ALCL, 68 % for BL, and 55 % for LL, according to the SEER 2000–2011 data (Fig. 4.17).

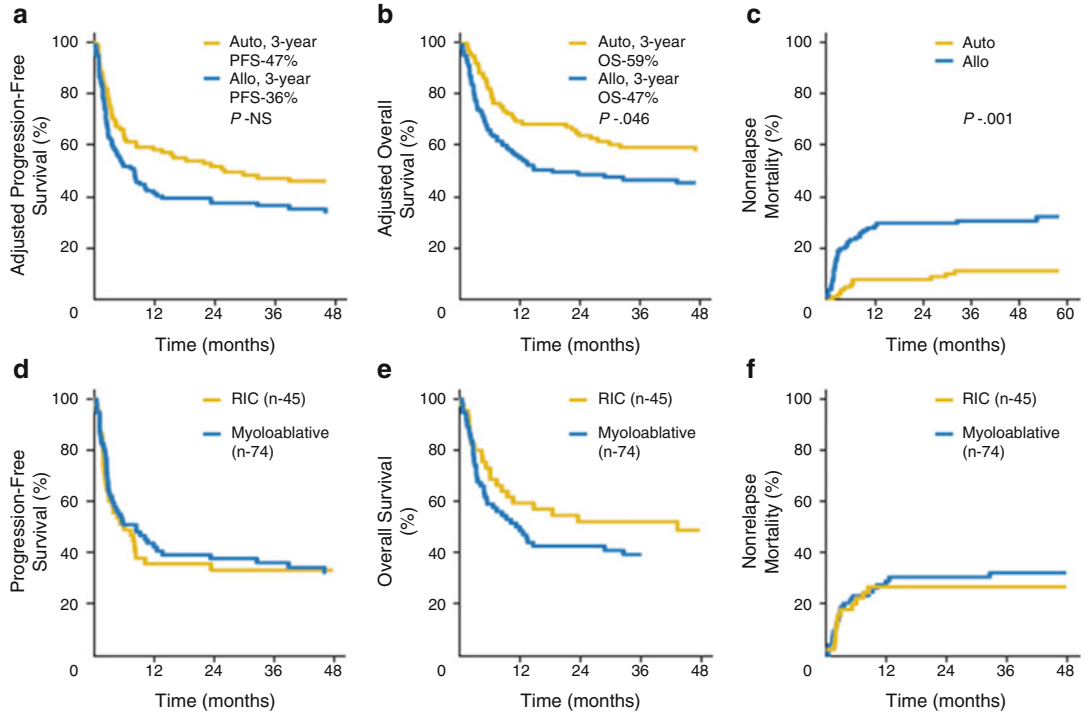


Fig. 4.21 (**a**) Adjusted progression-free survival (*PFS*), (**b**) adjusted overall survival, and (**c**) nonrelapse mortality (*NRM*) for all patients ($n=24$). (**d**) PFS, (**e**) OS, and (**f**) NRM for patients who underwent nonmyeloablative stem cell transplantation/reduced-intensity conditioning (*RIC*) versus myeloablative allogeneic hematopoietic cell transplantation (all). *NS* not significant (Smith et al. [211]. Reprinted with permission. © (2013) American Society of Clinical Oncology. All rights reserved)

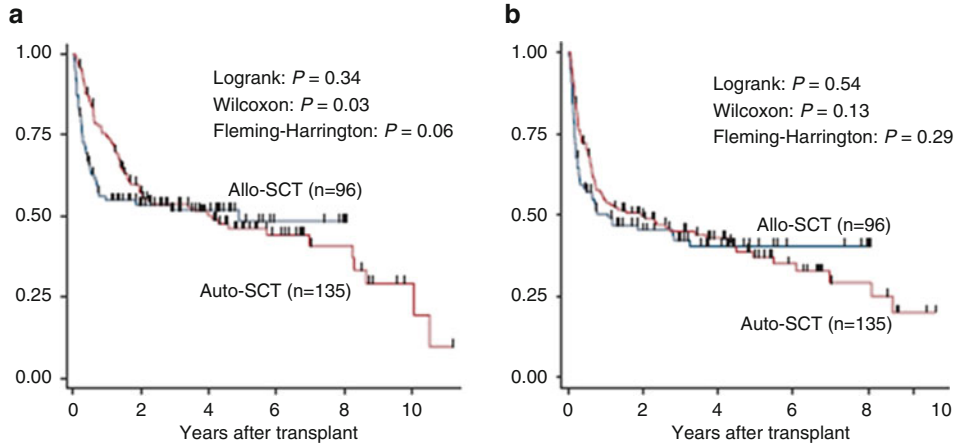
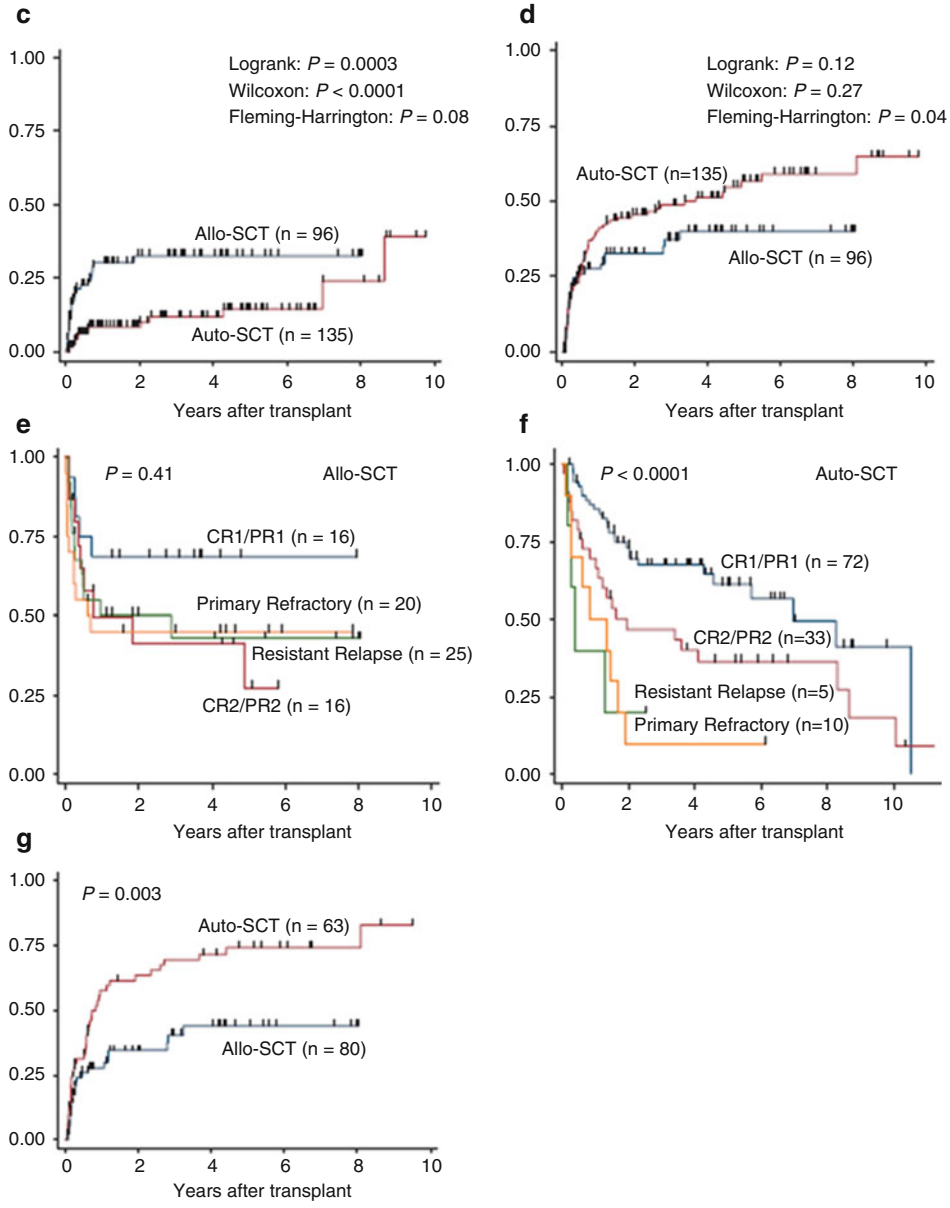


Fig. 4.22 Clinical outcomes. (**a**) OS in the allo- and auto-SCT groups. (**b**) Progression-free survival in the allo- and auto-SCT groups. (**c**) Non-relapse mortality in the allo- and auto-SCT groups. (**d**) Relapse/PD in the allo- and auto-SCT groups. (**e**) OS stratified according t the disease status at time of transplantation in the allo-SCT group. (**f**) OS stratified according to the disease status at time of transplantation in the auto-SCT group. (**g**) Relapse/PD in the non-CR1/PR1 in the allo- and auto-SCT groups (Reprinted by permission from Macmillan Publishers Ltd: Leukemia, 27:1394–1397, copyright (2013))



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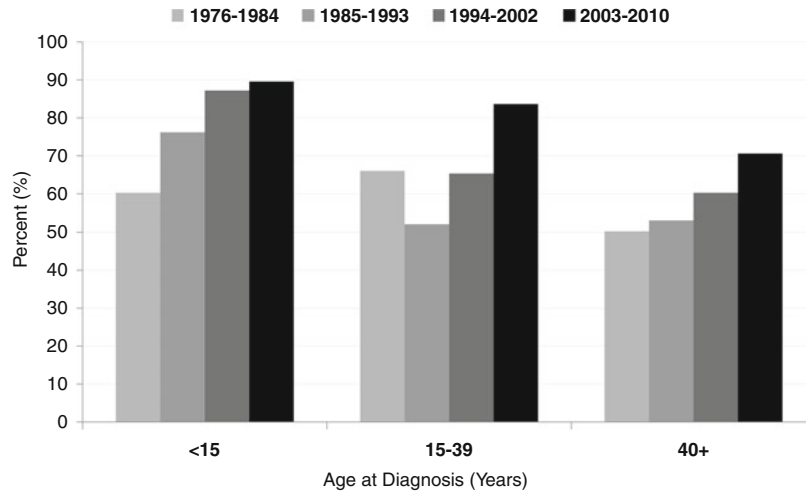

Fig. 4.23 Five-year survival of non-Hodgkin lymphoma patients by age between 1976 and 2010; United States, SEER data

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Hodgkin Lymphoma

5

Ralph M. Meyer

5.1 Introduction

Hodgkin lymphoma is a cancer of the lymphoid system that carries substantial importance in understanding the principles of cancer control for adolescent and young adult patients [1]. The disease typically involves lymph nodes with more disseminated disease patterns including the spleen, bone marrow, liver, and other extranodal sites. It is the most common cancer diagnosis in patients between the ages of 15 and 24 years and over 40 % of newly diagnosed Hodgkin lymphoma patients will be between the ages of 15 and 34 years [2]. Hodgkin lymphoma was an initial setting for demonstrating the curative potentials of radiation treatment and combination chemotherapy and patients with recurrent Hodgkin lymphoma were among the first to receive long-term benefits from treatment with autologous stem cell transplantation [3]. The 5-year survival of adolescent and young adult Hodgkin lymphoma patients is now in excess of 90 % [2]. With such curative potential in a population free of comorbidities that would otherwise affect survival, the management of patients with Hodgkin lymphoma characterizes the challenges of optimizing the balance between maximizing the eradication of the cancer and minimizing the late effects associated with the treatments provided.

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5.2 Epidemiology

5.2.1 Incidence

When considering patients of all ages, Hodgkin lymphoma is uncommon with an annual incidence in the United States of 2.7 persons per 100,000 and approximately 9,000 new patients diagnosed annually, thus accounting for 0.5 % of all new cancer diagnoses [2]. Unlike non-Hodgkin lymphoma, which has shown increases in incidence in the adolescent and young adult age groups (and also among older adults), no substantive change in the incidence pattern of Hodgkin lymphoma has been observed in the United States between 1975 and 2012 [2].

5.2.1.1 Age and Gender

The overall median age of patients with Hodgkin lymphoma is 38 years [2]. In respective 5-year age groups for patients between the ages of 15 and 39 years, the incidence of Hodgkin

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lymphoma is highest in 20–24-year-olds (4.3 and 4.6 per 100,000 in males and females, respectively) (Table 5.1) [2]. Because of the uncommon frequency of other cancer diagnoses in these age groups, the incidence of Hodgkin lymphoma accounts for a substantial percentage of cancer diagnoses that ranges between 13 % and 15 % in the 15–19-year males and females, respectively, to 3 % and 1 % in the 35–40-year males and females, respectively; this decreasing percentage of Hodgkin lymphoma related to other cancers is because of the more frequent diagnoses of other cancers associated with advancing age [2].

Hodgkin lymphoma is rare in patients less than 10 years of age (less than 0.5 per 100,000) and uncommon in those less than 10–14 years of age (1.3 per 100, 000; fewer than 3 % of all cases of Hodgkin lymphoma) [2]. Using Surveillance, Epidemiology and End Result (SEER) data, the most frequent age grouping for patients with newly diagnosed Hodgkin lymphoma is 20–34 years (Table 5.2) [2]. While traditionally Hodgkin lymphoma is described as being associated with a bimodal age distribution that includes an elderly population, the smaller size of the population greater than 65 years means that more than 80 % of newly diagnosed patients are younger than 65 years.

When considering all patients, the incidence of Hodgkin lymphoma in the United States is greater in males than females (3.0 vs. 2.4 per 100,000, respectively) [2]. Within the adolescent and young adult populations, Hodgkin lymphoma is associated with a greater incidence in females in the 15–29-year age groups and is more frequent among males in older patients. Such discrepancies were not observed in the United Kingdom [4], where Hodgkin lymphoma is more common among males within all ranges of the adolescent and young adult population (Table 5.3).

Table 5.1 Incidences of Hodgkin lymphoma by age and gender in the United States (Surveillance, Epidemiology and End Result data 2008–2012) [2]

Age group (years)	Incidence of Hodgkin lymphoma in the United States[a]		Percent Hodgkin lymphoma of all cancers		Estimated number of annual new cases of Hodgkin lymphoma
	Males	Females	Males (%)	Females (%)	
15–19	3.0	3.3	13	15	1,167
20–24	4.3	4.6	12	12	2,851
25–29	4.0	4.1	8	6	
30–34	3.8	3.5	6	3	
35–39	3.1	2.5	3	1	Not available

[a]Incidence is per 100,000 persons

Table 5.2 Percentage of annual new cases of Hodgkin lymphoma by age group in the United States (Surveillance, Epidemiology and End Result data 2008–2012) [2]

Age group (years)	Percent of all new cases of Hodgkin lymphoma
<20	12.9
20–34	31.5
35–44	14.0
45–54	12.8
55–64	11.0
65–74	9.0
75–84	6.5
>84	2.3

Table 5.3 Incidences of Hodgkin lymphoma by age and gender in the United States (Surveillance, Epidemiology and End Result data 2008–2012) [2] and United Kingdom (Cancer Research UK) [4]

Age group (years)	Incidence of Hodgkin lymphoma in the United States[a]		Incidence of Hodgkin lymphoma in the United Kingdom[a]	
	Males	Females	Males	Females
15–19	3.0	3.3	3.8	3.5
20–24	4.3	4.6	4.8	4.3
25–29	4.0	4.1	4.5	4.0
30–34	3.8	3.5	3.9	2.8
35–39	3.1	2.5	3.8	2.8

[a]Incidence is per 100,000 persons

5.2.1.2 Race and Ethnicity

The incidence of Hodgkin lymphoma is greatest in white populations with age and gender distributions as described above [2]. However, differences in incidence between white and black populations predominantly exist in the 15–24 age groups and disappear with advancing age through the young adult continuum. The incidence is lower among Hispanic populations, with these differences persisting through the entirety of the adolescent and young adult age ranges. Given the uncommon nature of Hodgkin lymphoma and high overall cure rates, it is not possible to reliably detect differences in mortality by ethnicity.

5.3 Etiology and Pathogenesis

New understandings of the etiology and pathogenesis of Hodgkin lymphoma have evolved over the past 5 years [5, 6]. Central to these understandings are the pathognomonic feature of the disease, the Hodgkin and Reed-Sternberg (HRS) cell of classic Hodgkin lymphoma (see Sect. 5.4, Pathology), and the role of the Epstein-Barr virus (EBV) [5, 7, 8]. The etiology of Hodgkin lymphoma remains uncertain and, like most cancers, likely includes a range of molecular subtypes that lead to common histologic appearances. The association of EBV with Hodgkin lymphoma has been known for decades [8]; recent observations show population-based heterogeneity in this association. In the Western world, 40 % of patients with classical Hodgkin lymphoma demonstrate infection of HSR cells with EBV; in contrast, 90 % of pediatric cases in Central America are infected [5, 8].

Hodgkin lymphoma is unusual in that the up to 99 % of the cancerous tissue is comprised of surrounding non-malignant cells that make up the tumor microenvironment [6]. The microenvironment includes neutrophils and macrophages, lymphocytes and plasma cells, and dendritic and mast cells. In classical Hodgkin lymphoma, as few as 1 % of the cellular material is comprised of malignant HRS cells. These HRS cells are germinal B-cells (GBCs) that, after acquiring unfavorable somatic mutations, undergo transformative molecular events that rescue these cells from apoptosis [5, 7]. This transformative process may be in association with EBV infection. The transformed HRS cells commonly overexpress the transcription factor NF kappa B (NFKB), with multiple molecular alterations in NFKB regulation described [5]. The dysregulation of the NFKB pathway promotes HRS cell survival and may be crucial to the pathogenesis of Hodgkin lymphoma. In addition to the NFKB pathway, other molecular pathways may be affected; alterations of the JAK/STAT pathway are commonly described and may be associated with changes in the tumor microenvironment that contribute to loss of immunosuppression, which permits HRS cell survival [5, 7].

Together these molecular findings are consistent with three main risk factors associated with Hodgkin lymphoma: previous EBV infection, immunosuppressive disorders including human immunodeficiency virus infection, and a family history of Hodgkin lymphoma. Family clustering of Hodgkin lymphoma is well described and may be a result of somatic mutations that facilitate the transformative molecular events that lead to HRS cells and their survival.

5.4 Pathology

The current pathologic classification of Hodgkin lymphoma is based on the Revised European American Lymphoma classification schema of 1994 [9], which was updated in the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues in 2008 [10]. Hodgkin lymphoma is subdivided into two major forms: classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). The diagnosis of classical Hodgkin lymphoma requires demonstration of HRS cells and comprises 95 % of cases. Classical Hodgkin lymphoma includes four histologic subtypes: nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted. The nodular sclerosing subtype is most common, especially in adolescents (approximately 85 % in adolescents and 65–75 % in adults) [11, 12]. In

comparison with adults, the incidence of mixed cellularity histology is less frequent in the adolescent population (20 % vs. 10 %).

About 5 % of Hodgkin lymphoma patients, both adolescents and adults, are diagnosed with the NLPHL subtype, which is associated with demonstration of lymphocyte-predominant (LP) cells [11]. In contrast to classical Hodgkin lymphoma, the pathogenesis of NLPHL does not include the same association with EBV as LP cells are rarely infected with the virus [5]. Separating classical Hodgkin lymphoma from NLPHL is integral to patient management as the clinical course, treatment, and prognosis include important differences.

While the pathognomonic HRS cell typically differentiates classical Hodgkin lymphoma from various forms of non-Hodgkin lymphoma, diagnostic uncertainties can exist, including histologic and molecular resemblances of the two diseases that overlap into the entity of grey zone lymphomas. Gray-zone lymphomas likely represent distinct genetic variants of lymphoproliferative cancers and need to be distinguished from the diagnostic challenges associated with differentiating forms of classical Hodgkin lymphoma from anaplastic large cell lymphoma and primary mediastinal large B-cell lymphoma (Sect. 5.6.1, Diagnosis).

5.5 Presenting Features

The presenting features of patients with Hodgkin lymphoma can be considered in two main categories: those who present with painless lymphadenopathy and those who present with other symptoms. Those presenting with other symptoms typically have one of the B symptoms associated with clinical staging (Table 5.4), which include fever, weight loss, and/or night sweats [13]. Approximately 35 % of patients will present with B symptoms, with no clear differences in symptom patterns observed between pediatric, adolescent, and adult populations [11, 12, 14].

The anatomical distribution of adenopathy includes supradiaphragmatic nodes in 95 % of cases; adenopathy limited to a subdiaphragmatic distribution is seen in less than 5 % of cases and is disproportionately associated with NLPHL pathology. The most common sites of adenopathy include the posterior triangle of the neck, the axilla, and the mediastinum. Across all age groups, mediastinal adenopathy is observed in 60 % of cases [11, 12, 14]. Among those with mediastinal adenopathy, half will have bulky disease, historically defined as a mass with a diameter that exceeds one-third of the thoracic diameter on standard imaging. These patients commonly present with persistent cough and less commonly with chest pain and shortness of breath. As with B symptoms, no differences in mediastinal involvement or presence of bulky disease are observed in adolescent versus adult populations. Rarely patients will present with distinct symptoms associated with Hodgkin lymphoma: two well-described syndromes are intractable pruritus and pain in a region affected by adenopathy associated with alcohol intake. For those patients with intractable pruritus and no palpable adenopathy, evaluations assessing for mediastinal adenopathy are crucial.

Given the most common presentation of painless adenopathy, differential diagnoses include

Table 5.4 Staging of Hodgkin lymphoma: Ann Arbor staging system including Cotswold modifications [13, 18]

Stage	Disease involvement
I	Single lymph node region (I) or one extralymphatic site (I_E)
II	Two or more lymph node regions, on the same side of the diaphragm (II) or local extralymphatic extension plus one or more lymph node regions on the same side of the diaphragm (II_E)
III	Lymph node regions on both sides of the diaphragm (III), which may be accompanied by local extralymphatic extension (III_E)
IV	Diffuse involvement of one or more extralymphatic organs or sites
A	No B symptoms
B	Presence of at least one of: unexplained weight loss >10 % baseline during 6 months prior to staging; recurrent unexplained fever >38 °C; recurrent night sweats
X	Bulky tumor: either a single mass exceeding 10 cm in largest diameter or a mediastinal mass exceeding one-third of the maximum transverse transthoracic diameter measured on a standard posterior-anterior chest radiograph

infectious etiologies, including EBV, noninfectious inflammatory etiologies, and malignancies. The differential diagnosis of EBV infection is more common in the adolescent and young adult population given the incidence of infectious mononucleosis in this age group.

5.6 Diagnostic Testing

Standard baseline investigations are listed in Table 5.5. Additional evaluations as prompted by patient specifics may also be applicable.

5.6.1 Tissue Diagnosis

The definitive diagnosis of Hodgkin lymphoma requires a tissue biopsy. Processing of the excised tissue should include evaluations of morphology, immunohistochemistry, and flow cytometry by an experienced hematopathologist. The characteristic findings of classical Hodgkin lymphoma include detection of HRS cells that express the CD15 and CD30 antigens and the typical cellular background of the Hodgkin lymphoma microenvironment [6]. While the diagnosis is strongly suggested by detecting these findings from cytologic examinations of material obtained by fine needle aspirates, histologic examination of tissue obtained from biopsy remains the recommended standard.

Table 5.5 Baseline investigations for patients with Hodgkin lymphoma

History	Presence of fever, night sweats, weight loss
	Respiratory symptoms including cough and shortness of breath
	Presence of back or bone pain
Physical examination	Presence of lymphadenopathy, hepatosplenomegaly, pleural effusion
Laboratory	Complete blood count and white cell differential
	Serum creatinine, calcium
	Serum bilirubin and liver enzymes
	Total protein and albumin
	HIV and hepatitis B serology
Imaging	Computerize tomography of chest abdomen and pelvis
Bone marrow	Aspirate and biopsy (can be omitted with limited-stage disease and a normal complete blood count and in patients with no marrow signal on FDG-PET)
Biopsy	Lymph node biopsy with specialized review (see Sect. 5.6.1)
Others	Positron emission tomography scanning (see Sect. 5.6.3)
	Specialized imaging according to symptoms and signs

FDG fluorodeoxyglucose, *PET* positron emission tomography

5.6.2 Other Laboratory Studies

Other laboratory tests are necessary to determine prognosis (Sect. 5.7 and Table 5.6) and to facilitate management. A complete blood count may yield multiple abnormalities, including hypoproliferative anemia due to chronic disease or, rarely, to bone marrow infiltration. Autoimmune hemolytic anemia with a positive direct antiglobulin test is an uncommon cause of anemia and signifies an important complication requiring timely management. Abnormalities of white blood cells carry potential prognostic significance including leukocytosis and lymphopenia [15]. Standard evaluations of renal and liver function are necessary to consider comorbidities or complications from Hodgkin lymphoma that will affect eventual chemotherapy dosing; abnormalities of liver function may provide signals of hepatic involvement with Hodgkin lymphoma. A bone marrow biopsy has previously been considered a standard staging evaluation, but is now considered

Table 5.6 Prognosis of Hodgkin lymphoma: the International Prognostic Index [15]

Variable	Risk level
Serum albumin	<40 g/L
Hemoglobin	< 105 g/L
Gender	Male
Stage	Stage IV
Age	≥45 years
White cell count	$\geq 15 \times 10^9$/L
Lymphocyte count	$<0.6 \times 10^9$/L or <8 % of total while cell count

The number of factors present is totaled

unnecessary in those patients who have low-risk disease and a normal complete blood count. Evaluation of the bone marrow may also be avoided in patients who undergo fluorodeoxyglucose positron emission tomography (FDG-PET) with results demonstrating no marrow uptake [16].

5.6.3 Imaging Studies

The minimum standard for evaluating newly diagnosed patients with Hodgkin lymphoma includes computerized tomography (CT) of the chest, abdomen, and pelvis [16]. Careful evaluations of all nodal areas, including the mediastinum and retroperitoneum, are essential. In contrast to non-Hodgkin lymphoma, mesenteric nodal involvement is uncommon. In planning for patients who are to receive radiation therapy, CT of the neck is required to map radiation target volumes. Additional imaging, including ultrasonography and magnetic resonance imaging (MRI), may be important for evaluation of patient-specific symptoms or other diagnostic findings.

The role of FDG-PET, including as part of CT imaging, is now considered by some to be a standard of care [16]. The sensitivity of PET-CT to detect sites of Hodgkin lymphoma is superior to CT alone and can lead to upstaging of disease extent. However, two risks associated with routine use of PET-CT for staging purposes are recognized [17]. The first issue relates to the specificity of PET-CT and the risk of false-positive upstaging of Hodgkin lymphoma because of FDG avidity associated with inflammation. The second issue relates to clinical utility and current debates about optimum management: the sensitivity of PET-CT in detecting additional sites of nodal involvement with Hodgkin lymphoma may lead to prescriptions of larger radiation treatment target volumes. These larger target volumes may then increase risks of long-term treatment effects from radiation (see Sect. 5.9). As the role of radiation therapy is a subject of debate, the role of larger target volumes is associated with risk-benefit trade-offs.

5.7 Staging and Risk Assessment

As Hodgkin lymphoma includes an element of contiguous spread according to the anatomy of the lymphoid system and radiation therapy was historically the primary treatment modality, anatomical staging has, and continues to be, essential in determining prognosis and therapy. The Ann Arbor classification [18], modified at the Cotswolds meeting [13] and recently validated at the Lugano meeting [16], remains standard (Table 5.4). In contrast to non-Hodgkin lymphoma, the presence of B symptoms carries important implications for management. In addition, disease bulk, historically defined as a mediastinal mass greater than one-third of the chest diameter on standard imaging or of 10 cm in any dimension and now defined as any mass of 7 cm, carries therapeutic implications.

In addition to anatomic staging, the International Prognostic Index [15] has been used to stratify patients into risk categories (Table 5.6). This index has been of particular importance in clinical trials, both in reporting baseline characteristics of the populations studied and in developing therapeutic approaches for risk-specific populations. The elements of the index are nonspecific indicators associated with prognosis as determined through mathematical modeling. No direct biomarkers related to Hodgkin lymphoma biology have yet been shown to be predictive in that the presence or absence of the biomarker can be used to direct therapy in individual patients [19].

5.7.1 Risk Strata for Treatment Determination

Managing patients with Hodgkin lymphoma requires a process of risk stratification that is based on pre-therapy patient characteristics. From clinical trials conducted in adults, patients can be considered as having limited-stage (sometimes referred to as “early-stage”) disease or advanced-stage disease. Between these two strata, some investigators and practitioners

have included a group categorized as having intermediate-stage disease [20].

The most favorable prognostic group includes patients with stage 1A and 2A disease who have no bulky disease. All patients with stage 3 and 4 disease are considered as having advanced-stage disease. Patients with stage 2B disease, and those with stage 1–2A disease that includes bulky masses, may be considered as a subset of those with advanced-stage disease or can be considered as having intermediate-stage disease. The implications of these strata include the nature and duration of chemotherapy treatment and the role of radiation therapy (see Sect. 5.8). While the specifics of chemotherapy and radiation therapy have differed between adult and pediatric populations, these risk-stratification premises are consistent between these two age groups and can be applied to the adolescent and young adult population.

5.8 Therapy

5.8.1 General Principles

The principles of managing Hodgkin lymphoma in adolescents and young adults mirror those that are well described for pediatric [21] and adult populations [1]: there is a need to carefully balance the desire to maximally control the underlying cancer while minimizing the risks of long-term treatment-related toxicities or "late effects" (Sect. 5.9). Because of high expectations of cure and the overall young age of Hodgkin lymphoma patients relative to other cancers, long-term survival is expected and treatment-related effects can thus become apparent decades later.

Two important methodologic issues exist when interpreting clinical research related to optimum treatment strategies for the adolescents and young adult Hodgkin lymphoma population. First, it is not possible to directly observe in a timely manner the risks of late effects that are associated with current therapy; the requirement to follow current patients for at least a decade, and now for even longer durations, means that new therapeutic options will exist when the late effects of current therapies become well understood [22]. Second, there are no randomized trials directly comparing application of specific pediatric-based versus adult-based Hodgkin lymphoma treatments to the adolescent and young adult population [23]. Best evidence is thus limited to concurrent cohort comparisons and these have failed to consistently detect differences in outcomes between pediatric or adult-based approaches [11, 12, 14, 23]. More commonly cited evidence includes comparisons across case series and methodologic limitations associated with these data preclude an ability to make treatment recommendations [23]. Essential to managing these patients is that the therapeutic environment includes comprehensive care within an integrated health-care delivery system and, when possible, enrolment in high-priority clinical trials.

5.8.2 Management of Limited-Stage Hodgkin Lymphoma

The principles and methodologic issues associated with developing optimum treatment policies for adolescents and young adults are well illustrated by the challenges associated with analyses of evidence evaluating those with limited-stage disease, defined here as patients with stage 1A and 2A disease and no bulky disease. The goals of therapy are to eradicate the cancer with minimum risks of short- and long-term toxicity. A general principle associated with contrasting pediatric and adult literature is that children have greater tolerance for the short-term and acute treatment-related toxicity risks but are at increased risks of long-term late effects [21]. In both children and adults, recent clinical trials have increasingly focused on selecting therapies that will have fewer long-term risks and thus reduce or eliminate the use of radiation therapy and chemotherapy that includes alkylating agents and procarbazine [24]. The use of FDG-PET to tailor therapy using response-adapted principles is an evolving tool in addressing the aim of reducing treatment in a safe manner.

Randomized trials evaluating patients, including adolescent and young adults, can be exemplified in three generations: those evaluating combined modality therapy with incremental reductions in treatment components and doses [25–27], those evaluating chemotherapy alone [28, 29], and those testing response-adapted therapy through incorporation of FDG-PET with those patients demonstrating favorable mid-therapy FDG-PET results receiving chemotherapy alone [30, 31] (Table 5.7). These trials are predominantly performed in adult populations; given the demographics of patients with Hodgkin lymphoma, more than 50 % of these patients fall into the adolescent and young adult age range. Several principles can be derived from these trials. First, maximum disease control is achieved through use of combined modality therapy and this therapy can be minimized to include two cycles of Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD) and involved-field radiation therapy (IFRT) [25, 27, 32]. Second, there is to date no evidence that the magnitude of improved disease control achieved through use of combined modality therapy improves overall survival in comparison with treatment with

Table 5.7 Selected randomized trials evaluating patients with limited-stage disease

Group and trial	Control group	Experimental group	Median age (years)	Median follow-up	Comment
Combined modality therapy with incremental reductions in treatment components and doses					
EORTC H8 [26]	STNI	MOPP-ABV × 3 plus IFRT	30	7.7 years	Combined modality therapy improves event-free and overall survival
GHSG HD10 [25]	ABVD × 4 + IFRT	ABVD × 2 + IFRT[a]	39	6.5 years	Experimental group freedom from treatment failure was non-inferior to control group
GHSG HD13[27]	ABVD+ IFRT	Reduced agent ABVD+ IFRT	39	7 years[a]	Freedom from treatment failure is not non-inferior when bleomycin and dacarbazine are omitted from ABVD
Chemotherapy alone					
NCIC CTG/ ECOG HD.6 [28]	STNI or ABVD × 2 + STNI	ABVD × 4–6	36	11.3 years	Combined modality therapy improves freedom from disease progression but chemotherapy alone improves overall survival (see text)
CCG 5942 [29]	COPP-ABV ×4 + IFRT	COPP-ABV × 4	83 % were 10–19 years	7.7 years[b]	Combined modality therapy improves event-free survival but no difference in overall survival was detected (see text)
Response-adapted therapy through incorporation of FDG-PET					
EORTC H10 [30]	ABVD × 3 + IFRT	ABVD × 3	30	1.1 years	Progression-free survival is not non-inferior to combined modality therapy (see text)
UK RAPID [31]	ABVD × 4 + IFRT	ABVD × 3	34	5 years	Progression-free survival is not non-inferior to combined modality therapy (see text)

EORTC European Organization for Research and Treatment of Cancer, *GHSG* German Hodgkin Study Group, *NCIC CTG* National Cancer Institute of Canada Clinical Trials Group, *ECOG* Eastern Cooperative Oncology Group, *CCG* Children's Cancer Group, *UK* United Kingdom, *STNI:IFRT* subtotal nodal irradiation/involved-field radiation therapy, *ABVD* Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine, *MOPP-ABV* nitrogen mustard, Oncovin (vincristine), procarbazine, prednisone, Adriamycin (doxorubicin), bleomycin, and vinblastine, *COPP-ABV* cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone, Adriamycin (doxorubicin), bleomycin, and vinblastine

[a]Median follow-up varied by randomized group; maximum median follow-up was 7 years

[b]Trial included patients with all disease stages; a subset analysis of those with limited-stage disease was performed

chemotherapy alone. In fact, in the randomized trial associated with the longest follow-up, overall survival with chemotherapy alone was superior to that observed with combined modality therapy that included subtotal nodal radiation therapy (STNI) because chemotherapy alone was associated with fewer late effects; the limitation of that trial is that STNI represents excessive and outdated radiation therapy [28]. Third, response-adapted therapy through use mid-treatment FDG-PET appears to both increase the proportion of patients that can be considered for treatment with chemotherapy alone and to reduce the differences in disease control between combined modality therapy and chemotherapy alone; differences in favor of combined modality therapy remain [30, 31]. Last, these trials demonstrate the methodologic issues associated with simultaneously addressing goals of maximum disease control and a reduction in late treatment effects as the duration of follow-up required to evaluate late effects will be associated with the treatments being evaluated becoming outdated.

Results of large pediatric trials demonstrated similar themes (Table 5.8). The German Society of Pediatric Oncology and Hematology-Hodgkin's Disease (GPOH) has conducted two large trials that have included patients with limited-stage disease, with each concluding that radiation therapy can be omitted in selected patients [33, 34]. In the GPOH-HD95 trial, patients with early-stage disease who achieved a complete remission following chemotherapy did not receive radiation therapy and were observed to have excellent long-term disease control and overall survivals [34]. With shorter follow-up, the GPOH-HD-2002 trial also demonstrates excellent disease control outcomes in early-stage patients who achieve a remission with chemotherapy alone [33]. These trials exemplify the additional theme of reducing use of teratogenic and sterilizing chemotherapy as, in boys, procarbazine was replaced with etoposide in combination with Oncovin (vincristine), prednisone, and Adriamycin (doxorubicin) (OPPA vs. OEPA).

In North America, the Children's Cancer Group trial conducted a randomized trial comparing combined modality therapy with chemotherapy alone in patients with all stages of disease (Table 5.7) [29, 35]. In the subset of patients with low-risk disease, 10-year event-free survival was superior in those assigned to receive radiation therapy with no differences in 10-year overall survival detected [29]. The magnitude of difference in event-free survival was 10%, indicating that further refinement of criteria for omitting radiation therapy is necessary [36].

These treatment principles are now associated with long-term disease control in approximately 90% of patients and overall survivals of 95%. Conclusions from these data that are particularly applicable to the adolescent and young adult population include the issue of trade-offs associated with the competing outcomes and the need to have better understandings of how to apply

Table 5.8 Selected pediatric cohort trials evaluating patients with limited-stage disease

Group and trial	Criteria for no RT	Chemotherapy	Age criterion (years)	Median follow-up	Comment
Combined modality therapy with incremental reductions in treatment components and doses					
GPOH-HD95 [34]	CR after 2 cycles of chemotherapy	OPPA for girls OEPA for boys	<19	10 years	10-year PFS with chemotherapy alone was 97%; radiation therapy can be safely omitted in these patients
GPOH-HD-2002 [33]	CR after 2 cycles of chemotherapy	OPPA for girls OEPA for boys	< 19	4.9 years	5-year PFS with chemotherapy alone was 93%; radiation therapy can be safely omitted in these patients

GHOH German Society of Pediatric Oncology and Hematology-Hodgkin's Disease, *RT* radiation therapy, *CR* complete remission, *OPPA* Oncovin (vincristine), procarbazine, prednisone, and Adriamycin (doxorubicin), *OEPA* Oncovin (vincristine), etoposide, prednisone, and Adriamycin (doxorubicin), *PFS* progression-free survival

individual prognostic factors and determine patient preferences [37, 38]. The prognostic factor that to date has been shown to be most important is the response observed with chemotherapy: in both pediatric and adult trials, those achieving a complete remission as assessed using standard modalities have especially excellent outcomes [28, 33, 34]. The use FDG-PET appears to expand the size of the population who may safely have radiation therapy omitted, with recognition that disease control versus late-effect risk trade-offs remain [22, 30, 31]. Thus, current guidelines indicate that treatment with combined modality therapy or with chemotherapy alone is appropriate; and the role FDG-PET as a standard of care continues to be debated [39].

5.8.3 Management of Advanced-Stage Hodgkin Lymphoma

The management of patients with advanced-stage Hodgkin lymphoma is also based on the goals to eradicate cancer with minimum of toxic effects. However, important additional principles include identification of those at greatest risk of progressive Hodgkin lymphoma and the potential need for specific strategies to manage patients with bulky disease. Again, more adolescent and young adult patients have been included in clinical trials comparing therapies in adults; however, more pediatric patients with advanced-stage disease have been included in clinical trials as compared with pediatric patients with limited-stage disease, thus providing important contributions to policies for adolescents and young adults with advanced-stage disease.

For the past decade, the major debate in managing adult patients with advanced-stage Hodgkin lymphoma has centered on the choice of ABVD or a more intensive regimen developed in Germany that includes bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), prednisone, and procarbazine (BEACOPP) [40–43]. While other regimens have been tested, including those with a more abbreviated course of weekly chemotherapy combined with IFRT (e.g., Stanford V [44]), these have not been associated with outcomes that are superior to ABVD. In contrast, multiple trials comparing BEACOPP with ABVD, or therapy deemed to be equivalent to ABVD, consistently show BEACOPP improves long-term disease control (85–90% vs. 70–75%) [40, 41, 43] with some trials suggesting superior overall survival [40, 41]. The increased toxicity associated with BEACOPP, including high rates of gonadal toxicity with resulting sterility, and the lack of certainty associated with survival advantages have resulted in variations in practice with BEACOPP more commonly used in Europe and ABVD more commonly used in North America. Since the original reporting of BEACOPP, modifications to reduce treatment duration and to more selectively use IFRT in those with a residual mass, including with FDG-PET positivity, have been recommended based on results of sequential randomized trials [42]. While these refinements represent important advances, there remains ongoing debate about patient-specific choices of ABVD or BEACOPP and the balance of initial disease control and long-term toxic effects.

Clinical trials evaluating therapies for pediatric patients have included principles of increasing the dose intensity of drugs less associated with late effects and using response-adapted approaches to determine the extent of therapy. In North America, the Children's Oncology Group incorporated these principles into a regimen that includes Adriamycin (doxorubicin), bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) [45], with mid-treatment evaluation leading to early responders receiving more abbreviated treatment. This regimen now forms the control arm of a randomized trial in which the experimental arm includes brentuximab vedotin and eliminates bleomycin (Bv-AVEPC). The GPOH also evaluated dose-intense treatment that excludes procarbazine in a regimen that includes initial therapy with Oncovin (vincristine), etoposide, prednisone, and Adriamycin (doxorubicin) (OEPA) followed by consolidation treatment, with duration based on risk, which includes cyclophosphamide, vincristine, prednisone, and dacarbazine (COPDAC)

[33]. These regimens result in long-term disease control in 85–90 % of patients.

The role of radiation therapy has been evaluated in both adult and pediatric trials. From these trials, several general principles have been observed. Patients most likely to benefit from radiation therapy are those with some combination of stage 2B or bulky disease and those with residual masses detected either during or following the completion of treatment [33, 42, 46, 47]. Increasingly, FDG-PET is used to evaluate residual masses during or after therapy [42]. For those patients who do not have pre-therapy evidence of disease bulk and who achieve a complete remission with chemotherapy, the results of randomized trials increasingly demonstrate that radiation therapy may be omitted.

5.8.4 Management of Recurrent Hodgkin Lymphoma

The principles of managing patients with recurrent or primary refractory Hodgkin lymphoma are largely based on cohort studies that have included adult patients initially presenting with advanced-stage disease. Based primarily on these cohort studies and supported by two small randomized controlled trials that are included in a meta-analysis [48–50], autologous stem cell transplantation is the initial treatment of choice. Superior outcomes are seen in patients who have relapsed from a previous remission (as compared with those with disease refractory to initial therapy) and in those with an antitumor response to second-line therapy [51]. Treatment pathways begin with second-line chemotherapy; several regimens have been evaluated and generally include agents such as cytarabine, gemcitabine, melphalan, etoposide, and carmustine and are associated with response rates of 70–80 % [52, 53]. These responding patients are best suited to proceed to autologous stem cell transplantation and their 3-year survival rates are 71 and 75 % in the two randomized trials reported [48, 49].

Treatment paradigms for patients with recurrent or refractory Hodgkin lymphoma are now changed because of the efficacy observed with brentuximab vedotin. An initial trial in patients with disease progression after autologous stem cell transplantation demonstrated that 73 % of patients had an antitumor response, and among these patients, the median duration of the response was 11 months [54]. These observations resulted in a randomized controlled trial comparing brentuximab vedotin with placebo in patient successfully completing autologous transplantation; superior progression-free survival was observed in the brentuximab vedotin arm [55].

In patients with progressive Hodgkin lymphoma following autologous stem cell transplantation, options for disease control are patient specific. These may include allogeneic transplantation including reduced-intensity conditioning [53], enrolment onto clinical trials, and palliative radiation therapy. Management should include integrating principles of supportive and palliative care.

5.9 Late Effects of Treatment

Management of patients with Hodgkin lymphoma during their survivorship phase includes needs to clearly understanding treatment-related risks and to carefully interpret evidence evaluating follow-up strategies [56]. It is essential to recognize that long-term mortality is influenced more by the late effects of the therapy as compared with risks of recurrent Hodgkin lymphoma. Long-term risks associated with current and future therapies will undoubtedly be less than those previously observed as treatment paradigms have been modified to tailor therapy and to reduce use those modalities most associated with late effects. Major late effects include those that increased risk of mortality and those associated with alteration in quality of life. Those most associated with increased mortality are second cancers and cardiovascular disease. Other important late effects include endocrinopathies with thyroid and gonadal dysfunction and musculoskeletal abnormalities. Gonadal dysfunction is associated with sterility, especially in males, and with ovarian failure in women. Musculoskeletal abnormalities are less frequent in the adolescent

and young adult population as compared with children and are now even less common because mantle and STNI radiation treatments are no longer used.

5.9.1 Second Cancer and Cardiovascular Related Mortality

The late effects most associated with inferior survival, as compared with an age- and sex-matched population, are second cancers and cardiovascular disease. Second cancers include acute leukemia, principally associated with use of specific chemotherapeutic agents, and solid tumors, which are predominantly a consequence of radiation therapy [57]. Chemotherapy-associated acute leukemia is related to alkylating agents such as nitrogen mustard and cyclophosphamide and to procarbazine. The standard use of ABVD has reduced the incidence of acute leukemia when compared with previous generations of alkylator-based therapy and represents a trade-off when considering treatment with BEACOPP [41]. In pediatric trials, reduced use of procarbazine is expected to be associated with greater safety, but conceptual risks of leukemogenecity associated with cyclophosphamide and etoposide remain.

While eliminating radiation therapy reduces risks of second cancers [28], changes in radiation technology that include target volume reductions, lower doses, and enhanced treatment precision have also reduced risks of second cancers [37]. Specific cancers associated with increased risks and greatest incidence are breast cancer [58], lung cancer, and skin cancer, including melanoma [56]. The relative risks of breast cancer are especially increased in the adolescent and young adult as compared with older adult population [59].

Cardiac late effects include coronary artery disease and cardiomyopathy with congestive heart failure [56, 60, 61]. Increased risks of valvular disease, pericardial disease, and dysrhythmias also exist. Major contributors to risk include preexisting cardiac disease [61], radiation therapy, and use of doxorubicin [60, 61]. Risks associated with radiation are dose and field dependent [57, 60]; use of doxorubicin may have increased risks in the adolescent and young adult as compared with an older adult population [60].

5.9.2 Implications for Follow-Up

Recommendations for follow-up management of patients treated for Hodgkin lymphoma are based on the magnitude of epidemiologic parameters (relative and absolute excess risk) and generalization of evidence obtained from other populations. Recommendations are thus pragmatic and not derived from randomized controlled trials [39]; limitations can include unconfirmed alignment with principles associated with prevention and screening, including harms associated with false-positive diagnostic tests and the uncertain efficacy of specific interventions. Recommendations are strongest when these are consistent with those provided to broader populations. Thus, modifiable lifestyle factors such as smoking status and interventions for smoking cessation, strategies to address diet and exercise, and sun protection are important as these relate to risks of obesity, metabolic syndrome, cardiovascular disease, and cancer. Screening and management of known cardiovascular risk factors, such as hypertension and hyperlipidemia, are integral to ongoing care.

Additional specific interventions are also recommended. These include breast cancer screening that includes MRI in women beginning 8 years after completing therapy that includes breast tissue radiation or at age 40 [39, 62] and annual evaluations of thyroid function and attention to vaccination status, especially in patients who have undergone splenectomy or splenic radiation. Special management is required for women with ovarian dysfunction and for fertility counseling for all patients. Integrating follow-up to include attention to the risk of late effects, the psychological ramifications of having been treated for cancer at a young age, and oversight of standard health issues requires careful planning and coordination at both a health-care

delivery systems level and among the providers responsible for individual patients.

5.10 Summary

The principles and processes for managing adolescent and young adult patients with Hodgkin lymphoma exemplify the unique issues of this age group. Careful diagnostic evaluations are necessary to provide therapy that maximizes curative potentials, minimizes risks associated with overtreatment, and mitigates the complications of necessary therapies. Management thus requires coordinated multidisciplinary teams and comprehensive consultation among those responsible for determining use of systemic and radiation therapies. Ongoing management must appropriately balance issues best managed through specialty and primary care so that patient-centered care is provided during all phases of treatment and follow-up.

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Acute Myelogenous Leukemia

6

Ursula Creutzig, Matthew Kutny,
and Richard F. Schlenk

Abstract

After a peak during the first 2 years of life, the incidence of acute myelogenous leukemia (AML) is low (five per million 5- to 9-year-olds per year in the United States) until after 9 years of age, when it slowly increases during adolescence and adulthood (to nine per million per year among 15- to 19-year-olds in the United States). Biological features including the prevalence of some genetic abnormalities appear to differ between pediatric and young adult AML. Treatment results in AML have improved during the last 30 years for all age groups; however, survival decreases with advancing age even when genetic risk factors are considered. In contrast to data about children and older adults, data on biological features and outcome are scarce in the adolescent and young adult (AYA) age group. This is partly due to the low number of patients of this age group participating in clinical trials. Differences in outcome for AYAs participating in pediatric trials compared to adult trials seem to be significant when different protocols are used, but minor with similar or identical protocols. As the needs of AYAs are different from those of young children and those of older adults, it is recommended to treat these patients in special units whenever possible.

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6.1 Introduction

AML represents approximately 15–20 % of all leukemias in children and about one-third in adolescents and young adults. Treatment results in childhood AML have improved considerably over the last 20 years, with a 5-year survival in the range of 60–75 % [1, 19, 26, 28, 59]. In young adults, outcome is less favorable, with overall cure rates in the range of 50 % [14, 34].

The number of adolescents and young adults (AYAs) included in clinical trials is relatively small, both in cooperative group studies of adults and in pediatric trials. Treatment protocols designed for children and adults often differ in various aspects from each other, and there is limited data elucidating which kind of therapy could be particularly appropriate for young adults [65]. It is our aim to describe the biological features, clinical symptoms and signs, treatment modalities, and outcome of this age cohort.

6.2 Epidemiology/Etiology

6.2.1 Incidence

Data herein were derived from US SEER during 2000–2012 [53] and the German Childhood Cancer Registry (GCCR) [35]. The data from these two registries suggest epidemiologic and survival patterns are slightly different, probably due to lower patient numbers or differences in race/ethnicity mix in different countries.

In the United States, 5 % of all invasive cancer in the adolescent and young adult (AYA) population is leukemia, and 40 % of all leukemia in AYAs is AML. The proportion of all leukemia that is AML is higher in AYAs than in younger (16 %) or older (31 %) patients. Figure 6.1 shows the age and sex dependence of incidence of AML in children and AYAs. AML rates are higher in the first years of life, but subsequently decrease with a nadir at approximately 9 years of age followed by slowly increasing rates during adolescence and adulthood. In contrast to most cancers, AML has little to no difference in sex variation below the age of 40. (In older adults, males have a higher incidence of AML.) In contrast, acute lymphoblastic leukemia (ALL) peaks between 2 and 5 years of age and declines during adolescence. Therefore, with advancing age the percentage of AML increases within the total acute leukemia spectrum, resulting in an inversion of the frequency of ALL and AML in late adolescence. Nearly half of all leukemias in AYA females were AML. In AYA males it was 35–40 % (due to the higher percentage of ALL in males). The incidence of AML, unlike that of ALL, was similar for white and black children for all age groups [53].

Incidence trends: According to SEER 2000–2012 [53], the incidence of AML has been stable since the late 1970s in AYAs, whereas in younger and older persons, the incidence has increased since the late 1970s. The German Childhood Cancer Registry [35] and the Nordic countries [42] have not reported an increase in the incidence in AML in children under 15 years. In Great Britain there is a small increase in incidence since 1975 (all leukemia subtypes combined) in most age groups (mainly in the elderly over 65), but not in the 15–24 age group. These trends have to be interpreted with caution, because changes in the diagnosis, classification, and registration are likely to explain at least some of the observed increase. Over the last decade, incidence rates remained relatively stable [60].

6.2.2 Etiology

There are only a few proven etiologic factors for childhood AML, for example, in utero exposure to alcohol, exposure to benzene, ionizing radiation, or different drugs that may contribute to AML in young children. The risk of AML is increased in children with congenital syndromes such as Fanconi anemia, Shwachman-Diamond syndrome, and Down syndrome. Somatic mutations of the *GATA 1* gene are seen in virtually all cases of AML associated with Down syndrome and may be implicated in the 500-fold increased risk of megakaryoblastic AML seen in these patients [22, 31]. Such mutations may also confer enhanced leukemic sensitivity to cytarabine via

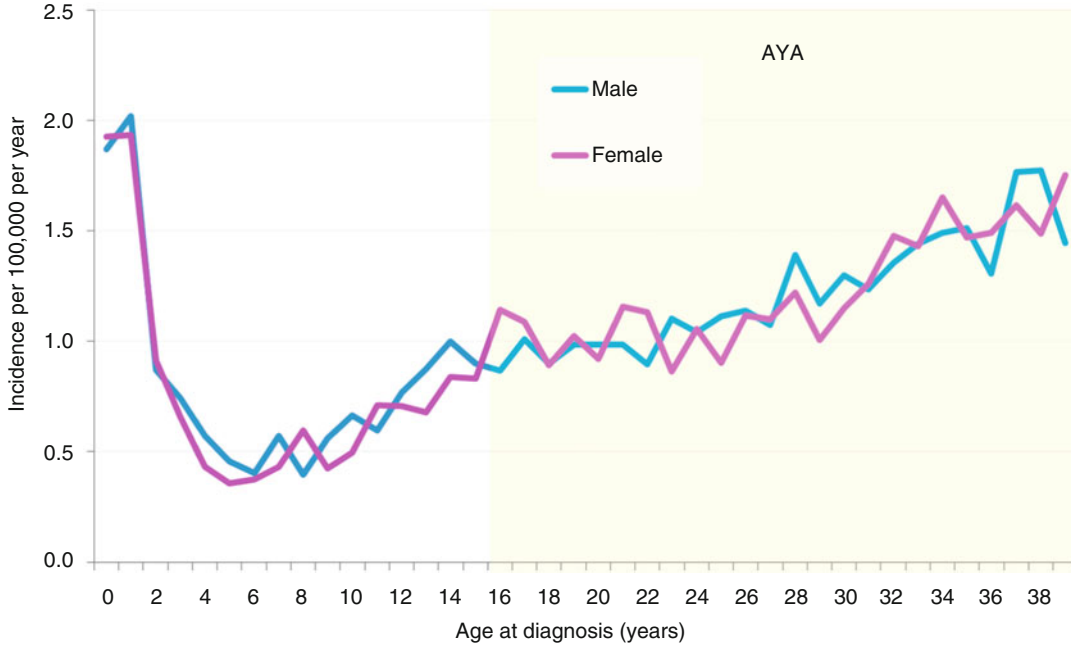

Fig. 6.1 Incidence of acute myelogenous leukemia (AML) by sex and single years of age in children and AYAs (Surveillance, Epidemiology, and End Results, US SEER 18 regions, 2000–2011)

dysregulation of cytidine deaminase gene expression [27]. AML as a secondary malignancy after intensive chemotherapy is quite often seen in older children and adults (cumulative incidence of 0.6 % for children treated for ALL or solid tumors by 10-year follow-up and 3.3–10 % for adults treated for different types of solid tumors) [38, 43].

AML is the most common and more likely to occur than ALL in the older age groups (especially >60 years old), correlating to prolonged duration of exposure to environmental carcinogens proportional to age and accumulation of mutations from genetic error events in cell division [8]. Only the incidence of acute promyelocytic leukemia (APL, t(15;17)/*PML-RARA*, WHO-2008 classification) appears approximately constant with respect to age after the first decade [62]. According to SEER data, APL had its highest proportion among subtypes of AML in AYAs, with 20–25 % of those with AML having the APL subtype (Fig. 6.2). A report from Japan ascertained a gradual increase of APL as a proportion in adolescence: 1–4 years, 5 %; 5–9 years, 8 %; 10–14 years, 12 %; 15–19 years, 19 %; 20–24 years, 22 %; 25–29 years, 21 % [33]. A more recent report from this group analyzing diagnoses from 2006 to 2010 again confirmed that APL made up an increasing proportion of AML diagnosis from childhood through adolescence (infants, 1.8 %; 1–4 years, 3.9 %; 5–9 years,

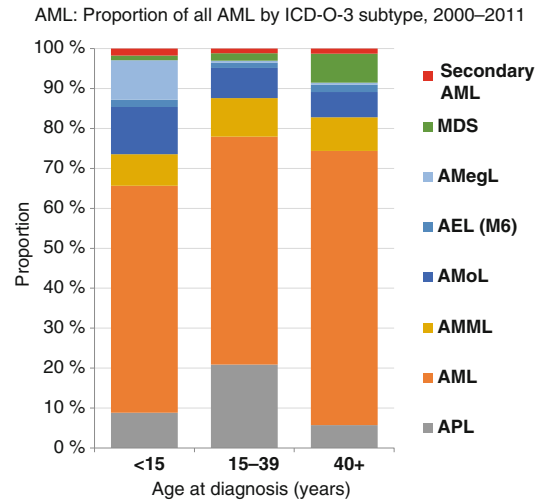

Fig. 6.2 Proportion of all AML by ICD-O-3 subtype, SEER 2000–2011

10 %; 10–14 years, 12 %; 15–19 years, 15 %) [32]. Acute promyelocytic leukemia shows a high frequency (20–24 % of AML diagnoses) in certain ethnic populations (e.g., Italian and Latin American) compared to other ethnic groups (5–8 %). In a single institute in Mexico, 20 % of all AML patients and 30 % of adolescents (11–21 years old) presented with APL [49]. This may suggest a genetic predisposition for acute promyelocytic leukemia and/or specific environmental exposures [25].

6.2.3 Trends in Survival

The 5-year AML-specific survival rate has doubled in all age groups since the late 1970s. Also, the rate of progress in improving the 5-year AML-specific survival rate is similar in children, AYAs, and older adults [53] (Fig. 6.3).

Survival rates for AYAs with AML have improved over the last three decades. Population-based estimates of 5-year survival increased from 18.6 % in the period 1975–1984 to 56.3 % in the period 2003–2010 [53]. Current 5-year survival in children, adolescents enrolled in clinical trials (which tend to be higher estimates because trials may exclude patients with unfavorable features or patients from small hospitals), is in the range of 60–75 % [18]. Results from the AML-Berlin-Frankfurt-Münster (BFM) studies (patients <18 years old) showed an improvement of 5-year survival from 49 % (study AML-BFM 87, in the period 1987–1992) to 60 % (period, 1993–1998), to 65 % (period, 1999–2003) and to 75 % (period, 2004–2010) [19, 21]. In young adults, 5-year survival rates are now in the range of 50 % according to population-based data [34]. In clinical trials the 10-year survival rate in the recent German-Austrian AML Study Group (AMLSG) studies is reported as 50–60 % for 18–45 years old patients [24].

The improvement in prognosis over the last decades in all age groups became possible by intensified chemotherapy in de novo AML and after relapse and supportive care. With intensive induction chemotherapy, 80–90 % of young patients achieve complete remission (CR).

Little data specifically analyzes overall survival (OS) for adolescents and young adults. Population-based data from regions of England and Wales showed that a 5-year survival improved significantly from 36 % in the period 1984–1988 to 46 % in the period 1989–1994 and to 56 % in the period 2001–2005 for AML patients between 15 and 29 years old (although the 2001–2005

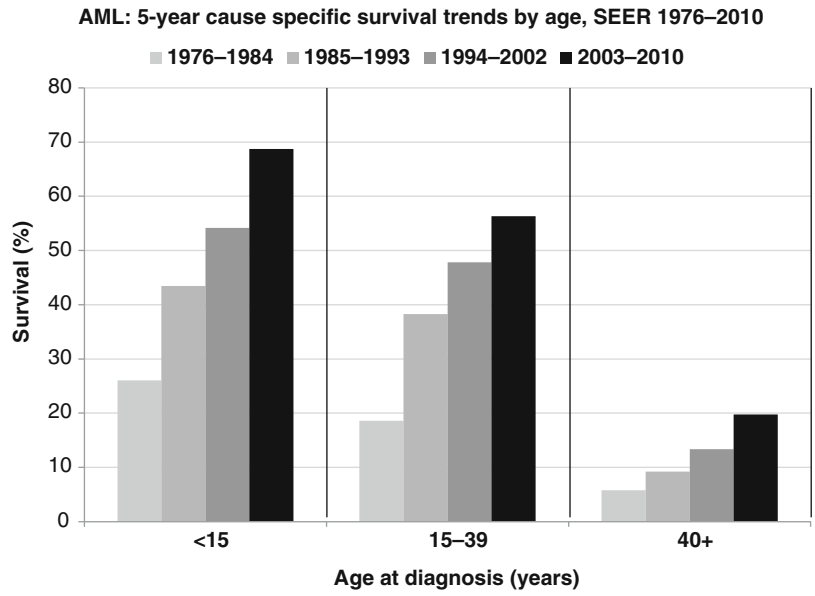

Fig. 6.3 5-year cause-specific survival trends by age, SEER 1976–2010 (Source: SEER 9 Areas, NCI)

period included only patients aged 15–24 years) [54, 61].

According to SEER data, 2000–2010 AYAs had nearly as good as a 5-year survival as younger patients (Fig. 6.4) [53]. Above age 40, the survival rate declined more rapidly.

6.2.4 Prognostic Factors

The 5-year AML-specific survival was similar in males and females, except for a lower rate in 20- to 29-year-old males (Fig. 6.4).

Whereas non-Hispanic white AYAs had an inferior survival in comparison to younger patients, other common races/ethnicities had relatively similar survivals in AYAs and younger patients [53]. However, this may be related to the lower incidence of APL.

Increasing age is a known poor prognostic factor in adults with AML [11, 17, 34]. In population-based studies, 5-year survival rates drop with age, but are now 64 % for patients aged 0–15 years and about 54 % for those aged 15–40 years (Fig. 6.4) [53]. However, prognosis in different age groups of children and older adolescents treated similarly has rarely been reported and is often conflicting.

Results of the former Children's Cancer Group (CCG) trials (CCG 213 [1986–1989] and CCG-2891 [1996–2002]) including children and adolescents less than 22 years old were conflicting with no difference in survival (5-year survival was 39 % and 50 %, respectively) in 2–10-year-old children and adolescents aged 10–21 years [63, 64]. However, in patients above 16 years event-free survival (EFS) and survival were inferior in the last CCG-2891 trial [36].

Recently, a cross-study analysis combining data from the CCG-2891, CCG-2941, CCG-2961, and AAML03P1 Children's Oncology Group (COG) trials showed that survival in AYA and younger patients with newly diagnosed AML was similar. However, older patients were at higher risk for treatment-related mortality (TRM): Overall survival in AYAs (16–20 years, $n=238$) was 49 ± 7 % versus the younger ($n=1602$, 54 ± 3 %, $P=0.058$); relapse was lower in AYA patients (30 ± 7 % versus 41 ± 3 %, $P=0.002$), but TRM was higher (25 ± 6 % versus 12 ± 2 %, $P<0.001$). Infection accounted for the excess TRM in AYA patients [16]. The COG also demonstrated similar outcomes for AYAs when combining data from the most recent trials AAML03P1 and AAML0531, which tested adding gemtuzumab ozogamicin to a MRC-

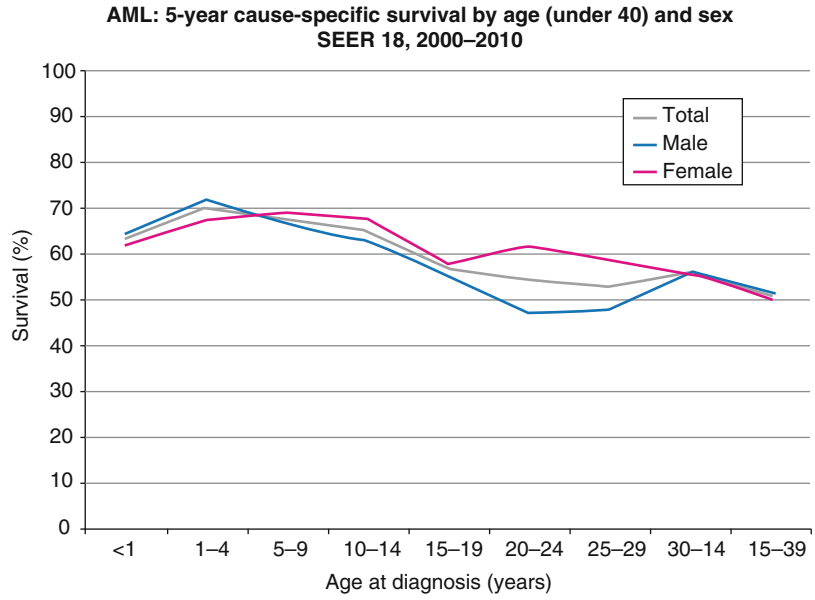

Fig. 6.4 5-year AML-specific survival by age (under 40) and sex, SEER 2000–2010 (Source: National Cancer Institute: SEER18 Areas)

based chemotherapy regimen. AYA patients aged 16–21 years compared to those <16 years had similar 5-year EFS (44.2 % vs. 50.2 %) and 5-year OS (60 % vs. 64.8 %). AYA patients were again found to have higher rates of TRM 13.3 % (compared to 7.3 % in younger patients, $P = 0.005$). Further, AYA patients who received gemtuzumab ozogamicin or stem-cell transplant had higher rates of TRM that appeared to attenuate the survival advantage seen with these interventions among young patients [2].

Similar results were reported by Rubnitz et al. when analyzing outcomes from the St. Jude AML protocols AML91, AML97, and AML02 covering the period of 1991–2008. The survival rate for older children with AML has improved in the recent trial (AML02) and was now similar to that of younger patients. However, deaths from toxicity remained a significant problem for patients in the older age group [48].

Unfortunately, no recent data for the AYA group are available from the British Medical Research Council (MRC) trials. In a study of MRC AML12 in <16-year-old children, 10-year EFS and OS were 54 % and 63 %, respectively [28]; in <60-year-old adults, OS at 8 years was 38 % [13].

The same trend to decrease in survival with age was reported for the EFS rates but not overall survival in more than 1,000 Japanese AML patients aged 1–29 years consecutively diagnosed in the period 1986–1999, who were treated in a variety of institutions and protocols. Seven-year probability of EFS for AML decreased from 34 % in the age groups 10–15 years to 32 % for 15- to 19-year-old adolescents and to 26 % in the 20- to 29-year-old young adults [33]. Recently, lower survival but not EFS rates were reported in Japanese patients aged 15–17 years compared to younger patients [58]. This was mainly due to a higher treatment-related death rate after relapse in AYAs.

Treatment schedules and dosing of the AML-BFM 93/98 studies for children and adolescents ($n = 891$) and the AMLCG92/AMLCG99 and AMLSG HD93/AMLSG HD98A studies for adults were similar during induction and consolidation [10, 12, 51, 52]. In the adult studies, 290 patients were 16–30 years old. A common analysis of patients of the studies showed that the CR rate was highest in the age groups 2–12 years (89 %) and lower in infants and patients of older age (<2 years, 79 %; 13 ≤ 21 years, 82 %; 21–30 years, 72 %). Long-term treatment results were also most favorable among 2–12-year-old children (5-year EFS ± SE, 53 ± 2 %), slightly inferior in adolescents (45 ± 3 %, $P = 0.03$), and unfavorable in young adults (28 ± 3 %, $P = 0.0001$) (for more details, see Table 6.1). Excluding patients with low-risk cytogenetics [t(8;21),

Table 6.1 Results in patients treated in pediatric and adult trials according to age groups

Age (years)	<2 *n* (%)	2 ≤ 13 *n* (%)	13 ≤ 21 *n* (%)	21 ≤ 30 *n* (%)	*p* (gray)
Total of patients	222	463	276	220	
Early death (ED)[a]	16 (7.2)	17 (3.7)	13 (4.7)	14 (6.4)	
Nonresponse (NR)	31 (14.0)	36 (7.8)	36 (13.0)	47 (21.4)	<0.001
Death in CCR (cumulative incidence) % (SE)	2 (1)	4 (1)	5 (2)	6 (3)	<0.093
Complete remission	175 (78.8)	410 (88.6)	227 (82.2)	159 (72.3)	
Relapse (cumulative incidence) % (SE)	35 (5)	30 (3)	32 (4)	38 (6)	0.098
5-year EFS % (SE)	42 (3)	53 (2)	45 (3)	28 (3)	<0.0001[b]
5-year survival % (SE)	57 (3)	62 (2)	56 (3)	42 (4)	<0.0001[b]

Modified from Creutzig et al. [16]
CR complete remission, *CCR* continuous complete remission
[a]Early deaths are defined as death until day 42
[b]$p_{(logrank)}$

inv16, and t(15;17)], results were inferior in adolescents (EFS 39 ± 5 %) and young adults (EFS 25 ± 6 %) compared with children aged 2–12 years (EFS 52 ± 4 %) [16].

6.2.5 Treatment Differences

Adolescents and young adults may be treated on pediatric or adult trials. Recently, 281 adolescents 16–21 years old treated on the pediatric cooperative trials groups CCG and COG trials (1986–2008) were compared with 149 patients of the same age group treated on the adult cooperative trials groups Cancer and Leukemia Group B (CALGB) and Southwest Oncology Group (SWOG) frontline AML trials (1986–2008). Patient characteristics were similar; however; age was a confounding variable (median, COG: 17.2 versus CALGB: 20.1 and SWOG: 19.8 years, $P < 0.001$). The 10-year survival rate for patients treated on the CCG/COG trials was 45 ± 6 % compared to 34 ± 7 % in the adult trials, $P = 0.026$ [65].

6.3 Biology/Pathology

Biological parameters across the entire age spectrum are reported rarely in literature. The frequency of cytogenetic subgroups of AML is age specific. There is an increase of the poor prognostic cytogenetic groups (e.g., unbalanced aberrations) in adults with older age (Fig. 6.5) [3, 29].

Clinical, morphological, and cytogenetic data were analyzed for children, adolescents, and young adults treated in the pediatric trials AML-BFM 93/98 ($n = 869$) and of 92 young adults (<30 years) of the AMLCG92 study. Age classifications were infants (≤2 years), children between 2 and 12 years of age (because there were significant differences in biological parameters in these age groups), adolescents between 13 and 21 years of age, and young adults between 21 and 30 years [20]. Results show that French-American-British (FAB) distribution was quite different in young children <2 years, 68 % (147/213), who presented with FAB subtypes M5 or M7, compared to 18 % (133/730) in the older age groups (χ^2 $P < 0.0001$) (Fig. 6.6). However, apart from a trend toward increasing M1 and decreasing M7, there was no difference in FAB types for children (2–12 years) and AYA patients 13–30 years old. The favorable karyotypes t(8;21), t(15;17), and inv16 were rarely seen in children <2 years (8/163 = 5 %) compared to the 2- to ≤21-year-olds (141/580 = 24 %; Fisher $P = 0.01$; Table 6.2). With the limitation of the low patient number, it is of interest that t(8;21) was seen less frequently in young adults aged 21–30 years compared to the 2–21-year-old group.

These data do not show significant differences in biological parameters between children 2–12 years old compared to AYAs, albeit there was a lower incidence of 11q23 and t(8;21) above age 12 years than below this age. Only patients younger than 2 years of age present with significant differences in comparison to older patients. APL, which is characterized by t(15;17), does vary as a proportion of AML diagnoses across age groups as discussed above in Sect. 7.3.2.

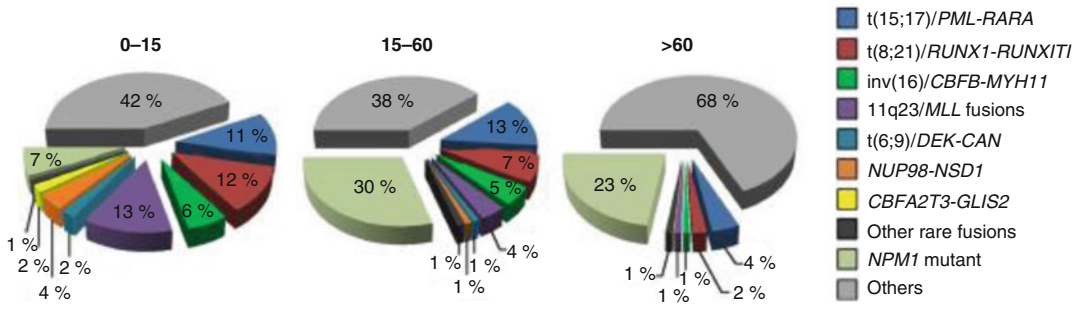

Fig. 6.5 Distribution of genetic groups according to age (Modified from Grimwade and Freeman [29])

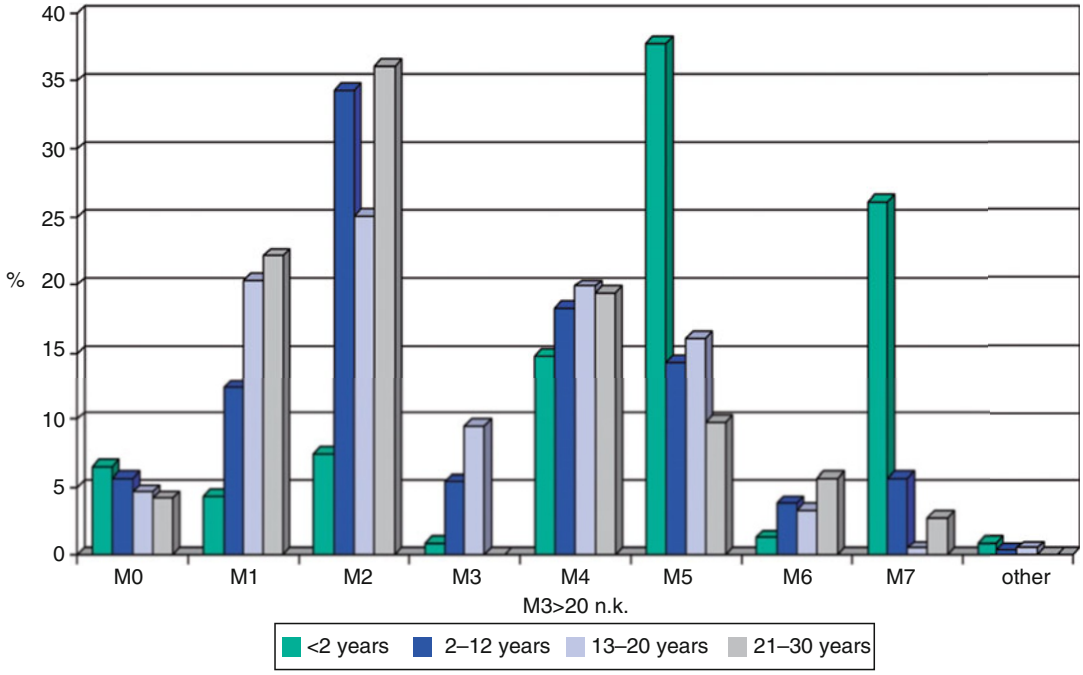

Fig. 6.6 Distribution of FAB (French-American-British) classification subtypes of AML as a function of age group (Data from the AML-BFM studies 93/98 and AMLCG92)

Table 6.2 Karyotypes in the different age groups

Age (years)	<2	2–12	13–21	21–30	p (χ^2)
t(8;21) (%)	1	18	10	5	0.0001
t(15;17) (%)	2	6	8	10	0.02
inv16 (%)	2	8	6	9	0.07
11q23 (%)	27	11	7	n g	0.0001
Total (n)	164	320	150	43	

Data from the AML-BFM studies 93/98 and AMLCG92

The COG analyzed genetic characteristics of AYAs 16–21 years old compared to those <16 years old treated on trials AAML03P1 and AAML0531. AYA patients were more likely to have the normal cytogenetics (36.5 % vs. 20.5 %, $P<0.001$) and the unfavorable genetic finding of *FLT3*/ITD (20 % vs. 14.3 %, $P=0.047$). AYA patients were also more likely to have some favorable prognostic markers including mutations in *CEBPA* (9.4 % vs. 4.8 %, $P=0.012$) and mutation of *NPM1* (12.8 % vs. 6 %, $P=0.001$) [2]. AYA patients did have a lower rate of 11q23/MLL rearrangement (11.5 % vs. 23.3 %, $P=<0.001$) due to the high rates of this genetic abnormality found in very young children and infants similar to the finding in the AML-BFM studies noted above.

6.4 Diagnosis: Symptoms and Clinical Signs

The clinical presentation in children, adolescents, and young adults is mostly similar (Table 6.3). It reflects the degree to which the bone marrow has been infiltrated with leukemic blasts and the extent of extramedullary involvement and can be both a reflection of tumor biology and health service factors (host- and provider-related delays in diagnosis). The most common symptoms and physical findings result from anemia, thrombocytopenia, and neutropenia and include pallor and fatigue, anorexia, petechiae, purpura, bleeding, and infection. The occurrence of initial hyperleukocytosis (white blood cell count >100,000/µl) did not vary significantly in the different age groups. Initial involvement of the central nervous

Table 6.3 Initial clinical data according to age groups (age, <2, 2–12, 13–21, 22–30 years)

Age (years)	<2	2–12	13–21	22–30	*p* value
Gender, male/female (%)	53:47	55:45	51:50	49:51	0.66
WBC median, range/μl	17,900	17,200	14,000	19,700	0.28
WBC >100,000/μl (%)	22	15	21	13	0.029
Hepatomegaly >5 cm (%)	24	25	27	35	0.36
Splenomegaly >5 cm (%)	28	27	34	26	0.61
CNS involvement (%)	17	8	10	n g	0.008
Extramedullary organ involvement (%)	36	19	26	n g	0.00001
Total (*n*)	231	448	210	72	

Data from the AML-Berlin-Frankfurt-Münster (BFM) studies 1993/1998 and AML Cooperative Group (AMLCG) 1992 trial

WBC white blood cell count, *CNS* central nervous system

system (CNS) is seen less often in adolescents (~10 %) and in children aged 2–13 years (~8 %) than in infants (~17 %) with AML (data not available for young adults, who rarely get diagnostic lumbar puncture). Infiltration of the skin, especially in monocytic leukemias, is also most frequent (~20 %) in young children (<2 years) and rarely seen in older children and adolescents. Likewise, leukemic infiltrations of the periosteum and bone occur more often in young children than in adolescents.

6.5 Treatment/Management

Treatment regimens for AML are often but not always similar in children, adolescents, and adults, generally starting with intensive induction courses with cytarabine and anthracyclines of an adequate dosage to achieve remission. Induction therapy is followed by postremission phases including in recent years also a maintenance therapy with novel agents (e.g., tyrosine kinase inhibitors, TKI) to destroy residual blasts in the bone marrow or at other sites. Induction therapy as well as duration and optimal strategy of postremission therapy is in continuous reassessment with frequently adapted standards over time. In general, intensive postremission chemotherapy cycles (referred to as consolidation and/or intensification courses) should include one or more courses of high-dose cytarabine (depending on the molecular subset of the disease in adults). They are administered together with CNS prophylaxis and may be followed by a less-intensive maintenance chemotherapy or in treatment approaches under current evaluation by specific inhibitors. Allogeneic or rarely autologous stem-cell transplantation may be included as another form of intensification, and indications and rates vary between countries and study groups and between pediatric and adult providers [18, 23]. Majhail et al. performed an analysis of data from the Center for International Blood and Marrow Transplant Research (CIBMTR) for allogeneic hematopoietic stem-cell transplant for AML and stratified by age group including children (<15 years, $N=900$), AYAs (15–40 years, $N=2{,}708$), and older adults (>40 years, $N=2{,}728$) [44]. This group found that outcomes after transplantation for AYAs improved over the three studied time periods (1980–1988, 1989–1997, and 1998–2005) and this improvement paralleled that seen among children and older adults. Overall survival for AYAs was intermediate between the superior OS seen among children and the inferior outcome seen in older adults during each time period. For the most recent period of 1998–2005 the 5-year OS for AYAs was 43 % compared to 64 % for children and 31 % for older adults. TRM decreased over the studied time periods and was a major contributor to improved survival; however, older age was correlated with increasing TRM risk. Compared to children, AYAs had twice the risk of TRM, while older adults had three times the risk of TRM.

For some specific subgroups, special treatment is available. The most successful special treatment was the introduction of the differentiating agent all-trans-retinoic acid (ATRA) for patients with APL, inducing cell differentiation and maturation instead of cell destruction [25, 30]. Most recently, the combination of ATRA and arsenic trioxide has shown high efficacy and reduced hematologic toxicity in adult APL patients with low and intermediate risk APL [41]. Clinical trials are currently in development in both Europe and North America to study this regimen in adolescents and children with APL.

Acute management and supportive care are required during all treatment phases, especially during the first few days and weeks of intensive induction therapy. As noted above and in Sect. 7.3.3, AYAs with AML experience a higher rate of treatment-related mortality with chemotherapy or stem-cell transplant compared to younger children, and yet they can usually tolerate more intensive regimens than elderly adults. With recent improvements in AML treatment results, the balance between treatment intensity, toxicity, and interrelation of both with the genetic background of the disease has become more important than in the past, requiring trials to perform risk- and genotype-adapted therapy.

In adolescents, a higher degree of anticipatory vomiting is seen and, in our experience, a somewhat less-rapid recovery from myeloablative treatment. Although the compliance during intensive treatment phases in the adolescent age group is not different from that in children and older patients, as most if not all chemotherapy is given in the hospital. In countries that utilize maintenance therapy for AML, such as Germany, the experience has been that AYA compliance may be lower during maintenance therapy, just as adherence to oral chemotherapy has been shown to be lower in adolescents with ALL [6].

The most difficult in the management of adolescents is the indispensable psychosocial care. The needs of adolescents are different from those of young children and are accompanied by the conventional problems that are associated with this age group (e.g., need of autonomy and independence, social development, sexual maturation, education, and employment) [46]. These problems are the same as for adolescents and young adults suffering from other types of cancer.

6.6 Participation in Clinical Trials

More than 90 % of children less than 15 years of age with AML are treated within clinical trials in the Nordic countries [39], 67 % in the United Kingdom [5], and more than 60 % in the United States. However, for all cancer patients aged >15 years, the percent enrolled in clinical trials is much lower [7, 57]. This was true for AML patients aged 15–29 years in the United Kingdom from 1989 to 1994, where only 39 % of patients aged >15 years were entered on clinical trials [54]. Data from the five German AML intergroup trials included in the Competence Network "Acute and Chronic Leukaemias" indicate that young adults are generally included in clinical trials [45]. Benjamin et al. reported on the percentages of patients with acute leukemia entered in the MRC trials from 1991 to 1995. Questionnaires were sent to 121 hospitals, and data from the 96 that responded showed that 82 % of pediatric AML patients (61 % aged between 15 and 19 years and 52 % between 20 and 29 years) were entered "always" or "whenever possible" into MRC trials [5]. This low percentage is also a reason for the lack of data in clinical trials regarding the adolescent age group and a possible bias of results including comparisons in age groups.

Several authors state that the prognosis for adolescent leukemia sufferers may be improved by introducing pediatric trials that take into account the prognostic biological features [50]. Treatment outcomes for AYAs may further be influenced by referring these patients to centers with experience in the management of leukemia or to centers that participate in clinical trials for children or adults. According to the data available, differences in outcome for patients treated in pediatric or adult trials were more pronounced for adolescent ALL than for AML patients [50, 55, 65].

6.7 Expected Outcome, Including Late Effects

Late effects among survivors of AML during childhood and adolescence may have a significant impact on their quality of life. Long-term sequelae of treatment can include impaired intellectual and psychomotor functioning, neuroendocrine abnormalities, impaired reproductive capacity, and second malignancies [47]. However, most of these late effects, especially side effects after CNS irradiation (neurocognitive deficits, growth hormone deficiency, and secondary CNS tumor) given in the AML-BFM studies for all age groups, but not in other AML trials, affect the younger age group. Anthracycline cardiotoxicity is also seen at lower cumulative doses (<300 mg/m^2) in patients younger than 18 years but rather at 550 mg/m^2 in those over 18 years [15, 40].

The risk of endocrine dysfunction is relatively low in AML patients who are treated with standard chemotherapy only (without alkylating agents); however, after stem-cell transplantation, there is an increased risk of endocrine dysfunction [4, 47]. Impairment of growth rates after busulfan/cyclophosphamide or cyclophosphamide/total body irradiation (TBI) conditioning regimens is a problem in children treated before or during their growth period. Gonadal toxicity occurs in all age groups, mainly as gonadal dysfunction; however, it is relatively low with modern conventional therapy [47]. Gonadal toxicity may cause disorder of pubertal development, infertility, sexual dysfunction, and the need for long-lasting hormone substitution. In adult women, high doses of alkylating agents and TBI increase the risk of ovarian failure, and the probability of restoring the ovarian function decreases by a factor of 0.8 per year of age [9]. The addition of busulfan to cyclophosphamide causes permanent ovarian failure in nearly all female patients. In males the effects of both cytotoxic chemotherapy and TBI will damage the germinal epithelium of the testis, and for the majority of males in all age groups, permanent infertility is likely after TBI schedules [9].

Second malignant neoplasms have been described mainly in ALL patients, with a cumulative incidence of approximately 2–3 % at 15 years of age [47]. Data regarding second malignancies following treatment for AML are scarce. The 10-year cumulative incidence of secondary malignancies was 1.5 %, SE 0.3 % (AML-BFM patients diagnosed from January 1993 to December 2010). Most of these patients had received chemotherapy only. After stem-cell transplantation, the risk of second malignancies is higher for any disease (standard incidence ratio from 6.7 to 11.6 in different studies compared to patients given chemotherapy only) [37, 56]. AML and myelodysplastic syndrome are often reported as second malignancies after chemotherapy with alkylating agents or topoisomerase inhibitors; therefore, it might be difficult to distinguish between relapse and second malignancy in de novo AML patients.

In all age groups with leukemia and lymphoma, more depression and somatic distress were reported in comparison with sibling controls [47].

6.8 Summary

AML incidence increases with age, such that the frequency in adolescents lies in between that of children and adults. Biological factors vary by age, but the biology of AML in adolescents and young adults appears most similar to that of children. Outcome has improved for all age groups during the last 20 years, with the advent of better chemotherapy (also after relapse) and supportive care. However, there continues to be a trend toward better survival in children than in young adults, which may be partly related to the intensity of treatment or to treatment in pediatric trials. As AYAs show less tolerance to intensive chemotherapy or stem-cell transplantation compared to children, improving supportive care is one option. Further research should be directed toward biologically based, not age-specific trials.

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Acute Lymphoblastic Leukemia

7

Jennifer L. McNeer, Archie Bleyer,
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Abstract

The incidence of acute lymphoblastic leukemia (ALL) in the AYA population has increased more in the recent decades than it has in younger or older age groups, the cause of which is unknown. While survival rates in the pediatric population have improved dramatically, outcomes have not improved as much in AYAs, and as of a decade ago, only half of the AYA ALL patients were surviving 5 years. There is mounting evidence that the "pediatric" treatment approach may be more favorable for this age group compared to traditional "adult" ALL treatment regimens. Hospitalizations are not required for the therapy, it is less toxic, and may be expected to have fewer adverse late effects. These regimens are quite intense, but on balance, the risk/benefit profile appears to favor the use of these more intense regimens in order to achieve superior outcomes with less residual morbidity. Biologically, the Ph-like subset may provide an "AYA ALL" approach to ALL therapy in the age group since Ph-like ALL has a peak incidence in AYAs and specific targeted agents are clinically available for a subset of these patients. An appreciation for the complex psychosocial underpinnings in these patients is paramount, in order to maximize compliance with the prolonged and complex treatment plans that must be implemented during the crucially formative AYA years.

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7.1 Epidemiology

7.1.1 Incidence

The incidence of acute lymphoblastic leukemia (ALL) is highly age dependent, with an early childhood peak, a nadir during the adolescent and young adult (AYA) years, and a continuously increasing incidence at the end of the age spectrum (Fig. 7.1). The estimated average annual number of Americans diagnosed with ALL between 15 and 40 years of age during 2000–2012 was 1,000 per year. Using exponential regressions, it is possible to identify an excess of cases that may be "AYA ALL" (Fig. 7.1, yellow area), estimated at 500 cases per year during 2000–2012 or half of all ALL during the AYA years (Fig. 7.1, inset). This "AYA ALL" subgroup likely represents a type or types of ALL that is biologically different (see Ph-like ALL below) from the types of ALL that occur in younger (e.g., trisomies of chromosomes 4 and 10, t[12,21], hyperploidy) and older (e.g., Philadelphia chromosome positive [Ph+]) persons. At all ages except early infancy, males have a higher incidence of ALL than females (Fig. 7.2, left panel). During the AYA years, the sex differential is not only greater than at other ages, with 65 % of the cases occurring in males (Fig. 7.2, right panel), but males also have a discrete peak in incidence between 15 and 20 years of age. Similar to ALL, lymphoblastic lymphoma (LL) has a higher incidence in males compared to females across age groups, and this is quite prominent in the AYA population (Fig. 7.3).

Since 1975 in the USA, there has been an increasing incidence of ALL in all age groups

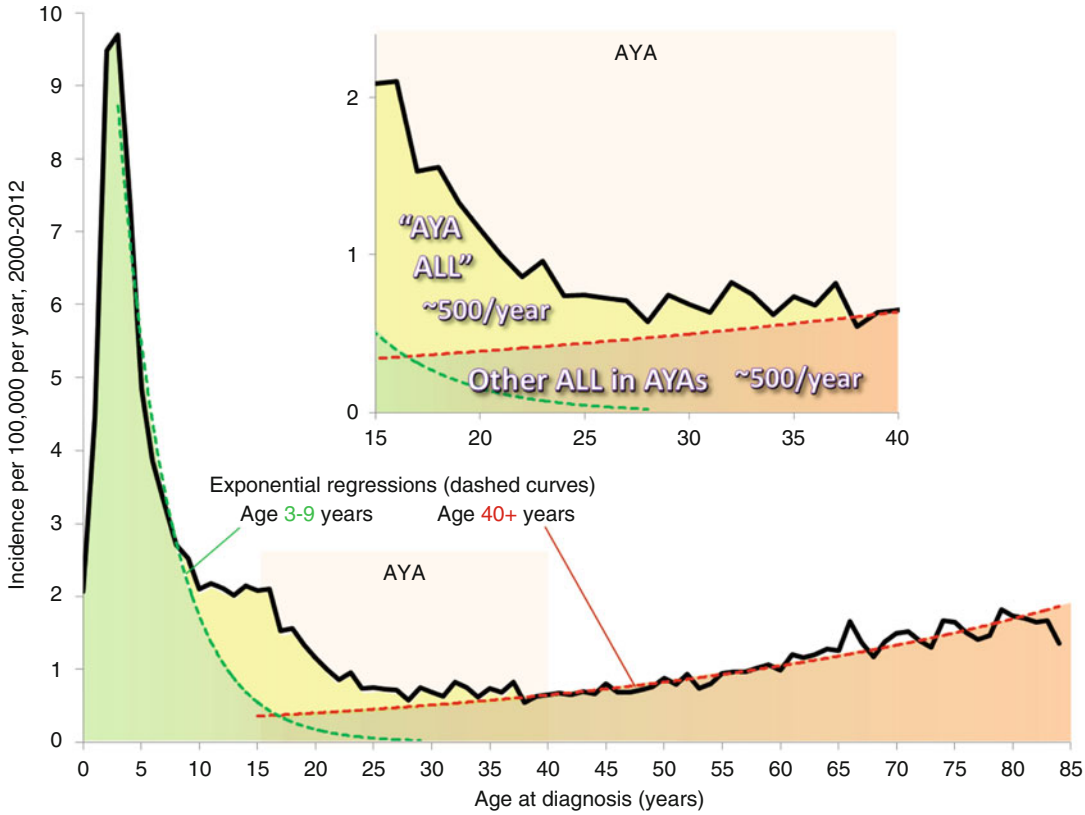

Fig. 7.1 ALL incidence by single years of age, 2000–2012, SEER 18 areas and area-under-the-curve (*yellow*) that represent "AYA ALL." The inset shows the same data on an enlarged y-axis for 15- to 39-year-olds. The number of AYA patients is annual average for 2000–2012 in the USA. "Other ALL" refers to types of ALL that occur predominantly in children or older adults

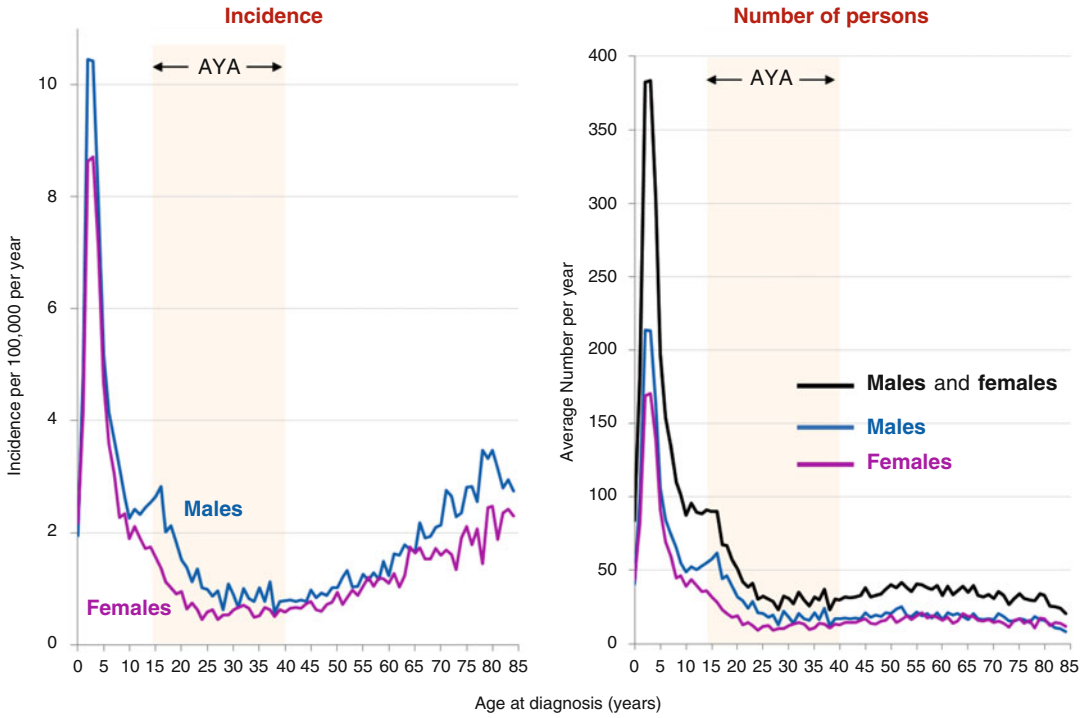

Fig. 7.2 ALL incidence and estimated number of Americans by single years of age and sex, 2000–2011, SEER 18 areas

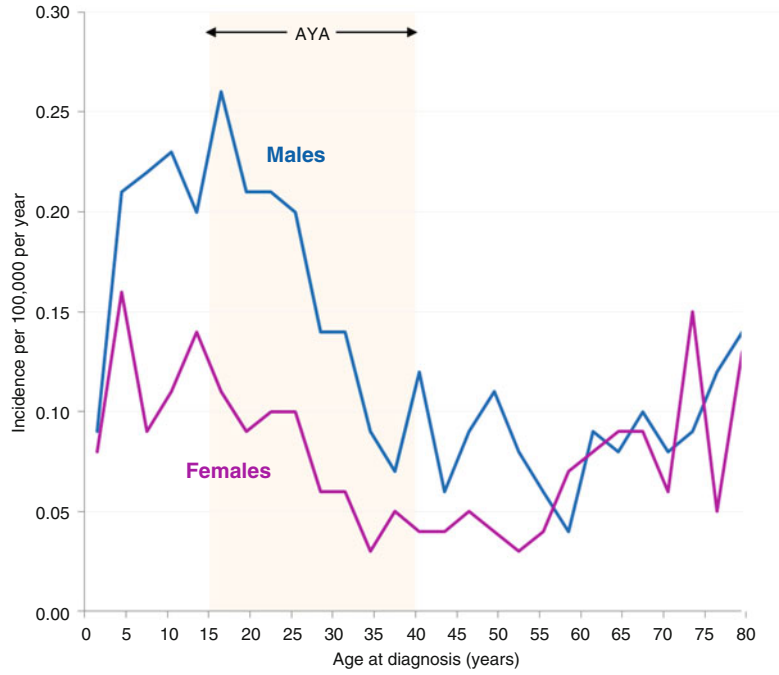

Fig. 7.3 Lymphoblastic lymphoma: incidence by 3-year age intervals and sex, SEER 18 areas

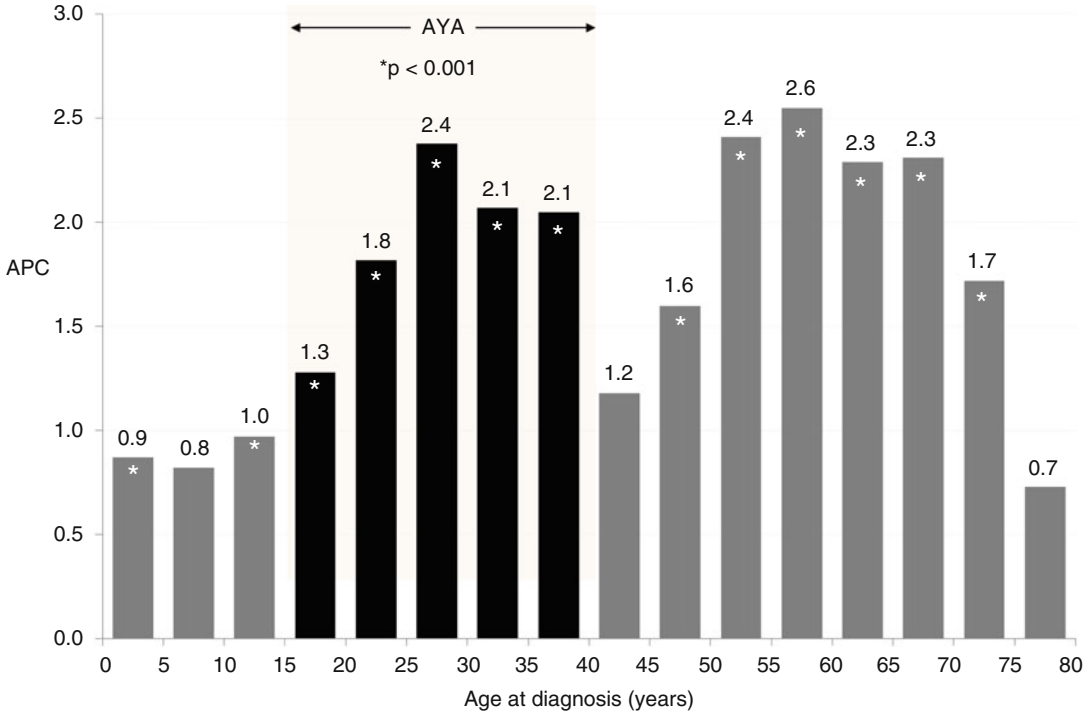

Fig. 7.4 ALL: annual percent change (*APC*) in incidence and age, 1975–2011, SEER 9 areas

(Fig. 7.4), especially in the AYA age group and particularly in females, which has continued to date (Fig. 7.5). In 20- to 49-year-olds, the incidence increased at a steady rate of 2.9 % per year in females and 1.5 % per year in males (Fig. 7.5, inset). The estimate of an average 1,000 new diagnoses of ALL per year in AYAs in the USA during 2000–2012 is likely considerably greater today, since the incidence in the age group has been steadily increasing.

In 2009, two groups identified a subset of B lymphoblastic leukemia (B-ALL) with a gene expression profile similar to that of Ph+ B-ALL, but without the presence of the BCR-ABL fusion protein [1, 2]. This entity has become known as Philadelphia-like (Ph-like) or *BCR-ABL1*-like ALL and occurs most often in the AYA population (Fig. 7.6). Roberts et al. reported an incidence of 21 % in adolescents (16–20-year-olds) and 27 % in young adults (21–39-year-olds), but only 10 % of children between the ages of 1 and 9 years harbored Ph-like disease [3]. This peak in the AYA population was confirmed in a German cohort of adolescents, young adults, and older adults, in which the incidence of Ph-like ALL was also highest in the AYA age group, and decreased with advancing age [4]. Philadelphia-like ALL is more common in males than in females [3], peaking in 20–30-year-olds. This may account for some of the incidence and outcome discrepancies between AYA males compared to females.

7.1.2 Survival and Mortality

Since 1975, the survival rates for pediatric, adolescent, and young adult patients with ALL have increased, but as of 2006, still fewer than half of AYAs survived 5 years from diagnosis (Fig. 7.7) [5]. Based on SEER data, from 2000 to 2011 the 5-year relative survival rate of ALL declined most strikingly between the ages of 16 and 21 years (Fig. 7.8); this was true both for males and females. Additionally, the average annual percent change (APC) in death rate

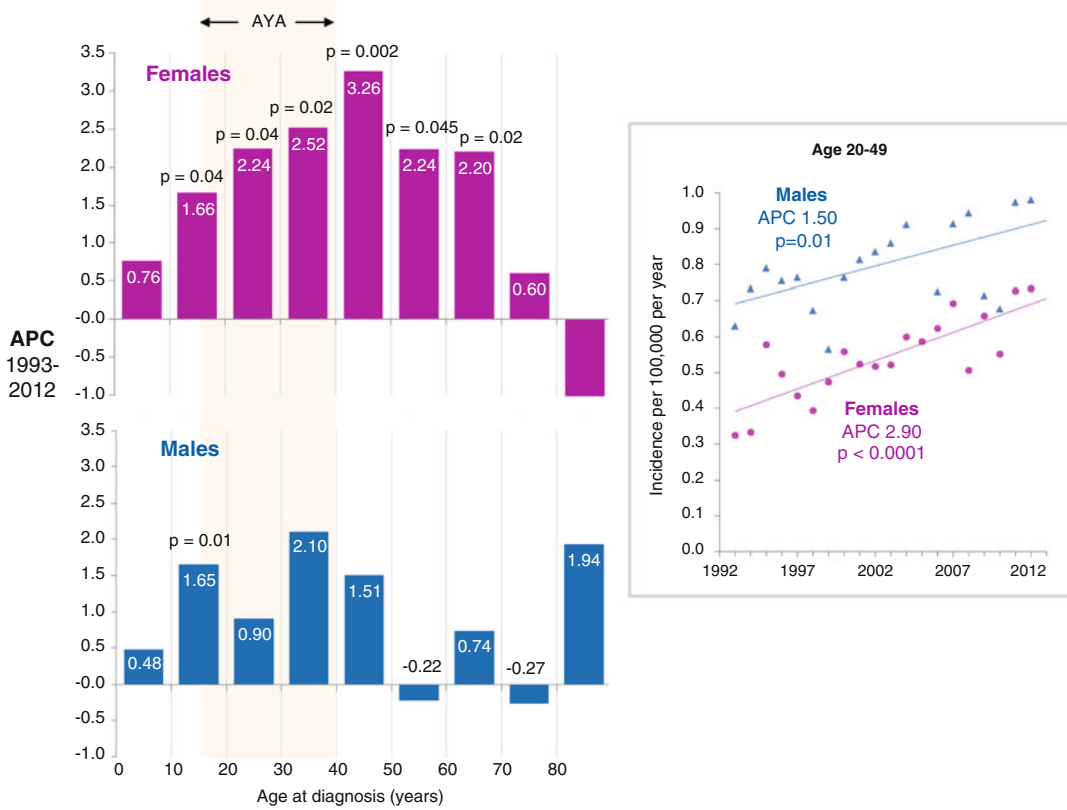

Fig. 7.5 ALL: annual percent change (*APC*) in incidence by sex and age, 1993–2012, SEER 13 areas. *Inset* annual incidence of ALL in 20- to 49-year-olds, by sex

declined from 1998 to 2011 in patients of all ages diagnosed with ALL, except for young adults aged 25–45 years (Fig. 7.9).

These trends are concerning, but they may be partially attributable to population-based reporting, since several groups have reported better outcomes for patients treated on clinical trials. From 1996 to 2001, the Children's Cancer Study Group (CCG) enrolled patients 1–21 years old with NCI high-risk disease (white blood cell [WBC] $>50\times10^3/\mu L$ or age ≥10 years at diagnosis) onto study CCG-1961 [6]. The 5-year event-free survival (EFS) for patients 16–21 years old was 71.5% (SE, 3.6%) and the 5-year overall survival (OS) was 77.5% (SE, 3.3%). St. Jude Children's Research Hospital (SJCRH) conducted the Total Therapy Study XV from 2000 to 2007 [7]. Of the 498 patients that were enrolled, 45 were older adolescents (15–18 years old) who had a 5-year EFS of 86.4% (95% CI, 72.1–93.6%) and a 5-year OS of 87.9% (95% CI, 73.1–94.9%). During a similar time frame, the Medical Research Council (MRC) enrolled patients 1–24 years of age on the UK ALL 2003 trial [8, 9]. While the outcomes for the AYA patients were not reported separately from those of the younger children, for all evaluable patients, the 5-year EFS was 87.3% (95% CI, 86.1–88.5%), and 5-year OS was 91.6% (95% CI, 90.6–92.6%).

The AYA patients enrolled on these clinical trials appear to have had better outcomes compared to the population of AYAs with ALL as a whole, as reported to SEER. This provides support for referral of AYAs with cancer to centers participating in AYA-inclusive therapeutic clinical trials, where there is experience treating this distinctive group of patients. In a population-based cohort of 4,336 children, adolescents, and young adults who were treated for a variety of

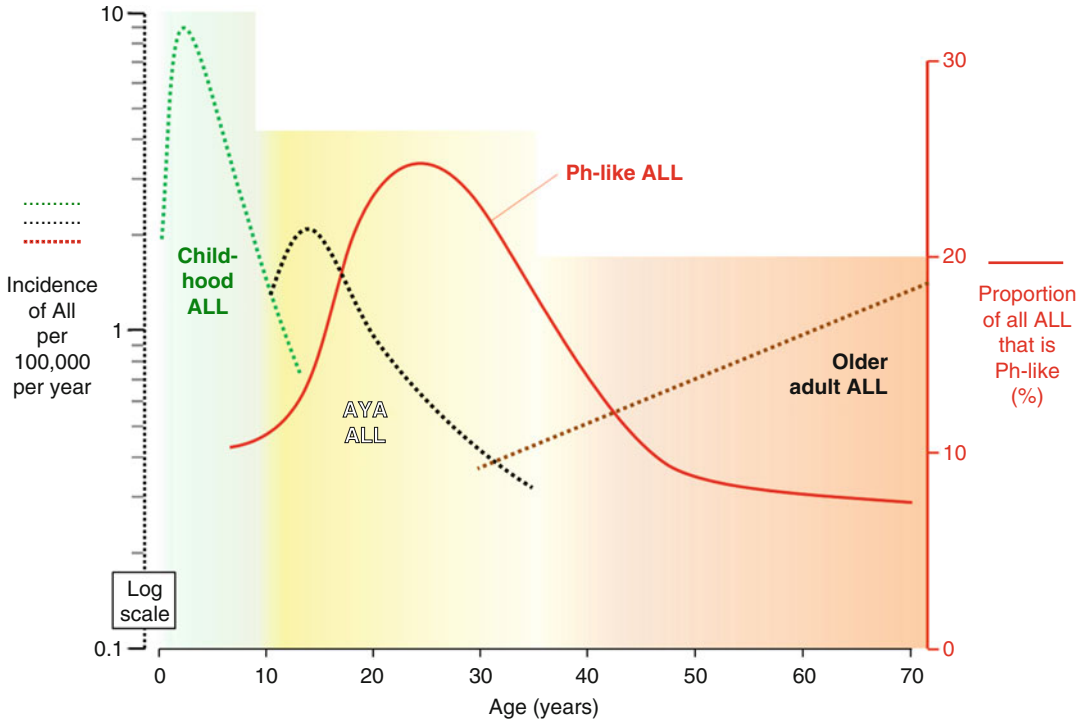

Fig. 7.6 Comparison of the incidence of all ALL and the proportional incidence of Ph-like ALL by age. All ALL incidence data are from SEER (Fig. 7.1) and Ph-like ALL data are derived from Roberts et al. [3] and Herold et al. [4]

hematologic malignancies between 1998 and 2008, AYAs between the ages of 15–39 years with ALL who were treated at community sites had worse outcomes than children between the ages of 10–14 years [10]. That difference was abrogated for 15–21-year-olds and greatly diminished for 22–39-year-olds though, if AYAs were treated at NCI Comprehensive Cancer Centers or Children's Oncology Group (NCICCC/COG) Institutions. Of note, in this study population, 69 % of children were treated at NCICCC/COG sites, but only 38 % of 15–21-year-old patients and 10 % of 22–39-year-old patients were treated at such centers.

Even on clinical trials though, AYAs with ALL are not faring as well as their younger counterparts [11, 12]. The discrepancy in survival between children and AYAs is certainly multifactorial, but disease biology is unquestionably important. As noted, up to 30 % of AYAs with ALL can be identified as having Ph-like ALL, and these patients have a particularly poor prognosis compared to patients without this gene expression signature [1, 2, 13]. In the study by Roberts et al. [3], which included more than 2,000 patients, adolescents with Ph-like ALL had a 5-year EFS and OS of 41.0 ± 7.4 % and 65.8 ± 7.1 %, respectively, compared to 83.3 ± 3.6 % and 92.5 ± 2.5 % in similarly aged patients with non-Ph-like ALL ($p < 0.001$ for both comparisons). For young adults with Ph-like ALL, the 5-year EFS and OS were 24.1 ± 10.5 % and 25.8 ± 9.9 %, outcomes which were significantly worse than young adults with non-Ph-like ALL, in whom the 5-year EFS and OS were 63.1 ± 9 % and 75.4 ± 8.2 %, respectively ($p < 0.001$).

Ultimately, survival outcomes for AYAs with ALL are improving, but continue to lag behind that of younger children. Contributing factors likely include, but are not limited to, disease biology, treatment location, and therapeutic regimens. A growing appreciation for the specific therapeutic and psychosocial needs of this age

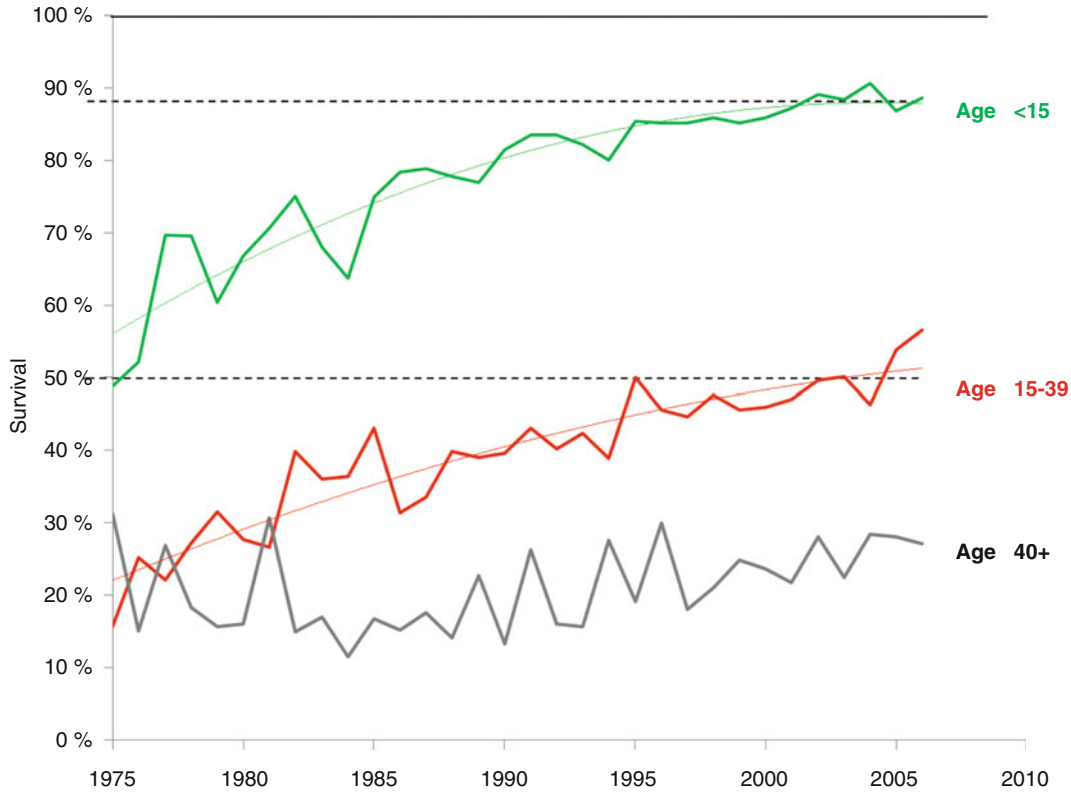

Fig. 7.7 Annual 5-year relative survival by age, 1975–2006, SEER 9, 13, and 18 areas. The regressions are 1° polynomials

group is expected to lead to further improvements in survival rates.

7.2 Clinical Presentation and Genetics

As a deeper understanding of the biology of ALL is developed, it is evident that AYAs present with higher-risk biology compared to their younger counterparts. The T lineage immunophenotype (T-ALL) is more common in the AYA population [14] and previously portended a worse prognosis, although with current therapies outcomes are approaching those of patients with B-ALL [15–18]. In fact in some adult ALL studies, patients with a T-cell immunophenotype fared better than patients with B-cell disease [19, 20]. Cytogenetic abnormalities, an important component of all risk stratification systems, shift toward more unfavorable profiles with increasing patient age [21]. The leukemic blasts in up to half of children between the ages of 1 and 10 years with B-ALL harbor either the favorable t(12;21) translocation or trisomies of chromosomes 4, 10, and 17, but these findings are rare in patients 20 years of age and older [11, 22]. Conversely, the incidence of intrachromosomal amplification of chromosome 21 (iAMP21) is more commonly found in the AYA and older adult population compared to younger patients [22–24], as is the t(9;22) translocation, which results in the Philadelphia chromosome, or BCR-ABL fusion protein [22]. It is important to note, however, that even though patients with Ph+ ALL are considered to have particularly aggressive disease, outcomes have been substantially improved by the incorporation of tyrosine kinase inhibitor therapy onto cytotoxic chemotherapy backbones [25–27].

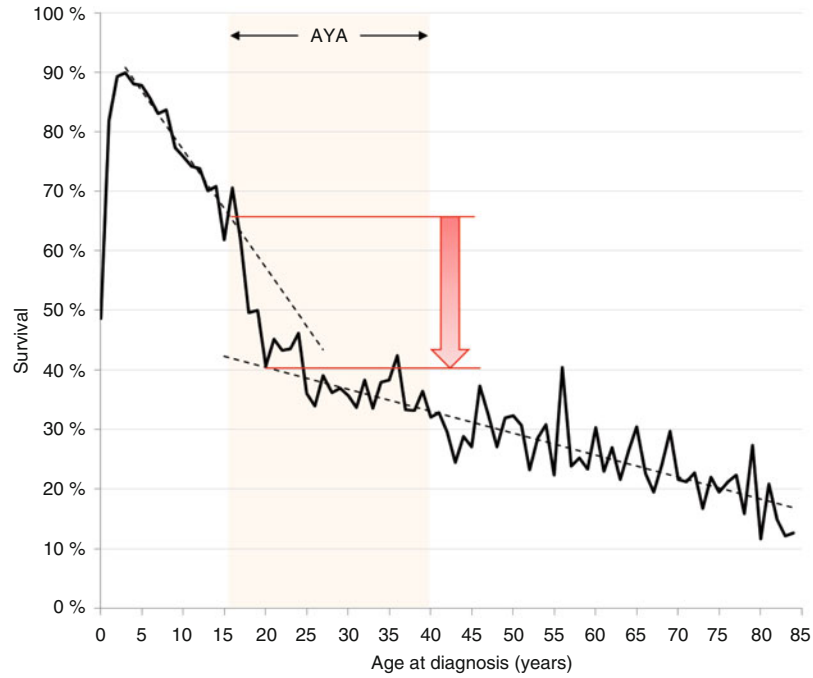

Fig. 7.8 ALL: 5-year relative survival, 2000–2011, at 1-year age intervals, SEER 18 areas. Arrow indicates 25 % absolute drop in 5-year survival from age 16 to 21. Dotted lines indicate linear regressions for ages 3–17 and 25–84 years

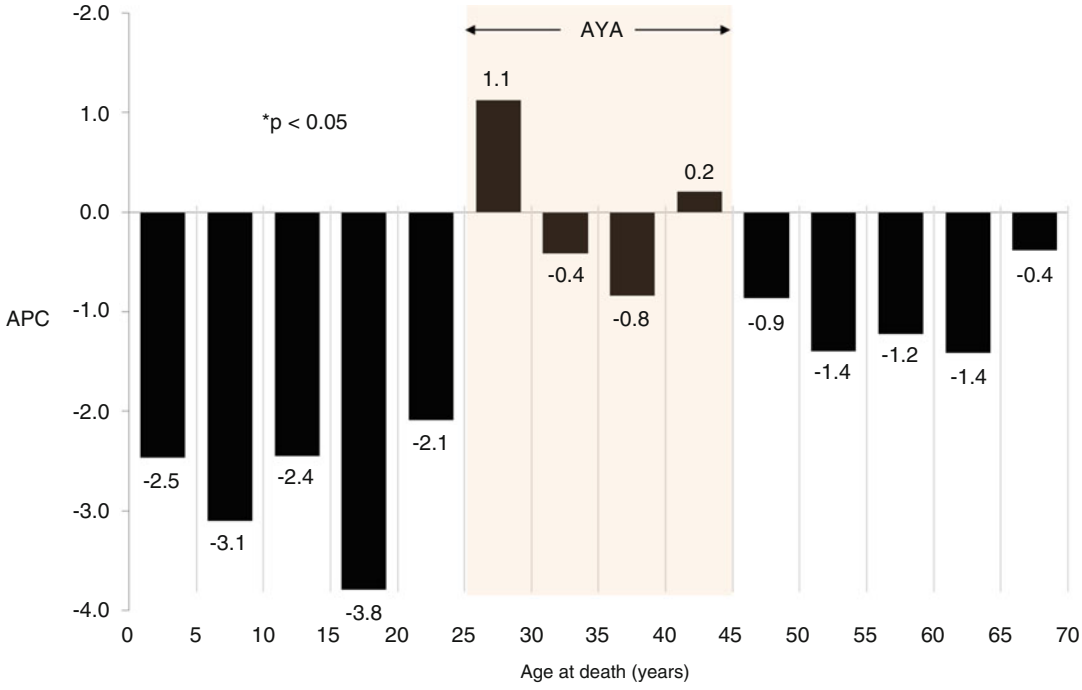

Fig. 7.9 ALL: annual percent change (*APC*) in death rate by age, 1998–2011. The data are from the National Center for Health Statistics

As described earlier, Ph-like ALL peaks in the AYA age group [1–4]. The Ph-like subset of B-ALL is characterized by deletions of *IKZF1* as well as aberrations in cytokine receptor and tyrosine kinase pathways [28]. Overexpression of cytokine receptor-like factor 2 (*CRLF2*) is particularly common in cases with *IKZF1* deletion and is correlated with *JAK* mutations and constitutive activation of the JAK-STAT pathway [29–31]. Using next-generation sequencing techniques, several other rearrangements (*ABL1*, *JAK2*, *PDGFRB*, *CRLF2*, and *EPOR*), mutations (*IL7R* and *FLT3*), and deletions (*SH2B3*, a gene which encodes a negative regulator of JAK2) have been identified in Ph-like ALL [32], many of which (*ABL1*, *ABL2*, *CSF1R*, *PDGFRB*, *CRLF2*, *JAK2*, *EPOR*, *IL2RB*, *NTRK3*, *PTK2B*, *TSLP*, and *TYK2*) are predicted to respond to various tyrosine kinase, JAK, or other signaling pathway inhibitors [3]. The relatively higher incidence of Ph-like ALL in AYA patients compared to younger and older counterparts may at least partially explain the lack of improvement in outcomes in these patients, and the effects of the incorporation of targeted therapies on such outcomes remains to be seen.

7.3 Treatment

7.3.1 The "Pediatric" Approach

The pediatric approach to ALL treatment relies on high cumulative doses of nonmyelosuppressive drugs, such as vincristine, glucocorticoids, and asparaginase, to be given during periods of neutropenia induced by anthracyclines, alkylators, and antimetabolite chemotherapy [15, 17, 18, 33, 34]. Most cooperative groups use an approach pioneered by the Berlin-Frankfurt-Münster (BFM) study group, with each group having made modifications based on the nuances of their own approach to risk stratification and their approach to treating particular subsets of patients. Remission induction (referred to as "protocol IA" in Europe) includes vincristine, prednisone or dexamethasone, asparaginase, and daunorubicin and is followed by consolidation therapy/protocol IB consisting of cyclophosphamide, cytarabine, and 6-mercaptopurine (6MP). Following these initial intense months, there is a phase termed "interim maintenance" (IM) in the USA, or "protocol M" in Europe, which consists largely of intravenous methotrexate (MTX) given in intermediate or high doses with leucovorin rescue, in conjunction with oral 6MP, and in the USA intravenous vincristine is administered as well. Subsequently, there is a return to intense therapy ("delayed intensification" in the United States, "protocol II" or "protocol III" in Europe) which is essentially re-induction and reconsolidation phases. Typically at this time, prednisone is replaced by dexamethasone, daunorubicin by doxorubicin, and 6-mercaptopurine by 6-thioguanine. On some US protocols, a second IM phase may be administered, but this time using vincristine, escalating doses of intravenous MTX without rescue, and asparaginase ("Capizzi methotrexate"). Debate continues regarding the benefits of this second IM phase. All protocols call for a prolonged maintenance phase that relies mainly on antimetabolite therapy. Dedicated treatment of the central nervous system (CNS) with intensive intrathecal chemotherapy begins during induction and continues throughout therapy. On many protocols, patients with overt CNS disease at diagnosis or with certain very high-risk features are also treated with cranial irradiation.

While there is a discrepancy between improvements in outcomes between younger children compared to the AYA age group, adolescents on cooperative group studies fare better now than in previous eras. On Children's Oncology Group (COG) ALL studies from 1990 to 2005, the 5-year OS for patients 15–22 years of age improved from 66.1 ± 2.3 % in the early 1990s to 75.9 ± 2.6 % in the early 2000s. Also improved was the percentage of adolescents diagnosed with ALL who enrolled onto clinical trials. From 1990 to 2005, 33.5 % of adolescents aged 15–19.99 years predicted to develop ALL were enrolled onto COG trials. Heightened awareness of the issues surrounding AYA oncology and the importance of enrollment on clinical trials led to that number increasing to 51 % by 2009 [12]. Similarly, good results have been reported by

other groups. For adolescents treated on Dana-Farber Cancer Institute (DFCI) protocols 91-01 and 95-01, 5-year EFS was 77 % (SE, 4 %) and 78 % (SE, 6 %), and 5-year OS was 78 % (SE, 4 %) and 81 % (SE, 6 %) for 10–15- and 15–18-year-olds, respectively [35]. DFCI protocols include frequent doses of vincristine, asparaginase, and corticosteroids, as well as high cumulative doses of anthracyclines. Untoward toxicities were not observed in the adolescent patients, although there were higher rates of pancreatitis and thrombosis compared to patients <10 years old [35].

The importance of enrollment onto clinical trials cannot be stressed enough. Treatment regimens for ALL are prolonged and complex, and adherence to therapy is crucial. Providers must be familiar with the entirety of the treatment, and must be vigilant in administration of chemotherapy according to the prescribed schedule. Medical professionals who care for AYAs with ALL must also recognize the challenges faced by AYAs as they attend frequent clinic visits while maintaining educational and employment responsibilities, and who struggle to comply with oral chemotherapy schedules while simultaneously exerting independence and autonomy from parents or other guardians. Uniform treatment of large numbers of patients on clinical trials will continue to raise awareness of appropriate treatment regimens as well as the unique needs of the AYA population.

7.3.2 The "Adult" Approach

There have been essentially two approaches by medical oncologists to the treatment of ALL in adults. One approach is administration of BFM-like chemotherapy, as outlined above. The other is the "hyper-CVAD" regimen, which consists of cycles composed of two alternating courses of chemotherapy (course A and course B) [36]. Course A consists of cyclophosphamide and mesna given every 12 h on days 1–3, followed by doxorubicin on day 4. Vincristine is given on day 1, and there are 2, 4-day pulses of dexamethasone on days 1–4 and 11–14. Course B consists of intermediate-dose methotrexate on day 1 with leucovorin rescue followed by high-dose cytarabine given every 12 h on days 2–3. Methylprednisolone is administered on days 1–3. Intrathecal MTX and cytarabine and cranial radiation are used for CNS prophylaxis and incorporated into both course A and course B, the amount of which depends on a risk categorization for CNS relapse. Rituximab is added to each A and B course for patients with CD20+ ALL. After eight cycles of therapy, patients receive POMP maintenance therapy, consisting of 6MP, vincristine, MTX, and prednisone, with two courses of intensification with hyper-CVAD and MTX/asparaginase at months 6–7 and 18–19 of maintenance therapy. When treated with hyper-CVAD, patients receive each course of myelosuppressive drugs followed by several weeks of rest while awaiting count recovery. With either the BFM or the hyper-CVAD approach, the maintenance phase of therapy tends not be as prolonged as that of pediatric protocols [36–40].

7.3.3 "Pediatric" Versus "Adult" Approaches

A number of studies have compared outcomes for similarly aged AYA patients treated with either pediatric or adult regimens or have reported outcomes specifically of AYA patients treated on pediatric-inspired regimens (Table 7.1). In many of these, survival was significantly better for those patients treated with a pediatric regimen [6, 39, 41–45]. Encouraged by these results, several adult groups have prospectively applied a pediatric-inspired treatment regimen to a young adult population, managed by medical, rather than pediatric, oncologists.

From 2002 to 2008, DFCI investigators administered a DFCI Pediatric ALL Consortium regimen to 92 patients 18–50 years of age, reaching an 85 % complete remission (CR) rate (90 % CI, 77–91 %) and 4-year disease-free survival (DFS) rate of 69 % (95 % CI, 56–78 %) for those patients achieving CR, which was much better than historical survival rates of <50 % [46]. The regimen, which relied heavily on intensive asparaginase administration, was well tolerated

Table 7.1 Outcomes for AYA ALL patients treated on pediatric compared to adult protocols

Regimens (Pediatric/Adult)	Patient Ages (Years)	Event Free Survival (95 % CI) (Pediatric/Adult)	Overall Survival (95 % CI) (Pediatric/Adult)
FRALLE-93/LALA-94 [39]	15–20	67 % (±13 %) / 41 % (±14 %) p < 0.0001	78 % (±11 %) / 45 % (± 11 %) p < 0.0001
DCOG / HOVON [41]	15–18	69 % (54–81 %) / 34 % (21–48 %) p = 0.0001	79 % (64–88 %) / 38 % (24–52 %) p < 0.0001
NOPHO-92 / Swedish Adult ALL Group [42]	15–18/15–20	74 % (60–89 %) / 39 % (19–59 %) p < 0.01	Not reported
ALL97 / UKALLXII [43]	15–17	65 % (52–78 %) / 49 % (37–61 %) p = 0.01	71 % (59–84 %) / 56 % (48–68 %) p = 0.04
CCG/CALGB [44]	16–20	63 % (24–44 %) / 34 % (55–72 %) p < 0.0001	67 % (58–75 %) / 46 % (36–56 %) p = 0.0002
NOPHO/Finnish Leukemia Group [50]	10–16/16–25	67 % (±5 %) / 60 % (±6 %) p = 0.25	77 % (±40) / 70 % (±6 %) p = 0.29
MD Anderson: ABFM/hyper-CVAD [36]	13–39/16–40	Not reported	74 % / 71 % p = ns
PETHEMA ALL-96* [45]	15–30	Adolescents: 60 % (43–77 %) Young Adults: 63 % (48–78 %)	Adolescents: 77 % (63–90 %) Young Adults: 63 % (46–80 %)
CCG-1961* [6]	16–21	71.5 % (SE 3.6 %)	77.5 % (SE 3.3 %)

*All patients treated on one, pediatric-inspired, protocol

in the young adult population, and in fact the primary endpoint of the study was the feasibility of weekly asparaginase administration for the 30-week intensification phase of therapy. Fifty-seven patients were evaluable for the endpoint, and 36 of them (63 %) completed all 30 doses. Forty-one (72 %) completed at least 26 doses, an important benchmark, as the pediatric DFCI data suggests that administration of at least 26 doses of asparaginase is as efficacious as administration of all 30 [47]. In a larger cooperative group trial (C10403) that was conducted from 2007 to 2012, 296 evaluable patients between the ages of 16 and 39 were treated by medical oncologists, using one arm of the most recent COG study (AALL0232) for patients with B-ALL [48]. The 2-year EFS was 66 % (95 % CI, 60–72 %) with a median EFS of 59.4 months, significantly longer than the null hypothesis, which was that the median EFS for this patient population would be ≤32 months. The observed toxicities were similar to that reported on the pediatric trial with the exception of higher rates of thrombosis, neuropathy, osteonecrosis (ON), and mucositis in patients ≥20 years of age on C10403, but higher rates of hypersensitivity and motor neuropathy on AALL0232 [49]. Taken together, these studies demonstrate that not only is pediatric therapy feasible in a young adult population but it also appears to improve outcomes.

Other retrospective studies have reported similar outcomes for patients treated on either adult or pediatric regimens. In a population-based study, Usvasalo et al. reported that consecutive patients aged 10–25 years treated in Finland for ALL from 1990 to 2004 had comparable outcomes when treated on either pediatric or adult regimens. The 5-year EFS/OS for pediatric versus adult patients were 67 % versus 60 % (EFS) and 77 % versus 70 % (OS) (p = ns for both) [50]. In a study from MD Anderson Cancer Center, 85 AYA patients (12–40 years) were treated with a BFM-based chemotherapy regimen, and outcomes were compared to a historical control group (71 patients aged 16–40 years) treated with hyper-CVAD [36]. Similar to the study out of Finland, outcomes on each regimen were comparable. Overall survival at 3 years was 74 % for patients treated with BFM-based therapy and 71 % for those treated with hyper-CVAD (p = ns).

It is worth noting that the adult regimens used in Finland tended to incorporate higher doses of MTX, epipodophyllotoxins, and anthracyclines than the pediatric protocols, but they also included high cumulative doses of vincristine, asparaginase, and corticosteroids – tenets of BFM-based

therapy. Furthermore, the authors point out that all patients in Finland, regardless of age, are treated at one of five centralized academic centers, and the culture and healthcare system is such that adherence to therapy is universally very good. Likewise, the study from MD Anderson Cancer Center is a single-institution study, and the treating physicians were very familiar with the complexity and nuances of the treatment regimens.

The potential and accrued toxicity of therapy and the late adverse effects are also increasingly major considerations, especially as the long-term survival and cure rates have improved in AYAs with ALL. As a result of decades of attempts by pediatric oncologists to reduce the adverse late effects of their regimens, the pediatric regimens have low gonadotoxic, cardiotoxic, infertility, and carcinogenic potential, achieved in part by successful limitation of their total alkylating, anthracycline, and radiation exposure, manifesting as favorable long-term follow-up results [51]. In contrast, the hyper-CVAD regimen has substantially greater exposure to alkylators, anthracyclines, and radiation, and for patients with CD20+ ALL, rituximab [52]. Hyper-CVAD requires hospitalization for the A and B courses, and there is a high rate of admission for fever and neutropenia and for other signs of infection or cytopenia [52]. Secondary acute myelogenous leukemia and myelodysplasia may also occur more frequently after hyper-CVAD than with a pediatric type of regimen, which has led to discontinuation of the regimen at some centers [52]. Hyper-CVAD is also regarded to have high potential for rendering males and females infertile, with more than 80% of women predicted to develop amenorrhea post-treatment and a majority of men predicted to have prolonged azoospermia [52].

7.3.4 The Role of Hematopoietic Stem Cell Transplant

Some studies have supported a role for hematopoietic stem cell transplant (HSCT) in first remission (CR1). In a joint trial between the MRC and the Eastern Cooperative Oncology Group (ECOG), patients aged 15–59 years were treated with two identical cycles of induction chemotherapy, followed by allogeneic HSCT if a matched sibling donor (MSD) was available, or if there was no MSD, randomized to chemotherapy alone versus autologous HSCT [53]. A donor versus no-donor analysis of Philadelphia chromosome-negative (Ph-) patients revealed a 5-year OS of 54% compared to 44% ($p=0.007$) for patients with and without a MSD, respectively. This survival benefit was observed in patients considered to have standard-risk disease (5-year OS 63% versus 52%, $p=0.02$), but not necessarily in high-risk patients (5-year OS 42% versus 35%, $p=0.2$). In a meta-analysis of 20 studies in which adult patients with ALL who had a MSD underwent allogeneic HSCT, and those who did not underwent either autologous HSCT or were treated with chemotherapy alone, there was no benefit found for autologous HSCT [54]. Overall survival was longer for those patients with a donor (OR = 0.87, 95% CI 0.79–0.96, $p=0.006$), despite higher treatment-related mortality (TRM) (OR = 2.36, 95% CI 1.94–2.86, $p<0.00001$). TRM was particularly high in patients ≥35 years of age, with 32% of those with a donor and 14% of those without a donor dying in remission. In patients <35 years of age, 19% of those with and 8% of those without a donor died without relapse. This led to higher 5-year survival rates for patients <35 years of age with a donor (55% versus 45.1%), but not for those ≥35 years of age (39.2% versus 37.2%).

Results such as these have led many oncologists to consider HSCT in CR1 for young adult patients with ALL, who are able to tolerate the toxicity of HSCT better than their older adult counterparts [55]. However, a benefit for HSCT in CR1 is not necessarily evident. A study from the International Bone Marrow Transplant Registry (IBMTR) compared outcomes between 422 patients aged 18–50 years who underwent related or unrelated HSCT and 108 patients aged 18–50 years who were treated with chemotherapy alone, according to a pediatric regimen [56]. Cumulative incidence of relapse was similar between the groups, but TRM was significantly lower in patients treated with chemotherapy alone. Disease-free survival at 4 years was significantly higher in the cohort treated with chemotherapy (71% [60–79%] versus 40%

[35–45 %], $p < 0.0001$), as was 4-year OS (73 % [63–81 %] versus 45 % [40–50 %], $p < 0.0001$). In a large study conducted by the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL), investigators evaluated the role of HSCT in adults (15–55 years) with Ph- ALL who were treated with a pediatric-inspired regimen [57]. Only patients who were considered to have high-risk disease based on a combination of cytogenetics/disease biology, CNS status, and disease response were eligible for HSCT; out of 522 study patients, 282 were in the HSCT cohort. For patients who underwent HSCT, there was no benefit regarding relapse-free survival (RFS) (hazard ratio [HR], 0.80; 95 % CI, 0.6–1.06; $p = 0.12$) or OS (HR, 0.76; 95 % CI, 0.57–1.02; $p = 0.069$). There was a lower cumulative incidence of relapse in the HSCT group (HR, 0.5; 95 % CI, 0.35–0.7; $p < 0.001$), but this was countered by higher rates of non-relapse mortality (HR 1.46; 95 % CI, 1.09–1.95; $p = 0.011$), leading to the similar survival outcomes. Note, however, that on subgroup analysis, there appeared to be a benefit with HSCT for patients with poor disease response, defined as residual disease $\geq 10^{-3}$ after induction chemotherapy; HR was 0.37 for RFS (95 % CI, 0.2–0.69; $p = 0.001$) and 0.41 for OS (95 % CI, 0.22–0.76; $p = 0.005$). Patients with *IKZF1* gene deletions also appeared to benefit from HSCT, but this may have been related to poor disease response, as often occurs in these patients. No randomized comparisons currently exist between continuation of intensive pediatric-inspired chemotherapy regimens and allogeneic HSCT in CR1 for AYAs with Ph- ALL, and these data suggest that there may not be a general survival benefit for HSCT in CR1 for this population. However, there may be identifiable subgroups of patients for whom HSCT in CR1 is beneficial.

7.4 Toxicity

Toxicity of therapy is certainly of concern for any patient with cancer, and the risks of treatment must be carefully balanced with the goal of cure. As pediatric-inspired regimens are administered to AYAs, the potential toxicity of therapy must be monitored closely, as the intensity of pediatric ALL therapy may not be as well tolerated in AYAs as it generally is in younger children. While many chemotherapy side effects are consistent across age groups, there are particular drugs and toxicities that warrant specific consideration in the AYA population.

7.4.1 Asparaginase

Asparaginase has long been established as an integral drug in pediatric ALL regimens [47, 58–62] and is effective for adults with ALL as well [6, 46, 63–65]. With its efficacy, however, comes not insignificant toxicity [66–69], and asparaginase toxicity is of concern as pediatric ALL protocols are being increasingly applied to the AYA population [70].

7.4.1.1 Hypersensitivity

Asparaginase is an enzyme derived from bacteria and is therefore a foreign protein. Three forms of asparaginase are available for clinical use: native *Escherichia coli*-derived L-asparaginase (*E. coli* asparaginase), a pegylated form of *E. coli* asparaginase (PEG-asparaginase), and a form derived from *Erwinia chrysanthemi* (*Erwinia* asparaginase). The development of hypersensitivity to this protein is multifactorial and is likely related to concomitant administration of steroids and prior asparaginase exposure, in addition to individual patient susceptibility.

Rates of hypersensitivity reactions vary and are highest with native *E. coli* asparaginase [71–73]. On the North American DFCI Consortium Studies, rates of asparaginase hypersensitivity are approximately 20 % [47, 74], and a report from northern Europe found a similarly low incidence of allergy (13 %) [75]. A wide range (~25–50 %) of incidence of allergic reaction has been reported on COG studies [6, 76]. The differences for these rates are unclear, but may be related to protocols that used native *E. coli* asparaginase with more continuous dosing of asparaginase and therefore steady exposure, compared to reexposure to asparaginase following an asparaginase-free interval during therapy. Administration by the intravenous route, rather than intramuscularly,

may lead to higher rates of hypersensitivity as well [77, 78].

In studies of adult patients, hypersensitivity remains a concern, but occurs at a lower incidence. In the Cancer and Leukemia Group B (CALGB) 8811 study, hypersensitivity reactions were reported in 11 % of patients [73], and an even lower rate of 5 % was noted in a study out of DFCI [46]. In a young adult population, the initial rates of hypersensitivity reactions were approaching 13 % on the C10403 study, but that rate declined to 7.9 % after an amendment requiring that patients be medicated with corticosteroids and antihistamines prior to each dose of PEG-asparaginase [49]. The antibodies that cause hypersensitivity reactions also inactivate asparaginase, resulting in decreased asparaginase activity [79, 80]. There is concern, therefore, that premedication will abrogate signs of neutralizing antibody (NA) formation, thereby leading to continued administration of a drug that now lacks efficacy. Besides causing overt hypersensitivity reactions, NAs can also lead to silent inactivation of asparaginase, another indication to change formulation [66, 68]. Silent inactivation occurs when NAs develop against asparaginase without clinical signs of allergic reaction [81, 82]. In either of these scenarios, it is possible to detect evidence of NA formation by obtaining asparaginase levels at particular time points following administration of asparaginase, with an assay that is now commercially available [83]. PEG-asparaginase appears to have a significantly lower rate of inducing neutralizing antibody than the native enzyme, in the range of 2–5 % after the immunizing dose [70]. Patients with silent antibodies may benefit from a switch to *Erwinia* asparaginase or theoretically from more frequent dosing of PEG-asparaginase, in that enough antigen (asparaginase) may saturate the antibody and overcome the neutralizing capacity [83]. Subtherapeutic asparaginase levels indicate the presence of NAs and can be addressed either via therapeutic drug monitoring with the asparaginase activity assay and dosing adjustments or replacement with a different bacterial-derived asparaginase. Patients with hypersensitivity to or silent inactivation of *E. coli*-derived asparaginase (native or pegylated) are often treated with *Erwinia* asparaginase instead. In these situations, *Erwinia* asparaginase is generally well tolerated, with acceptable rates of recurrent allergic reactions [84–87].

7.4.1.2 Pancreatitis

Incidence rates of pancreatitis are low on most protocols, and while this complication is largely manageable with appropriate medical therapy, very severe cases certainly occur. Most pediatric studies report incidence rates less than 10 % [88–93], and both DFCI and CALGB have reported modest rates of pancreatitis in their young adult population [46, 49]. Avoidance of alcohol is a key preventive measure. Treatment for asparaginase-induced pancreatitis includes bowel rest, nasogastric decompression, intravenous hydration, parenteral nutrition, and, as needed, antiemetics and analgesics [66]. In more severe cases, the somatostatin analogue, octreotide, has been used as a safe and effective intervention [94]. Asparaginase therapy can be continued in patients who develop asymptomatic chemical pancreatitis or in those who have abdominal pain ± vomiting but no laboratory or radiologic evidence of pancreatitis. However, all asparaginase therapy should be discontinued in those patients who develop clinical pancreatitis based on symptoms and elevated amylase/lipase levels with or without radiologic findings (including pancreatic pseudocyst) [66].

7.4.1.3 Hyperglycemia

Hyperglycemia is a common toxicity in patients undergoing treatment for ALL, often due to administration of corticosteroid therapy, but also during treatment with asparaginase. When compared with younger patients, rates of hyperglycemia are higher in AYAs. On the COG AALL0232 study for patients 1–30 years of age with high-risk B-ALL, concurrent corticosteroid and asparaginase use led to hyperglycemia during induction therapy in 22 % of those patients >16 years versus 15.4 % of those 1–15 years ($p = 0.0002$) [95]. Similarly, 29.3 % of AYAs enrolled on C10403 experienced grade 3–5 hyperglycemia during induction therapy, and that rate increased to 32 % of patients throughout post-induction phases of

treatment [49]. As patients may be asymptomatic, careful screening for hyperglycemia in AYA patients is warranted, especially since if left untreated, poor wound healing, ketoacidosis, and even hyperosmolar coma can result [96, 97].

7.4.1.4 Hepatotoxicity

Similar to hyperglycemia, hepatotoxicity occurs at a higher frequency in the AYA population compared to younger patients. Manifestations include transaminitis, hyperbilirubinemia, and hypoalbuminemia, as well as lipid abnormalities. Rates of elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have been reported as high as 30–50 % in AYAs being treated for ALL [46, 49]. Increased bilirubin, which is observed in 20–25 % of patients [49], can be of particular concern, since doses of other drugs that are metabolized by the liver (e.g., vinca alkaloids and anthracyclines) may need to be held or decreased at times of hyperbilirubinemia [66].

Lipid abnormalities in AYAs can be remarkable, in particular elevated triglycerides [98–100]. Asparaginase-induced hypertriglyceridemia tends not to lead to pancreatitis [101, 102], despite this being a known risk factor in the general population [103]. With appropriate medical management, it is possible to continue ALL treatment through hyperlipidemia. Success has been demonstrated with omega-3 fatty acids, fibrates, nicotinic acid derivatives, and statins [99, 104, 105].

Certainly strategies can be employed to minimize the risk of hepatotoxicity. In the AYA age group, it is important to stress avoidance of alcohol, as well as to at least limit the use of hepatotoxic prescription drugs, such as azole antifungals. Careful monitoring is needed at times of necessary concurrent use of hepatotoxic chemotherapy agents, such as MTX and cytarabine.

7.4.1.5 Coagulation Abnormalities

Asparaginase increases the risk of both thrombosis and bleeding, with venous thromboembolism (VTE) not only being more common [66, 67] but also age dependent [106–108]. In a study of 548 patients treated on DFCI protocols from 1991 to 2008, 43 (8 %) developed VTE. The incidence was 27/501 (5 %) in pediatric patients (0–18 years), but 16/47 (34 %) in adult patients (18–50 years) [108]. The mechanism for asparaginase-induced coagulopathy is related to reduced protein synthesis resulting in depletions of plasminogen, fibrinogen, antithrombin III (AT3), proteins C and S, and factors IX and X [67]. Rates seem to vary based on asparaginase formulation. Relatively low rates of thrombosis/bleeding have been reported with *Erwinia* asparaginase [85, 86], but due to prolonged (~21 day) AT3 depletion with PEG-asparaginase, there is potential for a higher risk of VTE [109]. There may not be a direct correlation, however, between depletion of anticoagulant factors and VTE risk. Investigators with the Italian Association of Pediatric Hematology and Oncology (AIEOP) investigated the rates of VTE in children with ALL enrolled on the AIEOP-BFM ALL 2000 study and found that AT3 was <50 U/mL in 4.7 % of cases and 3.7 % of controls, and AT3 levels were normal (≥80 U/mL) in 57 % of cases and 70 % of controls (p = ns) [107]. Fibrinogen levels were also not significantly different between cases and controls, with 60 % of patients with VTE and 69 % of controls having fibrinogen ≥100 mg/dL.

In patients with thrombotic or hemorrhagic complications, antithrombin III concentrates and cryoprecipitate can be used to replace AT3 and fibrinogen, respectively. Fresh frozen plasma can be used to replete AT3 if antithrombin III concentrate is not available, but since it contains asparagine, it may decrease the antileukemic effects of asparaginase. Anticoagulation with low-molecular-weight heparin (LMWH), and transition to warfarin if desired, is appropriate for those patients with thrombotic complications. If appropriate precautions are taken, asparaginase therapy can be resumed in many patients with VTE. This is of particular concern, since the importance of asparaginase as a component of ALL therapy has been well established, and inferior outcomes have been reported in patients with asparaginase-induced VTE [110]. Since AT3 is depleted by asparaginase, levels can be followed in patients in whom there has been

VTE, with repletion as needed in order to continue asparaginase therapy [108, 110], although this does not preclude recurrent VTE. Grace et al. reported a recurrence rate of 33 % in their series, with a trend toward significance in adult versus pediatric patients (47 % versus 17 %, $p = 0.07$) [108]. Patients with VTE also can be maintained on LMWH throughout the duration of their asparaginase therapy in order to prevent recurrence. On the UKALL 2003 study for patients aged 1–25 years with ALL, 59/1,824 (3.2 %) of patients developed VTE [111]. Fifty of the patients required further asparaginase therapy, 38 of whom received further doses, including 10 with cerebral sinus thrombosis. LMWH was administered as prophylaxis, and no recurrent VTE was reported.

7.4.2 Glucocorticoids

7.4.2.1 Osteonecrosis

Osteonecrosis (ON) due to glucocorticoid therapy is a well-recognized morbidity affecting patients with ALL. There are many studies that have reported a higher incidence in AYAs compared to younger patients [112–120]. Rates range from 1 % to 3 % for patients <10 years of age to 7–13 % for those 10–15 years of age and 16–29 % for those 16–20 years of age, with a decrease to 8 % in patients >20 years of age [121]. Some groups, including COG and DFCI, have found a stronger association between the use of dexamethasone and the development of ON [122, 123]. On the COG AALL0232 study for patients with NCI high-risk B-ALL, a higher risk of ON was noted in patients ≥10 years of age treated with dexamethasone compared to prednisone (17.2 % versus 12.6 %, $p = 0.006$) [124]. Furthermore, COG had found previously that discontinuous dosing of dexamethasone during delayed intensification resulted in a lower incidence of ON [76, 117]. This has led COG to use prednisone as the induction steroid for all patients ≥10 years of age with B-ALL, as well as discontinuous dexamethasone (i.e., days 1–7 and 15–21) in all patients during delayed intensification.

On the other hand, studies run by the MRC and the BFM groups in the United Kingdom and Germany, respectively, have not revealed a difference between patients receiving dexamethasone versus prednisone [124, 126]. On the UK ALL97 trial for patients 1–18 years of age, patients were randomized to dexamethasone or prednisone during various phases of therapy. Osteonecrosis was more frequently observed in older patients ($p < 0.0001$), but while there was an increase in general toxicity with dexamethasone, including significant differences in osteopenia between the dexamethasone and the prednisone regimens, there was no significant increase in the rates of ON in patients treated with dexamethasone, regardless of age [125]. Similar to the study in the UK, the ALL-BFM 2000 study enrolled patients 1–17 years of age and found an incidence rate of 3.6 % for ON (95 % CI, 3.0–4.4 %), with the highest rates in adolescent girls [126]. For children <10 years old, the rate in girls compared to boys was 0.8 % versus 0.7 %, respectively ($p = 0.68$), but for children ≥10 years of age, the rate was 18.4 % in girls and 7.6 % in boys ($p < 0.001$), with no difference if patients were treated with dexamethasone or prednisone (overall rates of 3.0 % versus 3.2 %, $p = 0.77$). Given these results, European protocols tend not to factor in a patient's age when assigning a particular steroid.

Treatment for ON varies and is dependent on a number of factors, including the location and extent of damage, age, and general health of the patient, as well as leukemia status. The damage is not reversible, and therefore therapy is focused on symptom management and stopping the progression of ON. In general, further glucocorticoid therapy is withheld once the patient has reached the maintenance phase of therapy, pertinent only for patients being treated on a protocol that includes glucocorticoid pulses in maintenance. Initial management is largely supportive, consisting of analgesia, avoidance of weight bearing, and physical therapy. For some, surgical options including core decompression, hemiarthroplasty, or joint replacement must be considered [121].

Since the pathophysiologic process of ON cannot be reversed, and early intervention may

improve functional outcomes, screening has been considered to identify patients with early ON. When magnetic resonance imaging (MRI) is obtained on asymptomatic patients undergoing therapy for ALL, rates vary, but low-grade ON can be seen in up to 70% of patients [114, 127, 128]. In a large study that involved at least one hip MRI on 462 patients, there was a cumulative incidence of ON of 21.7 ± 1.9% [129]. Age >10 years was an independent predictor of the development of ON, and 24 ± 4.4% of patients in this age group developed extensive femoral head ON, defined as affecting ≥30% of the epiphyseal surface. For the entire cohort, 20.1 joints (95% CI, 14.8–27.6) would need to be screened to identify one extensively affected one, but that number decreased to 4.4 joints (95% CI, 3.3–5.9) in patients >10 years of age. Whether screening and early intervention would improve outcomes and be cost-effective, however, has not yet been determined.

7.4.3 Other Toxicities

While the myriad of asparaginase toxicities, as well as the burden of ON in AYAs, is well described, other toxicities such as myelosuppression, infectious risks, neuropathy, and mucositis also become more pronounced in AYAs. In the PETHEMA (Programa Español de Tratamiento en Hematología) ALL-96 protocol, 35 adolescent (15–18 years) and 46 young adult (18–30 years) patients with ALL were treated with a pediatric-inspired regimen [45], and toxicities were compared between these two groups. During the consolidation-1 phase of treatment, grade 4 neutropenia occurred in 44% of adolescents and 59% of young adults, and grade 4 thrombocytopenia occurred in 10% and 33% of adolescents and young adults, respectively. This led to a delay in starting consolidation-2 therapy in 16% of patients – eight young adults and one adolescent ($p=0.031$). Febrile neutropenia occurred in 43 of all of these patients during induction with 1 death attributable to infection, and when looking at milder infections, young adults were more likely to have grade 1 infections (13 young adults versus 1 adolescent, $p=0.007$). Storring et al. also reported somewhat high rates of myelosuppressive and infectious complications in a cohort of 85 patients aged 18–60 years treated according to a pediatric-type protocol [65]. Febrile neutropenia with negative cultures occurred during induction therapy in 13 patients, bacteremia in 13, invasive fungal infections in 9, and suspected herpes simplex meningitis in 2. Five patients died during induction due to infection. COG investigators compared the toxicity profile of AYAs (16–30 years old) to that of younger patients (1–15 years old) on the AALL0232 study, and conversely found lower rates of febrile neutropenia during all of therapy for AYAs (35.6% versus 48.6%, $p<0.0001$) [95]. There was no difference in induction deaths (2.2% versus 1.7%, $p=0.39$); however, death in remission occurred more frequently in the AYA patients. The 5-year cumulative incidence of remission death for AYAs was 4.4 ± 1.1% compared to 1.8 ± 0.4% for younger patients ($p=0.0015$), with 69% of remission deaths in AYAs resulting from infections, compared to 52% of remission deaths in younger patients. When this cohort of patients was compared to young adult patients (16–39 years old) enrolled on C10403, induction rates of febrile neutropenia were higher in the C10403 patients (19.2% versus 7%), but induction mortality was low in both groups, approximately 2% [49].

Vincristine-induced neuropathy is more common in AYAs compared to younger patients. PETHEMA investigators reported that young adults were more likely to require dose adjustments of vincristine compared to adolescents during re-induction chemotherapy on ALL-96, with adjustments of either vincristine or asparaginase necessary in 25 of 165 cycles in adolescents versus 55 of 166 cycles in young adults ($p=0.03$) [45]. In the report by Storring et al., 22% of patients suffered neuropathy, and due to this, many patients had vinblastine substituted for vincristine [65]. Peripheral motor neuropathy was worse in AYAs enrolled on AALL0232 compared to younger patients (11.5% versus 7.4%, $p=0.0015$) [95]. Comparing both motor and sensory peripheral neuropathies experienced by patients enrolled on AALL0232 with those on C10403, no difference was noted, but on both studies, rates of neuropathy increased in patients ≥20 years old [49].

Other significant toxicities reported by Storring et al. include grade III mucositis in 6% during induction, as well as AST/ALT greater than five times the upper limit of normal in 13% and steroid myopathy in 4% of patients during intensification phases [65]. Mucositis was more frequent in AYAs enrolled on AALL0232 compared to younger patients (18.5% versus 11.3%, $p=0.0002$), with overall rates in AYAs similar to that observed on C10403. Similar to neuropathy, increasing rates of mucositis were noted on both studies in those patients ≥20 years of age [49, 95].

7.5 Compliance and Psychosocial Issues

For all AYAs with cancer, compliance with and adherence to therapy differs compared to that of both younger and older patients [130]. Complicating factors abound, but include educational and employment expectations; family, peer, and romantic relationships; and insurance status. Therapy for ALL is long and, at times, quite intense. It involves both treatment administered in the clinic as well as medications taken by the individual at home. Therefore, there is pressure on patients and their support networks to comply not only with frequent clinic visits but also with complex home medication regimens. For AYAs treated according to pediatric protocols, during the initial 6–9 months of treatment, patients must be seen in clinic almost weekly, so that intravenous and intrathecal chemotherapy can be administered according to schedule. This is disruptive to school and job attendance, requires reliable access to transportation, and in many cases a support network to assist a patient in traveling back and forth. While this time period is burdensome, the majority of therapy for ALL is maintenance therapy, during which a patient must take oral medications at home daily. Stakes are high, as adverse outcomes have been linked to nonadherence with chemotherapy regimens, but accurate assessment of adherence to home medication regimens is difficult.

Bhatia et al. studied adherence to daily 6MP during maintenance therapy for up to 5 months in a cohort of ALL patients enrolled on a COG study, using an electronic monitoring device that recorded the date and time of each pill bottle opening [131]. Adherence <90% was significantly associated with an increased risk of relapse (HR 3.9, $p=0.01$). Adolescents were not analyzed separately, but factors such as parental education level and the steady presence of a parent who supervised medication administration were significantly related to adherence rates, two factors which can easily be surmised as affecting the AYA population.

Other markers of myelosuppressive medication adherence include blood counts and drug metabolites. A NOPHO study analyzed MTX and 6MP administration in 59 adolescents (10–15 years of age) compared to 176 non-adolescents (1–9 years of age), using weighted mean WBC and erythrocyte levels of cytotoxic metabolites of 6MP and MTX [132]. The 12-year EFS was significantly worse for adolescents (71 ± 8% versus 83 ± 3%, $p=0.003$), and on multivariate analysis, the mean white blood cell (WBC) during maintenance was significant as a risk factor for relapse. The association of mean WBC count with relapse risk was stronger for adolescents compared to younger patients ($p=0.003$ versus $p=0.04$), and even though adolescents had a higher weighted mean WBC count and absolute neutrophil count during maintenance (3.3 versus 3.1×10^9/L, $p=0.29$, and 2.2 versus 1.9×10^9/L, $p=0.002$), they received moderately lower 6MP and MTX doses (52.1 versus 57.2 mg/m^2, and 13.9 versus 14.2 mg/m^2, both with $p=0.33$). Interestingly, for adolescents and non-adolescents with a mean WBC during maintenance of $<3\times10^9$/L, there was no difference in EFS (91 ± 4% versus 86 ± 6%, $p=0.57$), but for those with mean WBC $\geq3\times10^9$/L, outcomes were significantly worse for adolescents (12-year EFS 63 ± 8% versus 82 ± 4%, $p=0.009$), suggesting that achieving a target WBC $<3\times10^9$/L during maintenance, as suggested by the Ponte di Legno Group [133], is of particular importance in the AYA population.

These data support the notion that adherence to therapy has implications in terms of relapse risk and survival, yet the psychological and social burden of prolonged ALL therapy specifically on the AYA population has not been thoroughly

investigated. In a survey of AYAs being treated for hematological malignancies, one-third met diagnostic criteria for anxiety, depression, and post-traumatic stress disorder, but their physicians did not appear to appreciate these comorbidities [134]. To further describe these issues on a larger scale, investigators for the C10403 study have designed a 3-part survey to explore issues related to support networks, access to care, adherence to clinic visits, and psychological health of AYAs being treated for ALL, as well as the effects of the therapy on educational, employment, insurance, and general health status.

7.6 Summary and Conclusions

The incidence of ALL in the AYA population has increased more in the recent decades than it has in younger or older age groups, the cause of which is unknown. While survival rates in the pediatric population have improved dramatically, outcomes have not improved as much in AYAs, and as of a decade ago, only half of the AYA ALL patients were surviving 5 years. Some of this may be related to treatment regimen, as there is mounting evidence that the "pediatric" approach may not only be more favorable for this age group, compared to traditional "adult" ALL treatment regimens; it is less toxic and may have fewer adverse late effects. Despite the fact that there is more treatment-related toxicity in AYAs compared to younger patients, there is evidence that these regimens can be well tolerated with appropriate awareness and management of side effect profiles for particular chemotherapy medications. On balance, the risk/benefit profile appears to favor the use of these more intense regimens in order to achieve superior outcomes with less residual morbidity. Besides optimizing treatment, a deeper understanding of the biology of AYA ALL will be important as well, as biologically more aggressive disease occurs more frequently in this age group. The Ph-like subset in particular may provide an "AYA ALL" approach to ALL therapy in the age group since Ph-like ALL has a peak incidence in AYAs, and there are now specific targeted agents that are clinically available for a subset of these patients. Regardless of the ideal treatment approach to AYAs with ALL, an appreciation for the complex psychosocial underpinnings in these patients is paramount, in order to maximize compliance with the long and complex treatment plans that must be implemented during such formative years.

Acknowledgments We would like to dedicate this chapter to the late Dr. James B. Nachman (1948-2011), who dedicated his career to improving the lives of all children with cancer, especially those with hematologic malignancies. Jim co-authored this particular chapter in the first edition of Cancer in Adolescents and Young Adults, and his critical role in the development of AYA oncology can never be overstated. Through his work with the Children's Oncology Group, he conducted studies that modified existing therapy in ways that led to significant improvements in outcomes for adolescents with ALL, and encouraged one of the earliest comparisons between pediatric and adult trials to identify the optimal approach to therapy for AYA patients. He was instrumental in the design and execution of the pivotal C10403 trial, which provides a new standard therapy for young adults with ALL. Furthermore, Jim was a collaborator with cooperative groups nationally and internationally helping us all to learn from one another and improve together. We are fortunate to have known him, to have worked with him, and to have been compelled by him to think both bigger and better, for the benefit of patients of all ages everywhere.

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Breast Cancer Before 40

8

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Abstract

Approximately 6 % of women with breast cancer are diagnosed before the age of 40, and this disease accounts for more than 40 % of all cancers in women in this age group. Historically, survival rates are worse for younger women when compared to older women; younger age has proven to be an independent predictor of adverse outcome in multivariate analysis. While the basic principles of chemotherapy, radiation, and surgery between younger and older women with breast cancer remain similar, endocrine therapy recommendations for pre- and postmenopausal patients have evolved quite substantially over the past 5 years. When planning local and systemic therapies for young women with breast cancer, the late effects of treatment (i.e., bone health) should be carefully considered. Other factors important to the optimal care of young women with breast cancer include risk of premature menopause, managing the risk of future infertility, impact of therapy on sexual and psychological health, and the implications of inherited cancer syndromes, specifically *BRCA1* and *BRCA2*.

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8.1 Introduction

While a diagnosis of breast cancer is distressing at any age, breast cancer arising in young women is fraught with several unique challenges. This article, which is an updated review of breast cancer in young women, reviews the epidemiology, clinicopathologic characteristics, biology, treatment strategies, outcomes, and psychosocial challenges of breast cancer before 40 years of age [1]. The issues of familial breast cancer, future fertility, premature menopause, breast cancer during pregnancy, and bone health will also be reviewed in this manuscript. The US Surveillance, Epidemiology, and End Results (SEER) database was the source of data for the tables and graphs presented in this article [2].

8.2 Epidemiology

8.2.1 Incidence

Breast cancer is the most common AYA cancer in the USA (USA), accounting for15 % of all invasive cancer in men and women in the age group and 31 % of all cancer in women of that age group according to 18 SEER regions that represent 28 % of the US breast cancer, and is the second most common cancer worldwide, with 1.7 million cases annually [3]. The American Cancer Society estimates that 232,340 women in the USA were diagnosed with breast cancer in the year 2013 and that 39,620 women died of the disease. In 2013, an estimated 10,980 women under age 40 were diagnosed with invasive breast cancer in the USA, approximately 12,000 were diagnosed with either invasive or in situ breast cancer, and 1,020 died of the disease before age 40 [4]. Breast cancer accounts for more than 40 % of all cancers diagnosed in women by age 40, approximately 20 % by the age of 30, and slightly more than 2 % by 20 years of age (Fig. 8.1a). Breast cancer is rare in AYA men, accounting for 0.1 % of all cancer and 30–40 new cases per year in the USA.

The incidence of breast cancer appears to have a sigmoid function in women less than 55 years of age (Fig. 8.1b), with 6.2 % of all cases diagnosed before age 40, 2.3 % diagnosed before age 35 and <1 % diagnosed before age 30 (Fig. 8.2, inset). The incidence of breast cancer in AYA women is fairly similar between different countries worldwide, with no clear differences in between Westernized and developing countries [5]. During 2012 in the USA, the individual average risk of a woman developing invasive breast cancer was 1 in 166 by the age of 40 and approximately 1 in 419 by the age of 35 (Table 8.1). The corresponding rates for being diagnosed with either invasive or in situ breast cancers were 1 in 142 and 1 in 381 (Table 8.1).

In situ breast cancer increased after screening mammography was initiated nationally in the early 1980s in the USA with a baseline screen recommended at age 35 and the increased use of ductal carcinoma in situ (DCIS) as a pathologic diagnosis (Fig. 8.3). Since then, however, the incidence of all invasive breast cancer has not increased in AYA women since 1981 (Fig. 8.3, purple data). All invasive and DCIS increased slightly at a statistically significant average present change (APC) of 0.34 (Fig. 8.3, brown data). The incidence of localized and regional disease has remained constant since 1976 (Fig. 8.4). The incidence of distant disease in American women <40 years of age, however, has been increasing since 1976–1984 (Fig. 8.3, upper panel) [7]. In a study of 37 European countries, the incidence of breast cancer in women under age 40 increased by an average of 1.2 % percent per year between 1990 and 2008, with the largest increases in women under 35 [6].

In American women 40 years of age or older, the incidence of in situ and localized disease increased dramatically since 1976–1984, whereas regional disease has had a moderate decrease and distant disease has had no decrease at all (Fig. 8.3, lower panel). The striking increase in in situ and localized disease in women over 40 years of age is due to screening mammography that is

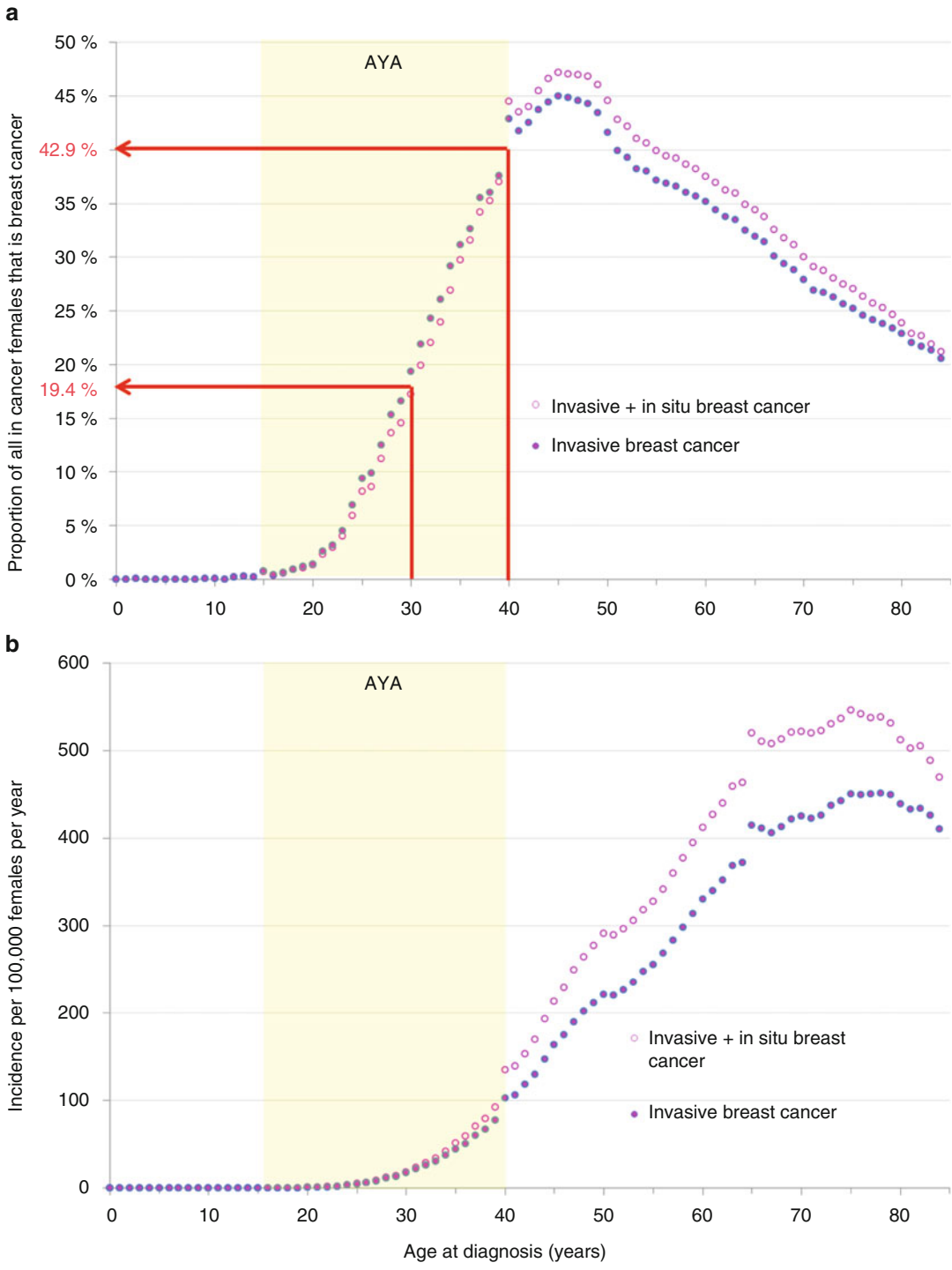

Fig. 8.1 (**a**) Proportion of all cancer in females that is breast cancer by single year of age, 2000–2012, SEER18. (**b**) Incidence of breast cancer in females by single year of age, 2000–2012, SEER18

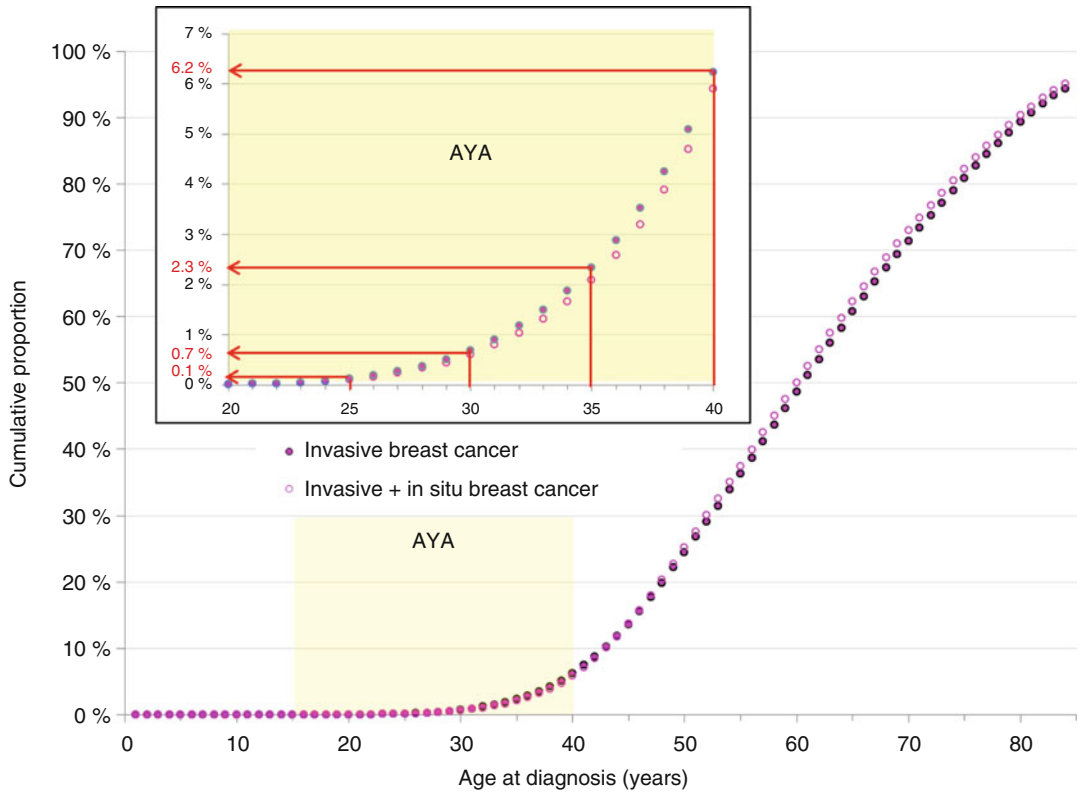

Fig. 8.2 Cumulative proportion of number of women with breast cancer by single year of age, 2000–2012, SEER18

Table 8.1 Risk of invasive and all breast cancer in women during 2012 as a function of age in the USA estimated from 18 SEER regions

	I in x	
Age (years)	Invasive	Invasive or in situ
15	196,078	196,078
20	42,735	42,735
25	7,452	6,592
30	1,392	1,284
35	419	381
40	166	142
45	80	63
50	45	34
55	29	23
60	21	16
65	15	12
70	11	9
75	9	7
80	8	6
85	7	5

routinely performed in the USA when women reach the age of 40.

SEER data show that the incidence of localized and regional disease in AYA women has remained constant since 1976 (Fig. 8.4). The incidence of distant (stage IV) disease at diagnosis is higher in AYAs than in older women (Fig. 8.4) and has been increasing over the past 30 years in the USA [7]. A smaller percentage of AYA compared to older women are diagnosed with localized (stage 0 or I) disease. Two of every three 25- to 29-year-olds have nonlocalized regional or advanced cancer (stage II, III, or IV) at diagnosis in comparison to slightly more than one in three women 40 or more years of age (Fig. 8.5). In older women, the decline in incidence in 2008–2011 has been attributed to reductions in the use of hormone replacement therapy (Fig. 8.4) [8].

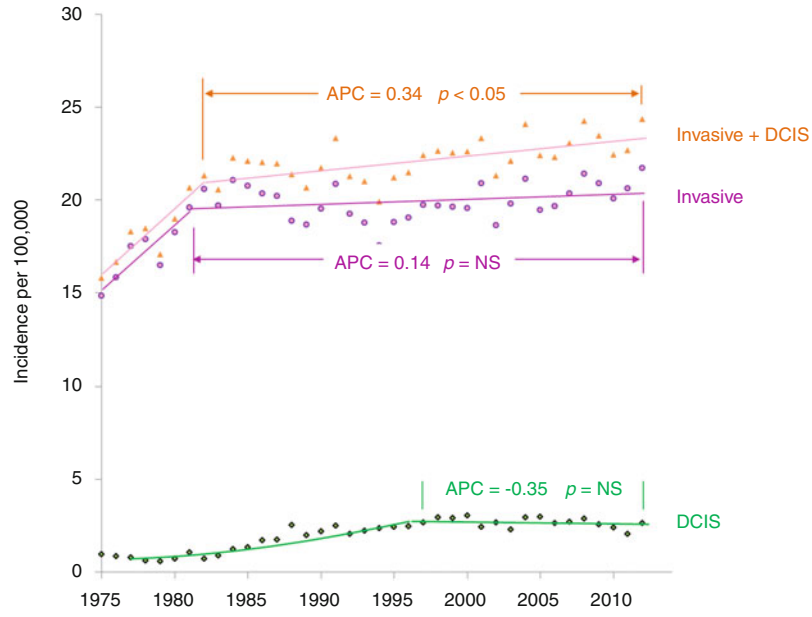

Fig. 8.3 Annual incidence of invasive breast cancer, invasive breast cancer plus DCIS, and DCIS in 15- to 39-year-old women by year of diagnosis, SEER9

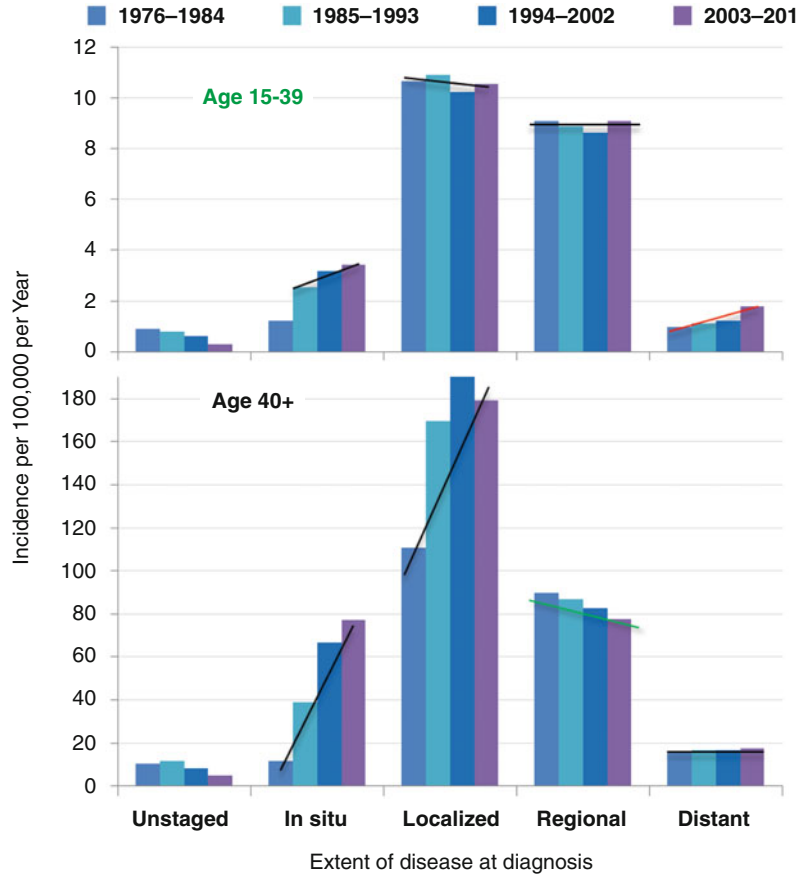

Fig. 8.4 Incidence trends in women with breast cancer by extent of disease at diagnosis, 1976–2011, age 15–39 and 40+, SEER9

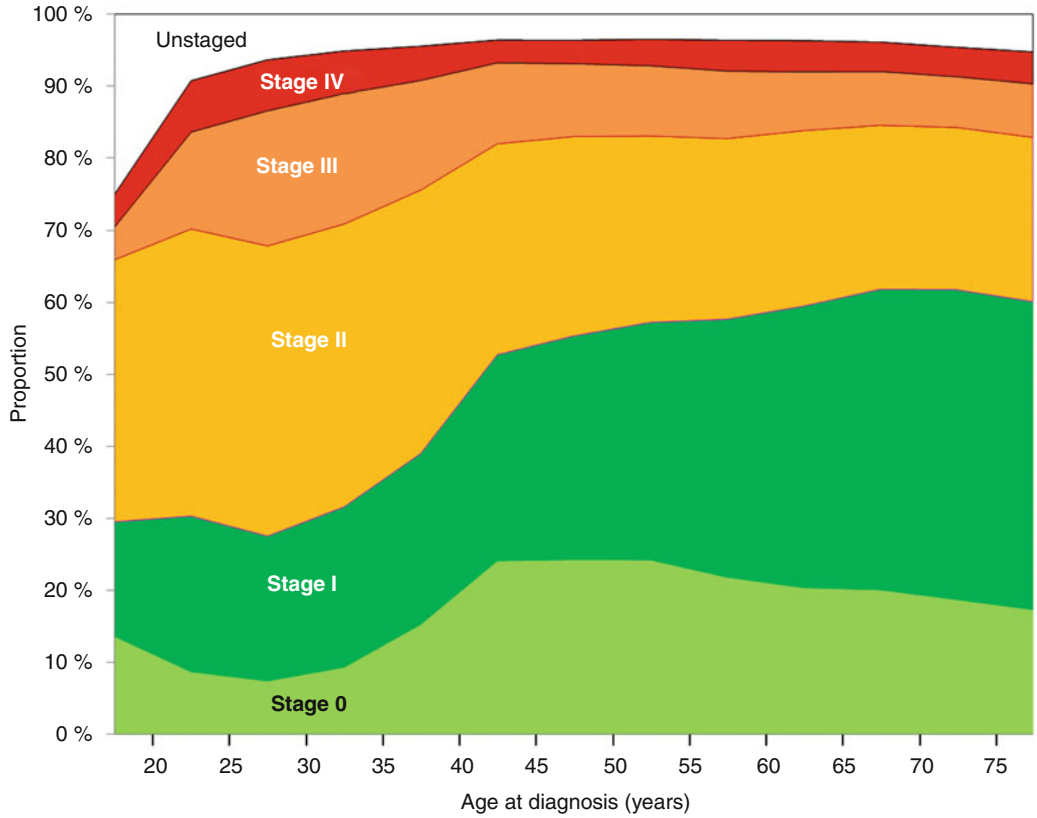

Fig. 8.5 Incidence of breast cancer in females by stage (AJCC6 5 categories), 2004–2011, SEER18

The incidence of breast cancer in young women in the USA also varies according to race and ethnicity. In women over 45, breast cancer is more common in whites than blacks. However, AYA black women under age 35 have a higher incidence of invasive breast cancer and three times the breast cancer mortality of young white women (SEER 18, and National Center for Health Statistics, data not shown [9–11]. In contrast, Native American women at all ages have a lower incidence of breast cancer compared to the general population (RR = 0.7 for women 20–44 years of age) [12]. Women of all age groups with low socioeconomic status as well as young black, Hispanic, and Native American women have an increased likelihood of presenting with advanced disease [13–15].

The overall incidence of breast cancer in males is approximately 1/100th that of the rate in females. Analysis of the SEER 9 database (data not shown) indicates that the incidence of breast cancer has increased for older men but not AYA men during the past three decades. For invasive breast cancer, female AYAs have a worse survival than either older females or AYA males, who have a better survival than older males (Fig. 8.6). One quarter of men with breast cancer die of the disease within 10 years. The age dependence of breast cancer differs significantly between men and women, with an older age predominance seen in men and only 2.6 % of cases occurring before age 40. Breast cancer in males is not further reviewed in this article.

8.2.2 Risk Factors

8.2.2.1 Familial

A positive family history of cancer is a very strong risk factor for women under 35 (RR, 3.22)

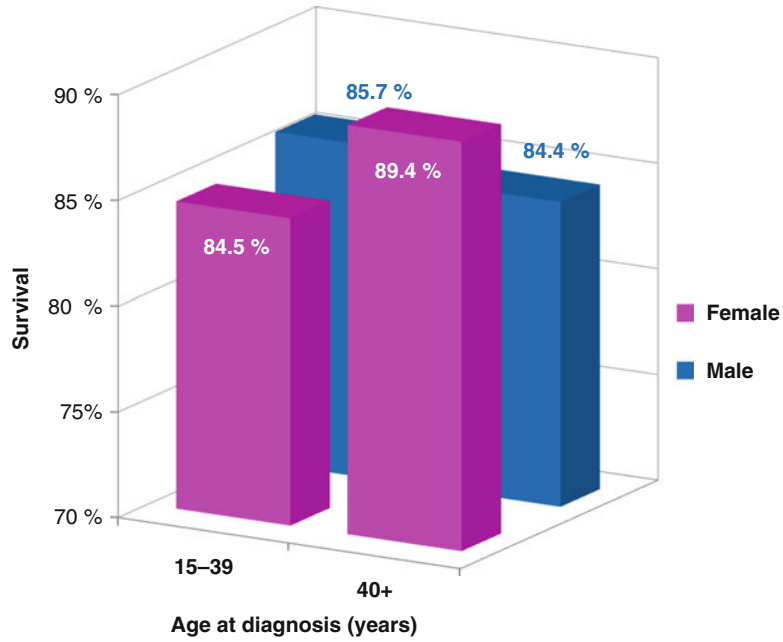

Fig. 8.6 Invasive breast cancer 5-year relative survival by sex and age, 2000–2012 SEER

and suggests the presence of a familial cancer syndrome [9]. Early-onset breast cancer in AYAs is more likely to be associated with a positive family history of breast cancer, especially in women harboring a germline *BRCA1* mutation [16]. Patients with *BRCA1* mutations develop aggressive triple-negative tumors in about 80% of cases. Conversely, constitutional *BRCA* mutations are found in 11–16% of women diagnosed with triple-negative breast cancer [17]. In a study of women with breast cancer diagnosed before age 30, *BRCA1*, *BRCA2*, and *TP53* mutations were found in about half of patients with strong family histories of breast cancer but less than 10% of women with negative family history of breast cancer [18]. Compared to the general population, women with constitutional *PALB2* mutations have at least an eightfold increased risk of developing breast cancer under 40 years of age [19]. Women with constitutional *PTEN* mutations (Cowden's syndrome) also have an increased risk for early breast cancer [20].

8.2.2.2 Hormonal

Some hormonal risk factors are similar between AYA and older women. Breast cancer risk is increased by later age (>30 years) at first birth (RR, 1.10; 95% CI, 0.80–1.50 for women under age 40), early menarche (age <40: RR, 0.93; 95% CI, 0.87–0.99 for each additional year after age 12 for onset of at menarche), and breastfeeding (age <40: RR, 0.84; 95% CI, 0.57–1.22) [21].

Other hormonal risk factors are somewhat different for AYA in comparison to older women. For women aged less than 35, recent oral contraceptive use is a risk factor for early-onset breast cancer (RR, 2.26), particularly for ER-negative tumors [22]. For AYAs under 40, current oral contraceptive use for ≥5 years prior to diagnosis is associated with and increased risk of ER(−) tumors (OR, 3.5; 95% CI, 1.3–9.0) and triple-negative tumors (OR, 3.7; 95% CI, 1.2–11.8) [23]. *BRCA1* carriers who use oral contraceptives prior to age 20 have an increased risk for early-onset breast cancer before age 40 (OR, 1.45; 95% CI 1.20–1.75; $p = 0.0001$). Risk increases by 11% for each additional year of contraceptive use prior to age 20 [24].

Childbearing and multiparity are risk factors, due to a short-term elevation in breast cancer risk for several months immediately following a birth [22]. There is a positive association between high estradiol levels in the first trimester of pregnancy and risk of hormone receptor-negative cancer

diagnosed under age 40 [fourth vs. first quartile OR 1.60 (1.07–2.39), but a negative association with the overall risk of breast cancer diagnosed after age 40 [25]. Women with anovulatory infertility are at high risk for early-onset breast cancer [26].

8.2.2.3 Personal and Lifestyle

The combination of obesity, high-energy (caloric) intake, and sedentary lifestyle imparts a higher risk of breast cancer for premenopausal women [27]. Large hip circumference (whether or not abdominal obesity is present) is also a risk factor for premenopausal breast cancer [hazard ratio (HR), 2.85; 95 % CI, 1.33–6.13] for ER−/PR− tumors before and also after adjustment for BMI and for ER + PR+ tumors after adjustment for BMI [HR, 1.65; 95 % CI, 1.04–2.62].

Other risk factors for breast cancer in premenopausal women include a history of prior mantle irradiation for Hodgkin lymphoma, heavy alcohol consumption, and a high intake of red meat [9, 20, 28]. Intense physical activity and a high intake of certain fruits and vegetables (e.g., citrus fruits, cruciferous vegetables [29], tomatoes) are associated with a decreased breast cancer risk in premenopausal women [30–32]. Substituting legumes for one serving of meat per day was associated with a 19 % lower risk of breast cancer in premenopausal women (0.81; 95 % CI, 0.66–0.99) [33].

Increased mammographic density is a risk factor for breast cancer at all ages [34]. Breast density in premenopausal women is mediated by intake of vitamin D, calcium, dietary fat, and alcohol in premenopausal women [35]. Mammographic density is genetically mediated, but no causative genes have been conclusively identified. Genetic variations in IL6 correlate with mammographic density [36]. Also, high levels of endogenous sex hormones such as dehydroepiandrosterone sulfate (DHEAS) in early adolescence have been positively associated with breast density during young adulthood [37].

Several studies suggest that high vitamin D intake, with or without calcium, may protect against premenopausal breast cancer. Low calcium/vitamin D intake has been associated with larger and higher-grade breast tumors [38–40]. Premenopausal women who consumed at least 400 IU vitamin D and 1,000 mg calcium daily were noted to have an 8.5 % (95 % CI, 1.8–15.1) lower mean breast density than those who consumed less [41]. One study noted an inverse association between plasma 25-hydroxyvitamin D level and breast cancer risk in premenopausal women with high mammographic density. No significant association was noted for premenopausal women with lower mammographic density [42].

In a series of women with breast cancer aged 20–44, significant weight gain (BMI increase of >10 kg/m2) after age 18 conferred a 2.0-fold increased risk of ER-negative breast cancer (95 % CI, 1.2-fold to 3.3-fold increased risk). Height, current weight, and weight at 18 years of age had no effect on risk. Smoking history of >10 pack-years increased risk of ER-positive breast cancer by 1.6-fold (95 % CI, 1.1-fold to 2.4-fold increased risk), but did not increase risk of triple-negative breast cancer [43].

8.3 Clinicopathologic Features, Biology, and Prognosis

Clinicopathologic and prognostic features of breast cancer arising in young women compared with their older counterparts have been the subject of published studies for decades [44–46]. Traditionally, breast cancer arising in a younger host aged less than 40 is characterized by a more aggressive phenotype. Among 185 premenopausal women with a diagnosis of invasive breast cancer at the European Institute of Oncology from April 1997 to August 2000, those aged less than 35 had a higher percentage of estrogen receptor (ER)-negative ($p < 0.001$), progesterone receptor (PR)-negative ($p < 0.001$), and pathologic grade 3 tumors ($p < 0.0001$), as well as higher incidence of vascular or lymphatic invasion (48.6 % versus 37.3 %, $p = 0.006$) compared with women aged 35–50 years [47]. Differences in tumor size, lymph node involvement, and Her2/neu status between younger and older women diagnosed with breast cancer have historically been less clear [47–50].

Younger age has been shown in several studies to be an independent predictor of adverse outcome [48, 49, 51–53]. A retrospective evaluation of over 1,200 women diagnosed with early-stage breast cancer showed young age (<35 years) was an independent prognostic factor for time to recurrence (RR, 1.70, $p<0.001$), time to distant failure (RR, 1.60, $p<0.009$), and overall mortality (RR, 1.50, $p<0.04$) in multivariable analysis [52]. A second retrospective study evaluating over 200,000 women in the SEER database diagnosed with breast cancer between the years of 1988–2003 revealed that those under the age of 40 were 39 % more likely to die when compared to those 40 or older (HR, 1.39; 95 % CI, 1.34–1.45). Moreover, the highest mortality disparity between younger (<40 years) and older women (≥40 years) was present in early-stage, rather than later-stage disease [54, 55]. Although disparities in outcome between younger and older women diagnosed with breast cancer have been attributed traditionally to adverse prognostic features and later stage at diagnosis, this report implicates biologic underpinnings that may unify breast cancer arising in the younger host.

Several comprehensive, large-scale genomic analyses have been conducted to examine the biology of breast cancer arising in young women with the goal of providing insight into this historically aggressive disease process. Azim et al. aimed to define the role of gene expression signatures in the prediction of prognosis in young women and help elucidate biological differences according to age [53]. Using a three-gene classifier (*ESR1*, *ERBB2* [HER2], and *AURKA*) and defining age ≤40 as young, gene expression data from over 3,500 breast tumors illustrated a higher proportion of young women's tumor were triple negative (34.3 % vs. 17.9 %). Younger women had a higher risk of relapse compared to the older age group, a comparison that held true after adjusting for tumor size, nodal status, grade, and breast cancer subtype in multivariable analysis ($p=0.04$). Moreover, the prognostic value of three proliferation-related, three stromal-related, and three immune signatures were evaluated by age and subtype. The most notable finding was that the stromal-related signatures showed a significant interaction with age in the triple-negative subtype of patients (HR, 2.4; p, 0.04). Finally, using a candidate gene approach and after adjusted for subtype, over 12 gene sets were found to be associated with young age including those related to an immature mammary cell population, growth factors (i.e., mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)), and downregulation of apoptosis genes.

In a second series of studies, Anders et al. evaluated clinically annotated gene expression data from over 700 early-stage breast cancers within two age-defined cohorts (≤45 years and ≥65 years of age). In this analysis, genomic expression profiling demonstrated significantly lower total mRNA levels of ERα, ERβ, and PR, with higher mRNA levels of both Her2/neu and epithelial growth factor receptor (EGFR, Her1) [48]. In a non-subtype-specific manner, Gene Set Enrichment Analysis (GSEA) revealed 367 significant gene sets enriched among young women's tumors distinguishing them from tumors arising in older women [48]. Representative gene sets included those involved with immune function, hypoxia, BRCA1, stem cells, apoptosis, histone deacetylase, and multiple, targetable oncogenic signaling pathways, including Myc, E2F, Ras, and mTOR [48].

Following their initial analysis, the authors hypothesized that (1) breast cancer arising in younger women was enriched for more aggressive subtypes and (2) age-specific biologic differences were highly subtype dependent [56]. Additional analyses, including those from an independent microarray breast tumor data set, illustrated that younger women (age ≤45 years) as compared to older women (age ≥65 years) were more commonly diagnosed with basal-like and Her2-enriched breast tumors as defined by the PAM50 [57]. Moreover, when comparing breast tumor gene expression by age alone, hundreds to thousands of genes were differentially expressed; however, when correcting for subtype and other significant clinicopathologic features (i.e., grade), gene expression differences were no longer seen.

One recent study identified age-dependent expression of individual genes, even after correction for tumor subtype and grade. *BUB1*, *KRT5*, *and MYCN* were overexpressed in women under age 40 compared to older women, and *CXCL2* underexpressed in young women ($p \leq 0.05$). Within tumor subtypes, gene expression appeared to have an age-related impact on outcome. High levels of cytokeratin 5 and cytokeratin 6 expression were associated with inferior disease-free survival for young, but not older, women with basal-type (triple negative) and HER2-enriched breast cancers. Overexpression of *ANGPTL4* predicted inferior disease-free survival in young, but not older, women with basal-type tumors [58].

Collectively, this series of analyses illustrates that while biological differences are clearly seen between breast carcinomas arising in a younger vs. an older host, intratumoral differences may be driven in large part by the higher distribution of aggressive subtypes (i.e., basal-like and Her2 enriched) among young women. The cause for the overrepresentation of more aggressive subtypes and the impact the pre- versus postmenopausal microenvironment on breast tumor biology have yet to be fully elucidated and are worthy of additional research.

8.4 Treatment and Management

Although the general principles of managing invasive breast cancer in young women are the same as in older women, there are a number of management and therapeutic issues requiring special consideration.

8.4.1 Early-Stage Disease

For many reasons, including lactation, sexual function, body image, and quality of life, breast-conserving surgery, whenever possible, is desirable for most young women. However, one of the most important risk factors for local recurrence after breast-conserving surgery is age <35 years at presentation [59]; these patients were found to have a nine times higher risk of local recurrence after conservative surgery than patients over 60 years [60]. Nevertheless, no studies have demonstrated conservative surgery in young women to have a negative impact on survival, so breast conservation remains appropriate for many. Breast conservation surgery should always be followed by radiation in young women, and adjuvant radiation is more often considered after mastectomy for young patients [61]. Patients who carry deleterious *BRCA* mutations (which are more common in those diagnosed with breast cancer at a young age) have been hypothesized to harbor a greater risk of radiation-induced malignancies, but data are limited [62].

In addition, young women are at heightened risk for distant recurrence, so adjuvant systemic therapies (e.g., chemotherapy and endocrine therapy) are usually warranted [63]. Young women are more likely than older women to have ER-negative tumors, which benefit more from chemotherapy. Adjuvant chemotherapy for early breast cancer in patients under 50 years old reduces the relative risk of recurrence by 35 % and of death by 27 % [64]. The choice of whether or not to give chemotherapy, and what regimen to give, is based more on stage and receptor status (i.e., clinical subtype) of disease than on age. However, it is important to recognize that the use of adjuvant therapies in young women can cause unique long-term side effects, including the induction of an early menopause, and associated fertility impairment, bone loss, and menopausal symptoms. Reductions in risk of recurrence with more aggressive therapies must be weighed against associated quality of life impairments and fully discussed with patients.

For young women with ER-positive early-stage breast cancers, adjuvant endocrine therapy reduces the risk of recurrence by approximately half [65]. Until recently, 5 years of tamoxifen was standard endocrine therapy for premenopausal early-stage breast cancer patients, but data from the ATLAS trial, aTTom trial, SOFT trial, and TEXT trial have revealed additional treatment

options. ATLAS and aTTom found that 10 years of tamoxifen were superior to five [66, 67]. SOFT revealed that the addition of ovarian suppression to tamoxifen reduces risk of recurrence in patients under 35 and premenopausal patients who receive chemotherapy, and both SOFT and TEXT showed that treating these same patients with ovarian suppression and an aromatase inhibitor reduces risk of recurrence to an even greater degree [68, 69]. These findings are consistent with older studies showing that both relapse-free and overall survival are worse in patients who do not become amenorrheic following chemotherapy [70–73]. However, the SOFT trial data did not convincingly show that patients over age 35 who did not receive chemotherapy benefit from ovarian suppression. There may be a real, but small, risk reduction from ovarian suppression (with either tamoxifen or aromatase inhibitor) in some higher-risk patients aged 35–40 even if the disease was not biologically aggressive enough to warrant chemotherapy. On the contrary, it is important to consider the impact of ovarian suppression on physical and emotional health for very young women, including menopausal symptoms, insomnia, depression, and bone loss. Additional research is warranted to identify strategies to minimize the toxicities of endocrine therapy in young women diagnosed with breast cancer.

8.4.2 Metastatic Disease

Metastatic breast cancer in young patients is treated palliatively, with sequential systemic therapy regimens given until time of progression, just as in older patients. One caveat is that premenopausal patients with advanced ER-positive disease should additionally be treated with either bilateral salpingo-oophorectomy at the time of diagnosis with metastatic disease or receive an ovarian-suppressing medication (i.e., gonadotropin-releasing hormone (GnRH) agonist) throughout their subsequent endocrine therapies (including tamoxifen, aromatase inhibitor, fulvestrant, etc.) [74–76].

8.5 Outcomes

8.5.1 Age Disparities

AYA women diagnosed with breast cancer experience worse cancer-specific survival and relative survival compared to all other age groups below age 75 (Fig. 8.7). Young women had a worse survival from breast cancer compared to other cancers; in older age groups, breast cancer survival was superior to survival from other cancers. Breast cancer survival rates are lower for AYA women compared to older women, both cumulatively and stage by stage (Fig. 8.8) [1, 77]. The lowest overall rate of breast cancer survival for females diagnosed during 2000–2012 was in those aged 15–39 years, with 5-year rates of 81–88 %. In contrast, breast cancer survival for women between age 45 and 75 was 90–93 % (Fig. 8.7).

The age-related disparities in breast cancer survival vary by stage at diagnosis, although survival is inferior for AYAs compared to 40–50-year-old women at all stages of breast cancer (Fig. 8.8). Above the age of 40, stage 0 in situ breast cancer has a 100 % 5-year relative survival, even in elderly women. For all age groups with stage 0 disease, only AYAs have less than 100 % 5-year survival. For stage I breast cancer, women greater than 50 years of age have the highest survival rates and 25–35-year-olds have the lowest survival rates. Women with stage II–IV cancer who are 40–50 years of age have the best prognosis, with comparatively inferior prognosis for AYA women. Stage IV breast cancer has a far worse prognosis than any other stage. Within the AYA age group, survival is inversely proportional to age for all stages of breast cancer, with the most inferior survival rates occurring in the youngest AYA women (Fig. 8.8).

Most histologic subtypes have a worse prognosis in AYA women than in older women. The 5-year relative survival for AYA was also inferior for women with each histologic subtype of breast cancer, including infiltrating ductal, medullary, lobular, and inflammatory breast cancer, as well as Paget's disease of the breast (SEER 18 data,

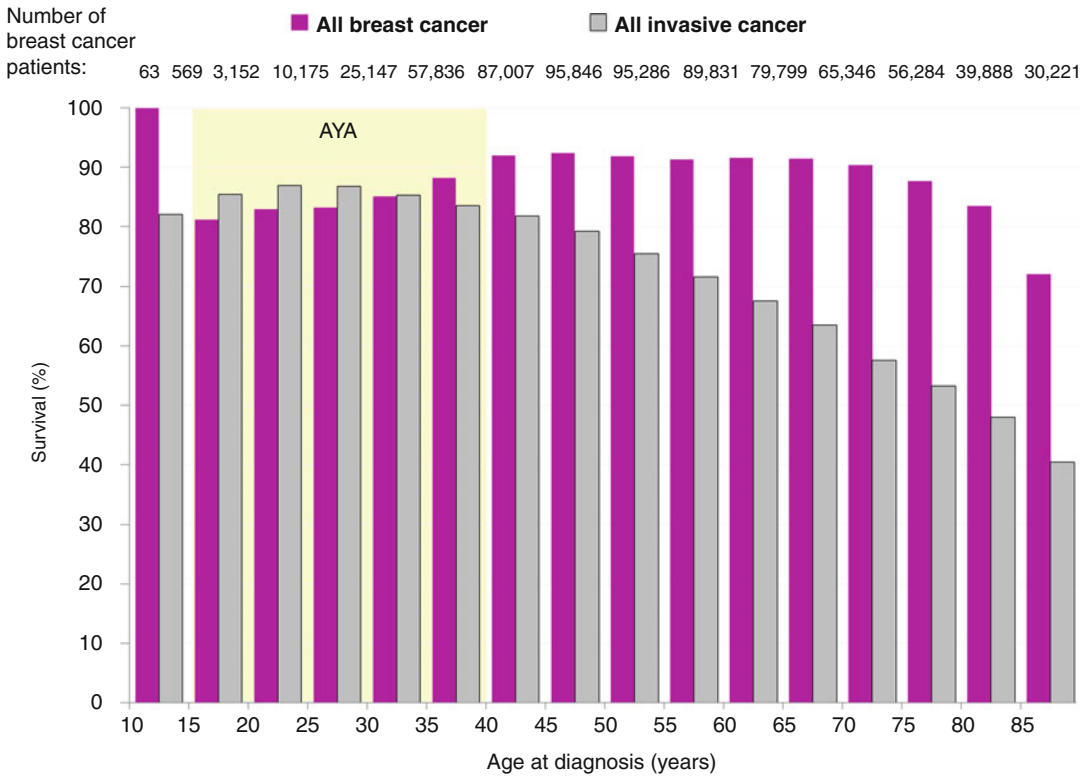

Fig. 8.7 5-year breast-cancer-specific survival in females, 2000–2012, SEER18

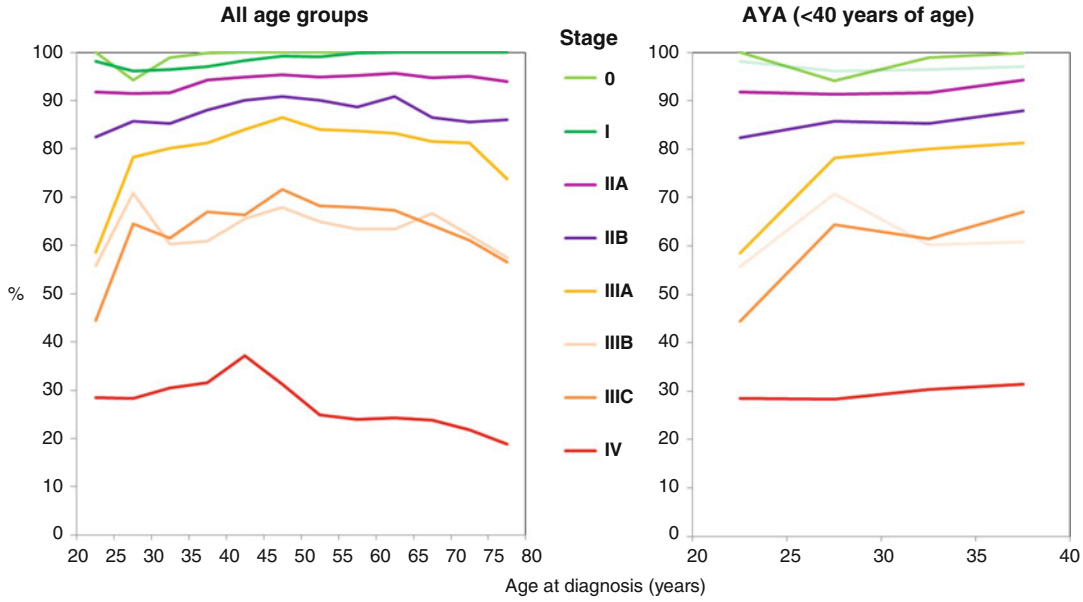

Fig. 8.8 5-year relative survival of women with breast cancer by stage at diagnosis, AJCC6 (all eight categories), 2004–2010, SEER18

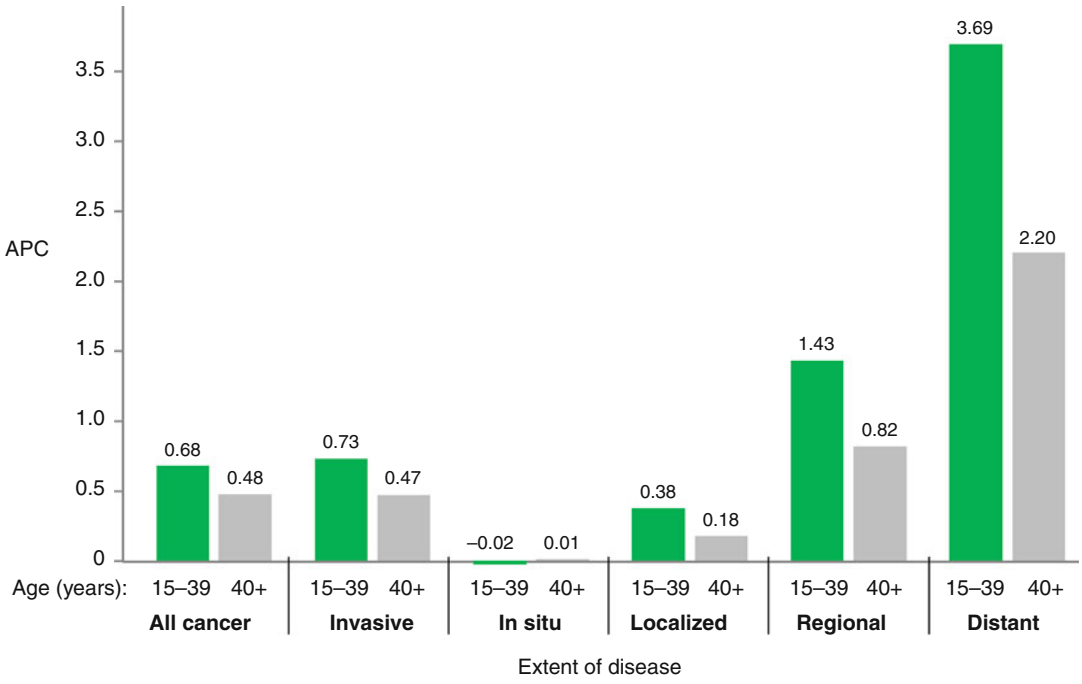

Fig. 8.9 Annual % change (APC) in 5-year relative survival of women with breast cancer by age and extent of disease at diagnosis, from 1985 when the impact of screening on incidence had stabilized, to 2006, SEER9

not shown) [78]. The outcome disparity between age groups by histologic subtype is most apparent for invasive ductal carcinoma ($p<0.001$, SEER 18 data, not shown).

Since 1985, the rate of survival improvement has been greater in AYA women than in older women for all stages at diagnosis (Fig. 8.9). The rate of survival improvement in AYA women has been directly proportional to the extent of disease at diagnosis, with the greatest relative gains for women with distant disease at diagnosis (Fig. 8.9). Thus, the discrepancy in survival between younger and older women is narrowing over the last three decades, possibly due to increasing clinical focus on the distinctive healthcare needs of young women with breast cancer and to more effective palliative and supportive care strategies for previously healthy women diagnosed with advanced disease.

The recent Prospective Outcomes in Sporadic versus Hereditary breast cancer (POSH) study examined breast cancer outcomes for British women diagnosed at age 18–40 years of age at diagnosis. Young patients had similar and inferior outcomes regardless of hormone receptor expression, with the incidence of relapse peaking at 2 years post-therapy for patients with ER-negative tumors and continuously declining over an 8-year period for patients with ER-positive tumors [79]. Patients with a positive family history of breast cancer were more likely to have high-grade tumors, but were not more likely to have an adverse outcome by multivariable analysis [80]. Obesity was associated with adverse biological features and was an independent risk factor for death from breast cancer [81].

8.5.2 Racial Disparities in AYA Women

In women <40 years of age (as in all age groups), African Americans and Native North Americans have the worst survival, and Asians have the highest survival rates. Young African American women have disproportionately high breast cancer mortality in comparison to other racial groups (Fig. 8.10). One study found that black women

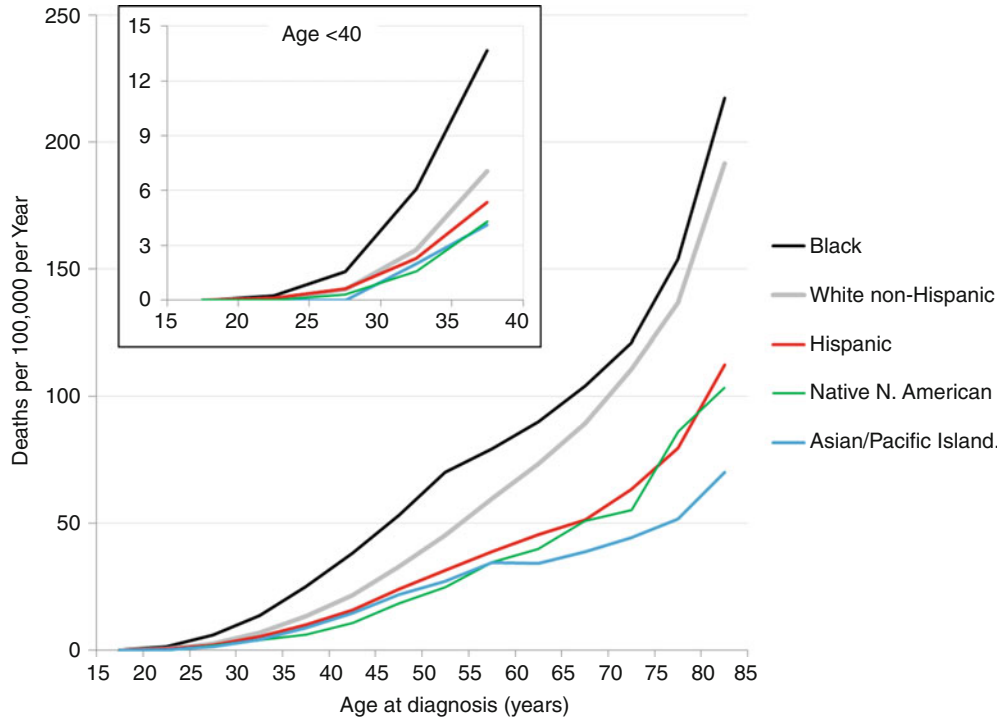

Fig. 8.10 Mortality in women with breast cancer by race/ethnicity and age, USA, 2000–2011, National center for health statistics. Hispanic may overlap with black, Asian/PI, AI/AN; AI/AN: American Indian/Alaska Native

<40 had larger tumor size, higher rates of local and distant metastasis, a higher proportion of ER negativity, and a higher rate of medullary tumors. Relative risk for death was 1.94 for localized disease, 1.58 for regional disease, and 2.32 for metastatic disease compared to white women [82]. Another study showed that young black women with stages III and IV disease had worse prognosis despite standard therapy [82]. In the POSH study, black race was associated with adverse biological features and with adverse outcome despite equal access to health care, with 71.1% 5-year OS in black compared to compared to 82.4% in white patients ($P=0.0160$) [83]. Because 10% of black women (vs. 5% of white women) with breast cancer are diagnosed prior to age 40 and because young black women have worse outcomes, they are considered a particularly high-risk group [84].

After black women, the highest mortality in AYAs with breast cancer is seen in white, non-Hispanic women, followed by Latinas, Native Americans, and Asian women (Fig. 8.10). Decreases in mortality between 1975 and 2000 were three times greater for white compared to black AYA women [20].

Interestingly, and in contrast to women in the USA, young women <40 years of age in Asia did not have worse outcomes compared to older women, despite more advanced disease at diagnosis and higher-grade tumors, suggesting a possible environmental role for outcome discrepancies [85].

8.5.3 Other Disparities

Delay in surgical treatment for breast cancer is significantly more common in black compared to white AYA women, as well as patients without private insurance or of low socioeconomic status. Delays of surgical treatment longer than 6 weeks are associated with significant decrements in survival ($p<0.005$) [86].

8.5.4 Risk Factors for Death

AYA women with early-stage disease are more likely than older women to have disease progression to metastatic breast cancer. Young age is a risk factor for death following local recurrence (HR for age >45 compared with age ≤45 years: 0.61; 95 % CI, 0.38–0.95; *p*, 0.03) [87]. Following disease progression, however, there are no significant differences in median 5-year survival in AYA compared to older women [88]. A higher risk of cancer-related death was observed in AYA women with triple-negative (HR, 2.7) and hormone receptor-negative, HER2-enriched (HR, 1.6) breast cancer subtypes compared to AYAs with hormone receptor-positive, HER2-non-enriched disease [89].

Tumor and host genotype may exert a marked effect on breast cancer outcome. For example, somatic mutations within exons 5 through 8 of the tumor suppressor gene *TP53* occur in approximately 30 % of malignant breast tumors. These mutations occur somewhat more frequently in young, compared to older, women with breast cancer and are associated with poor outcome, particularly in the setting of hormone receptor-negative disease. In a series of 1,794 patients with breast cancer, the presence of a *TP53* mutation conferred a 10-year relative risk tumor-related death of 2.27 ($P < 0.0001$) [90]. In addition, recent studies demonstrate markedly decreased survival in the 1 % of breast cancer patients who harbor constitutional PALB2 mutations, particularly in patients with tumors larger than 2 cm [91]. Decreased overall survival has also been reported in *BRCA* mutation carriers under age 41 who did not receive chemotherapy (HR, 3.0; 95 % CI, 1.2–7.7), in comparison to non-carriers. Prognosis of *BRCA* mutation carriers who did receive chemotherapy was similar to that of non-carriers (HR, 1.1; 95 % CI, 0.5–2.5) [92].

Comorbid diseases may affect breast cancer mortality in AYAs. Premenopausal breast cancer patients with either obesity [93] or type 2 diabetes mellitus [94] have inferior outcomes compared to age-matched breast cancer patients without these conditions.

8.5.5 Second Malignancies

AYA women treated for breast cancer have disproportionately high rates of second malignancies. Compared to older patients, women treated for breast cancer under age 50 have a significantly increased incidence of tumors of the bone, ovary, thyroid, colon, corpus uteri, kidney, lung, melanoma and non-melanoma skin, leukemia, and lymphoma [95, 96]. AYA breast cancer survivors also have substantially elevated relative risk for myelodysplastic syndrome compared to other age groups (RR, 30.44; 95 % CI, 19.63, 44.62) [97].

Contralateral breast cancer is by far the most common second malignancy diagnosed in breast cancer survivors [98], and risk increases with younger age at diagnosis [99]. Women treated for early-stage breast cancer under age 36 have been observed to have a 13 % 10-year cumulative incidence of contralateral breast cancer [95]. Relative risk is extremely high in women diagnosed under the age of 30, with relative risk (RR) of 100 for women diagnosed between 20 and 24 years of age, 33.3 for women diagnosed between 25 and 29 years of age, and 10.2 for women diagnosed between 30 and 34 years of age in one study. Collectively, RR was 5.4 for women diagnosed between 15 and 44 years of age [96, 100].

Family history of breast cancer increases the risk for contralateral breast cancer in AYAs. Risk is significantly elevated in women diagnosed with breast cancer under age 45 who have a first-degree relative with early-onset breast cancer (RR = 2.5) or a family history of bilateral breast cancer (RR = 3.6). Family history of bilateral breast cancer in young women confers a risk of contralateral breast cancer similar to that of BRCA mutation carriers [101].

Surgical and medical management decisions also affect the risk for contralateral breast cancer. The use of post-lumpectomy, compared to post-mastectomy, radiation confers an additional 50 % increased risk of contralateral breast cancer in women under 45 years of age [102]. Irrespective of surgical technique, radiation therapy causes a disproportionate risk of contralateral breast cancer in young compared to older patients. In one

study, breast cancer patients under the age of 35 treated with radiotherapy had an increased risk for contralateral breast cancer compared to patients treated at older ages (HR, 1.78; 95 % CI, 0.85–3.72).

Patients with a strong family history of breast cancer had particularly high rates of contralateral breast cancer following post-lumpectomy radiation. For all ages, adjuvant chemotherapy decreased the rate of contralateral breast cancer for 5 years after therapy, but not thereafter [102].

8.6 Fertility and Pregnancy

Young breast cancer patients may have not only the added stress of undergoing local and systemic therapy for their breast cancer but also the long-term effects of these therapies on fertility and future childbearing [103]. ASCO is addressing this recognized concern with guidelines to help practitioners counsel patients on crucial fertility concerns [104]. Fertility, in and of itself, is difficult to assess, and resumption of menses is often used as a surrogate, although many women may continue or resume menses many months after the administration of chemotherapy. Data suggest that young women who do not immediately experience chemotherapy-induced amenorrhea may subsequently experience premature ovarian failure (POF), shifting their natural age of menopause to a younger age than expected, thus potentially limiting later childbearing years [105].

8.6.1 Risks of Infertility

Many chemotherapeutic agents used for breast cancer are associated with POF. Goodwin et al. [106] evaluated 131 women who received chemotherapy, either CMF or CEF, for breast cancer. The risk of menopause after 1 year approximated 50–60 % by age 40 with the trend showing that the closer in age one is to natural menopause the more likely one is to experience sustained POF. ASCO has published guidelines to help clinicians estimate the risks of infertility from different chemotherapy regimens, with anthracyclines and cyclophosphamide having a major role. The available data with taxanes suggests a much lesser, if at all, impact on POF [104, 107, 108].

8.6.2 Fertility Preservation

As the use of reproductive technologies improves, more options are available to younger breast cancer patients. Women interested in fertility preservation should be referred to a reproductive endocrinologist prior to the initiation of any systemic therapy. Ovarian stimulation with either embryo or oocyte cryopreservation is now considered standard options. For even younger women, freezing of sections of ovarian cortex is currently under investigation. Given the concerns of surges in estradiol levels for breast cancer patients, the use of letrozole in the ovarian stimulation process has been shown to be efficacious with a much lower level of circulating estradiol [104, 109]. *BRCA* mutation carriers may also consider preimplantation genetic diagnosis, identifying embryos that carry the mutation prior to implantation should they chose to avoid passing on their mutation to any offspring. Although only a very few mutation carriers describe that they would want to use this technology themselves, the majority felt that this was an important piece of clinical information and choice that should be part of their genetic and cancer counseling [110].

Gonadotropin-releasing hormone analogues have been used in clinical trials before and during systemic chemotherapy to decrease POF. However, these studies have been plagued with multiple design limitations and have used resumption of menses as a surrogate for fertility with varying results [111–115]. There is also the added concern that previous studies have shown decreased efficacy of chemotherapy when endocrine therapy has been given concurrently for hormone receptor-positive breast cancer [116]. Moore et al. evaluated the use of goserelin in 257 women whose tumors were defined as hormone receptor negative, with 218 women considered evaluable [117]. Goserelin was administered monthly and started 1 week prior to the start of chemotherapy and discontinued within 2 weeks

of the end of chemotherapy. Although this study was not able to complete accrual, there was a significant finding of POF of 8% in the goserelin-chemotherapy arm vs. 22% in the chemotherapy-alone arm, $p=0.04$, as well as statistically significant improvements in DFS and OS. Thus, concurrent administration of goserelin plus chemotherapy to decrease the risk of POF can be considered an option for patients with hormone receptor-negative cancer.

8.7 Pregnancy and Breast Cancer

Current estimates of breast cancer during pregnancy are 1.3 cases per 10,000 births [118], and, when cancer is diagnosed in women 30 years old or younger, an estimated 10–20% of cancers are detected either during pregnancy or within the first year postpartum [119, 120]. Additionally as women are delaying childbearing and with the use of reproductive technologies, there does appear to be a measurable increase in the incidence of breast cancer diagnosed during pregnancy [114, 115].

8.7.1 Breast Cancer Diagnosed During or After Pregnancy

Women who are diagnosed during pregnancy often are more commonly diagnosed with locally advanced tumors given the changes in the breast associated with pregnancy which may obscure the clinical detection of breast masses. Although older case series suggest that breast cancer diagnosed during pregnancy carries a worse prognosis, those studies often had significant delays in therapy until after childbirth or used substandard therapies [121, 122]. More recent data demonstrates that when women receive standard therapies in the second and third trimester, outcomes appear to be similar to nonpregnant breast cancer patients [123–125]. However, there is increasing data that women who are diagnosed with breast cancer within a year after pregnancy may have differing biologic features and worse survival [114, 122, 126, 127]. Therefore, it may be important to separate these two groups of women with respect to evaluating outcomes.

In contrast, pregnancy following a diagnosis of breast cancer does not increase mortality, with estimates of improved survival the further from the diagnosis of breast cancer. Mueller et al. found that 438 women age <45 at diagnosis, who delivered a child 10 or more months following a diagnosis of breast cancer, had a decreased relative risk of death (RR, 0.54; 95% CI, 0.41–0.71), compared to women who did not bear children following diagnosis. Multiple other studies have also confirmed this finding, including a large, meta-analysis by Azim et al. of 14 studies showing a relative risk of death decreased to 0.59 (95% CI, 0.50–0.70) among women who had a child after a breast cancer diagnosis [128].

8.7.2 Pregnancy Diagnosed During or After Breast Cancer

Physiologic changes in the breast during pregnancy may make self-palpation difficult. However, masses that do not resolve within 1–2 weeks should be investigated [129]. Imaging should include mammography with fetal shielding, as well as breast ultrasonography [130, 131]. A core biopsy of the mass is needed to confirm invasion as well as to assess for ER, PR, and HER2/neu status. Staging to rule out metastatic disease can include MRI of the thoracic and lumbar spines without gadolinium, a chest X-ray with fetal shielding, and an ultrasound of the liver. CT scans are not routinely recommended during pregnancy due to fetal radiation exposure. Once diagnosed, the woman should be seen in a multidisciplinary setting with medical oncology, surgical oncology, radiation oncology, and maternal-fetal medicine [132].

Breast surgery can be done safely during pregnancy, although many surgeons will wait until the end of the first trimester when the rate of spontaneous abortion is lower. Radiation therapy is not done routinely for breast cancer until after delivery in order to avoid radiation to the fetus. Chemotherapy has been administered safely

during pregnancy in the second and third trimesters [133]. Anthracyclines have the most safety data given during pregnancy. The largest prospective data from MD Anderson Cancer Center has used FAC chemotherapy in the second and third trimesters, although more data regarding the use of AC and a small series of dose-dense therapy has also been reported [125, 134–136]. Other chemotherapies, such as taxanes, have been reported with acceptable safety profiles [137]. The use of trastuzumab and monoclonal antibody therapy should be avoided during pregnancy due to oligohydramnios and fetal renal failure. They should be initiated after delivery [138–140]. Tamoxifen has been associated with multiple birth defects, and endocrine therapy should also be delayed until after delivery [141]. The outcomes of children exposed to chemotherapy in utero continues to be followed; however, to date, no specific pediatric syndromes have been identified, and no specific recommendations for pediatric monitoring have been made for these children [142]. They should receive all standard and routine pediatric medical care and surveillance.

8.8 Inherited Breast Cancer

Inherited breast cancer syndromes account for approximately 5–10 % of all cases of breast cancers [143]. It is estimated that the prevalence of *BRCA* mutations is 1:300 for *BRCA*1 and 1:800 for *BRCA*2 [144]. In persons of Ashkenazi Jewish ancestry, the three most common founder mutations are estimated at 1:40 [145]. Women who are diagnosed at younger ages are at a higher risk of having a hereditary cancer syndrome, for example, in some estimates, a 30-year-old diagnosed with a breast cancer in the absence of a known family history can have as high as a 50 % chance if having a *BRCA* mutation [146]. Therefore, age alone is a valid reason for referral for genetic counseling and strong consideration of testing. Current recommendations by the National Cancer Comprehensive Network (NCCN) (http://www.nccn.org/professionals/physician_gls/PDF/breast-screening.pdf) recommend referrals for genetic counseling for women diagnosed at 50 or younger. Counseling has become even more important not only to discuss the risk of *BRCA* mutations but also simultaneous evaluation of multiple genes in the era of next-generation sequencing (NGS), which has become widely available.

*BRCA*1 and *BRCA*2, located on chromosomes 17 and 13, respectively, are thought to account for the majority of inherited breast cancers [147]. The estimated lifetime risk of developing breast cancer among *BRCA*1 and *BRCA*2 carriers is 47–66 % and 40–57 %, respectively, compared to a 12.5 % risk among the general population [148]. In addition, young patients harboring *BRCA* mutations are at higher lifetime risk for the development of ovarian cancer and breast cancer, including significantly higher risks of bilateral or metachronous contralateral breast cancers [149]. *BRCA*2 mutation carriers have also been described to have increasing incidences of male breast cancer and pancreatic cancer [150].

In addition to *BRCA*1 and *BRCA*2, multiple other genes have been identified that are considered to have a high enough of a risk to discuss similar surveillance and risk-reducing strategies as for *BRCA*. These include *p53* (Li-Fraumeni syndrome), *PTEN* mutations (Cowden's syndrome), *STK11* (Peutz-Jeghers syndrome), and *CDH-1* (hereditary diffuse cancer syndrome) [151]. In addition, several of the more expanded NGS genetic testing panels have multiple other genes considered moderately penetrant such as *PALB2*, *CHEK2*, and *ATM* among many other with even less data regarding penetrance and associated cancer risks. Given a known increase in the risk of breast cancer, high-risk breast surveillance should be considered. As we continue to gain more information and knowledge regarding breast cancer risks with these and genes to be identified in the future, improved counseling and recommendations will be forthcoming. It may be important, and as part of pretesting counseling, to strongly consider *which* genes to test and to discuss that for several genes listed on larger NGS panels, there may not yet be recommendations. Furthermore, with more genes tested, there is a higher chance of variants of uncertain significance adding to this ambiguity.

Although there is no universal approach, it is recommended that clinicians discuss intensive surveillance of the breasts and ovaries for hereditary cancer mutation carriers, chemoprevention, and prophylactic surgery (i.e., bilateral mastectomy and bilateral salpingo-oophorectomy) with their patients diagnosed with a *BRCA* mutation on an individualized basis. The NCCN does specifically address the referral guidelines for genetic counseling and testing, in addition to recommendations for surveillance and prevention for *BRCA* mutation and other genes associated with hereditary cancer syndromes. The NCCN currently recommends annual mammography and every 12 months, starting at age 30 alternating with annual bilateral breast MRI starting at age 25 or 5–10 years prior to earliest age of onset. Annual mammography should be added to high-risk screening starting at the age of 30. This can be done at the same time or mammography staggered every 6 months with MRI given the risk of interval cancers [152]. Prophylactic surgeries are a very individualized and personal choice and should be done after counseling regarding risk reduction and reconstructive options. Counseling regarding body image postmastectomy should also be encouraged if available.

8.9 Bone Health

A large majority of young women diagnosed with early-stage breast cancer will survive decades following diagnosis and treatment; thus, bone loss associated with both adjuvant endocrine and cytotoxic chemotherapeutics must be taken into consideration to prevent long-term complications including osteopenia, osteoporosis, and potentially disabling fractures. Traditionally, the postmenopausal breast cancer population had been the focus of bone health research, given the success of aromatase inhibitors, agents well known to cause bone loss across both class and schedule [153]. Over the past decade, the adverse effects of premature menopause on future bone health have received appropriate attention as accelerated bone loss has the potential to affect survivorship significantly. Moreover, several studies have also illustrated improvement in breast cancer outcome among young women who receive adjuvant bisphosphonate therapy [154]. The final analysis of CALGB study 79809 which reported on 439 premenopausal women with early-stage breast cancer was randomized to zoledronic acid (Zometa, Novartis Oncology) 4 mg intravenously every 3 months for a total of eight treatments beginning within 1–3 months after starting adjuvant chemotherapy or 1 year after randomization. Of the 150 women who developed ovarian failure (defined as >3 months of amenorrhea and FSH >30) following adjuvant chemotherapy, those who received early zoledronic acid had less bone loss then those randomized to later zoledronic acid (+1.2 % versus −6.7 %, $p<0.001$). Side effects were minimal [155]. A second randomized, double-blind, multicenter phase III study evaluated the addition of zoledronic acid (4 mg intravenously every 3 months) versus placebo for 1 year among 101 women receiving chemotherapy for early-stage breast cancer. Consistent with the previous report, placebo was associated with a significant decline in lumbar spine bone mineral density (BMD) at both 6 (2.4 %) and 12 (4.1 %) months. In contrast, BMD remained stable among patients receiving zoledronic acid ($p<0.0001$) [156]. Therapy was well tolerated and there were no reports of either renal insufficiency or osteonecrosis of the jaw.

Zoledronic acid has demonstrated antitumor and anti-metastatic activity in preclinical and early clinical studies, providing a rationale for the Austrian Breast Cancer Study Group (ABCSG) 12 trial. Over 1,800 premenopausal women with endocrine-responsive early-stage breast cancer were randomized to ovarian suppression with the GnRH agonist goserelin with tamoxifen or anastrozole (Arimidex, AstraZeneca) with or without zoledronic acid 4 mg every 6 months for 3 years. At a median follow-up of 62 months, the addition of zoledronic acid reduced the risk of disease-free survival events (HR, 0.68; 95 % CI, 0.51–0.91; p 0.009), although there was no significant difference in survival between the groups (HR, 0.67; 95 % CI, 0.41–1.07; p 0.09). Interestingly, while there was no significant difference in disease-free

survival in the tamoxifen and the anastrozole arms (HR, 1.08; 95% CI, 0.81–1.44; *p* 0.59), overall survival was worse with anastrozole compared with tamoxifen (HR, 1.75; 95% CI, 1.08–2.83; *p*, 0.02) [154].

Finally, the Early Breast Cancer Trialists' Collaborative Group conducted a meta-analysis of over 17,000 women with early-stage breast cancer enrolled in a trial of adjuvant bisphosphonate therapy [157]. While recurrence and survival were not improved by bisphosphonate therapy across the entire study population, reductions in distant (18.4% vs. 21.9%, *p*, 0.0003) and bone recurrence (5.9% vs. 8.8%, $p<0.00001$), as well as improvements in mortality (10 year, 15.2% vs. 18.3%; *p*, 0.004), were observed among postmenopausal women. It is unclear if young, premenopausal women receiving ovarian suppression would have derived similar benefit. While formal guidelines regarding bisphosphonate use tailored specifically to young women do not yet exist, awareness of the issue of BMD among young, premenopausal women facing systemic therapy for breast cancer is paramount. Moreover, early incorporation of bisphosphonate therapy may not only improve bone health but possibly breast cancer prognosis.

8.10 Psychosocial Issues

Adolescents and young women are at particular risk of emotional and psychosocial problems during and after treatment for breast cancer and require appropriate support from age- and disease-specific psychosocial and medical multidisciplinary teams [158]. Although a diagnosis of breast cancer can be distressing to patients across all age groups, diagnosis at a younger age presents a variety of unique psychosocial and emotional challenges including, but not limited to, interactions with spouse/children, interruption of career, body image, sexuality, and loss of fertility/premature menopause [159]. A retrospective study evaluating over 500 breast cancer survivors aged 25–50 years illustrated that emotional and social functioning, vitality, and depression at 6 years (range, 2–10 years) following diagnosis were inversely proportional to age at diagnosis [160]. A recently published study comparing three groups of women confirmed these findings [161]. Recurrence-free breast cancer survivors who had been diagnosed at age 45 or younger and treated 3–8 years ago with doxorubicin, cyclophosphamide, and paclitaxel ($N=505$) were compared to 404 age-matched controls and 622 breast cancer survivors diagnosed at 55–70 years of age (and treated 3–8 years previously with doxorubicin, cyclophosphamide, and paclitaxel). Those who had been diagnosed with cancer at a young age reported worsened depression, fatigue, attention, sexual function, and spirituality than age-matched controls. They also experienced more problems with body image, anxiety, sleep, marital satisfaction, and fear of recurrence than both age-matched controls and women diagnosed at an older age.

Fertility concerns can be a major source of distress for young survivors. A decade ago, a web-based survey evaluating the effects of breast cancer diagnosis and treatment among over 600 young breast cancer survivors (median age, 32.9 years) indicated that 57% were concerned about infertility with treatment and 29% reported that these concerns affected treatment decisions. Approximately 75% discussed these concerns with their physicians, and 51% felt that their concerns were addressed adequately [159]. These findings were confirmed by a more recent cohort study of 620 young survivors (median age, 37) in which 51% reported concern about fertility [103]. Greater concern about fertility was associated with younger age, nonwhite race, not having children, and receipt of chemotherapy.

To address the concern that psychosocial issues might play a role in cancer recurrence, a population-based study of over 700 Australian women aged less than 60 was conducted. While this study did not reveal an association between breast cancer recurrence and measured psychosocial factors, it did indicate that greater anxious preoccupation was associated with younger age ($p=0.03$) [162]. Preliminary evidence suggests that mindfulness meditation may help young breast cancer survivors reduce stress and behavioral symptoms, though larger studies are needed

[105]. Other interventions to improve psychosocial outcomes are also under development including online supports for patients and their families [163].

Conclusions

Although thought to be a relatively uncommon condition, approximately one-third of all breast cancers are diagnosed among premenopausal women. Women who present with breast cancer at a young age are more likely to be diagnosed with an aggressive breast cancer subtype. Moreover, younger age at breast cancer diagnosis has historically conferred an inferior prognosis when compared to older women. Special considerations, including premature ovarian failure, infertility, pregnancy, bone health, familial syndromes, and psychosocial issues, must be addressed when developing treatment algorithms for young women facing a breast cancer diagnosis. More recently, advances in optimal endocrine therapy recommendations have been refined. Finally, optimal care of young women diagnosed with breast cancer requires a multidisciplinary team to provide optimal care with the overall goal of improving outcome while preserving quality of life and maximizing survivorship.

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Thyroid Cancer

9

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Abstract

Thyroid cancer accounts for 13 % of invasive cancer in the adolescent and young adult (AYA) population of 15–39 years of age. The proportion is 17 % in females and 6 % in males. Nowadays, the existence of two therapeutic approaches, that is radical versus conservative therapy, is still an area of great controversy. Nonetheless, we think that both options should be considered whenever treating a child or adolescent with a non-medullary thyroid carcinoma. Not least, permanent posttreatment complications of both surgery and metabolic irradiation (RAI therapy) should be taken into account, with all the damage in the quality of life and the economic costs that are implied. Our hope is that in the future, the conservative approach will be considered in the suitable cases, with a decrease of overtreatment of a type of cancer that still shows an about 100 % overall survival (OS) independently of stage, occurrence of relapse, and type of approach applied.

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9.1 Introduction

Thyroid cancer is one of the most common cancers in the adolescent and young adult (AYA) population, accounting for 13 % of all invasive cancer and 11 % of all cancer, invasive and in situ, in the age group, in contrast to corresponding proportions of 2.4 and 2.1 % for all ages (Table 9.1). By sex, the proportion of invasive cancer is much greater in females than males, 17 % for AYA

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Table 9.1 Incidence of thyroid cancer and all invasive cancer with or without in situ cancer, 2000–2012, SEER18

	Invasive cancer			Invasive + In situ cancer		
	Incidence[a]		Thyroid	Incidence[a]		Thyroid
	All sites	Thyroid	%	All sites	Thyroid	%
	All ages					
Male and female	466.4	11.0	2.4 %	522.5	11.0	2.1 %
Female	413.4	16.3	3.9 %	482.3	16.3	3.4 %
Male	542.5	5.6	1.0 %	585.9	5.6	1.0 %
	Age 15–39					
Male and female	68.0	8.7	12.7 %	80.5	8.7	10.8 %
Female	83.4	14.5	17.4 %	101.4	14.5	14.3 %
Male	52.7	3.0	5.6 %	59.8	3.0	4.9 %

[a]Rates are per 100,000 and age adjusted to the 2000 US Standard Population (19 age groups – Census P25-1130) standard

females versus 4 % for all-age females and 6 % and 1 %, respectively, for males (Table 9.1). Thyroid carcinoma represents approximately 7.5 % of all invasive cancer in the 15- to 19-year-old age group and 10.6 % of all invasive cancers in persons 20–24 years of age [1, 2]. In children younger than 15 years of age, it is a much rarer malignancy, and it has been reported that sporadic papillary thyroid carcinoma constitutes only 0.57 % of all malignancies in children under 15 years old in Europe [3]. Fortunately, in young patients diagnosed with thyroid carcinoma, the overall 5-year survival rate is 98–100 % [3], assuring an excellent long-term prognosis in most cases. Because of the small number of cases in children each year and because of the extended follow-up necessary to perform prospective clinical studies, pediatric thyroid carcinoma remains a poorly studied disease, with most treatment recommendations based upon the experience treating adults. This has been taken as adequate in most cases, while the differences in the biology of pediatric thyroid carcinomas need to be appreciated by the clinician who is providing care to this group of patients. Furthermore, as with any rare disorder, optimal treatment for pediatric thyroid carcinoma is best accomplished at a center with familiarity and multispecialty expertise in treating this disease.

Pediatric thyroid malignancies arise typically from one of two normal thyroid cell populations, either the thyroid follicular epithelium or the parafollicular C cell, which has a distinct embryologic origin. Differentiated thyroid carcinoma (DTC) – including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and their variants – arises from the former, whereas medullary thyroid carcinoma (MTC) arises from the latter. Appreciating this major histologic distinction is fundamental to understanding the differences in the biologic behavior and treatment applicable to these very different thyroid cancers. While the majority of PTC subtypes are represented by low-risk ones like the classic, the solid/trabecular, microcarcinoma, diffuse sclerosing, follicular, and encapsulated follicular [4, 5], rare cases also belong to high-risk PTC according to adult prognosis. As an example, we have recently described three patients with tall cell variant that has in adult a fourfold risk of relapse and twofold relapse-related risk of death. These three patients, on the contrary, despite hemithyroidectomy in two of them, were alive without relapse after almost 30 years thus showing the peculiar good outcome of childhood and adolescence DTC despite any other adult-customized feature [6].

During the last decades, changes in clinical presentation have been found in children: specifically, palpable cervical adenopathy, once a common presenting symptom, has decreased from 63 to 36 %; invasion of contiguous structures has dropped from 31 to 6 %, and distant metastases has fallen from 19 to 6 %; on the other hand, presentation as a solitary thyroid nodule has increased from 37 to 73 % among children [7].

Although poorly differentiated and frankly anaplastic thyroid carcinomas can occur in the adolescent and young adult population, they are exceedingly rare. Therefore, the current chapter will focus only on DTC and MTC.

9.2 Epidemiology, Survival, and Overdiagnosis

9.2.1 Incidence During 1975–2011

The incidence of thyroid cancer among 15- to 39-year-olds in the USA has increased steadily since 1990, especially in females in whom the thyroid cancer occurred in one in every five females by 2010 (Fig. 9.1).

9.2.2 Incidence During 2000–2011

During 2000–2011, the incidence of thyroid cancer was distinctly more common in females, at all ages. The peak incidence occurred at an older age in males, between 65 and 75 years, than in females, between 50 and 55 years of age. In AYAs (Fig. 9.2), the incidence increased eightfold between 15 and 40 years of age in females and ~5-fold in males. AYAs had the highest ratio incidence in females to male, ranging from 4.3 to 6.4 by 5-year age subgroup and peaking between 20 and 25 years of age.

Metastatic cancer at diagnosis of thyroid cancer was uncommon before age 50 and didn't account for more than 5 % of the cases until age 70 (Fig. 9.3). In AYAs (Fig. 9.3, yellow highlight), regional + distant stage accounted for 40–50 % of all cases in patients <30 years of age, and localized presentation accounted for 45–65 %. Males had proportionately more regional and distant disease at diagnosis up to the age of 75 than females. In AYA males (Fig. 9.3), the incidences of localized and regional disease at diagnoses were similar, whereas in women, localized disease predominated from the age of 20 and up.

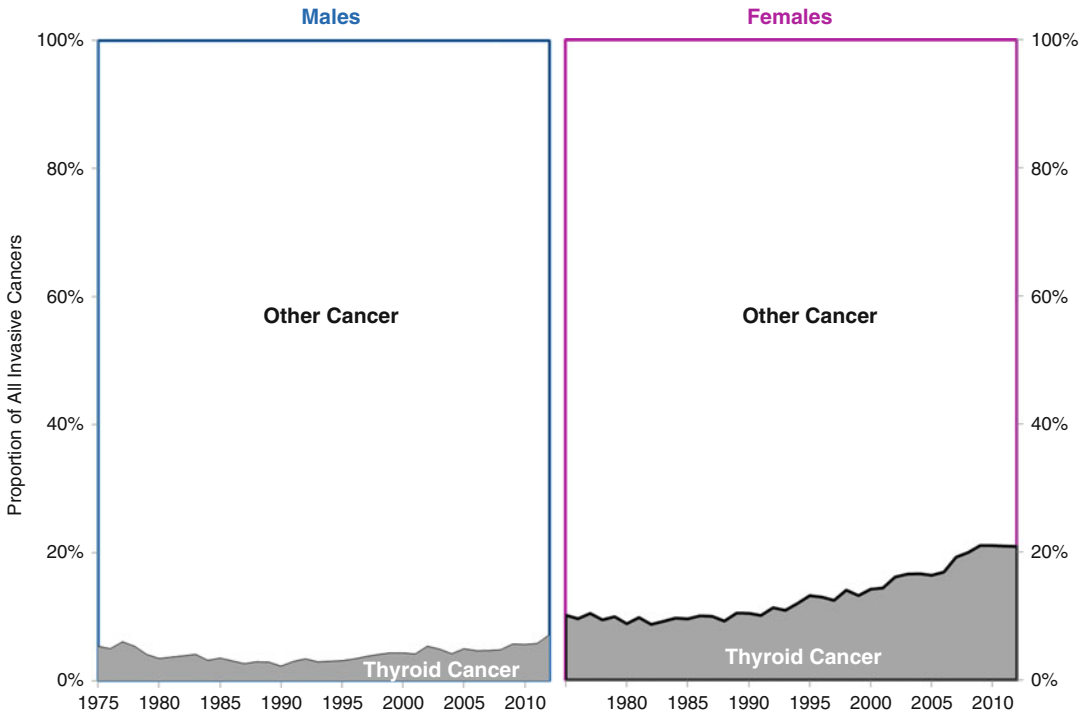

Fig. 9.1 Proportion of all invasive cancers that is thyroid cancer in AYAs of age 15–39, by year, 1975–2011, SEER9

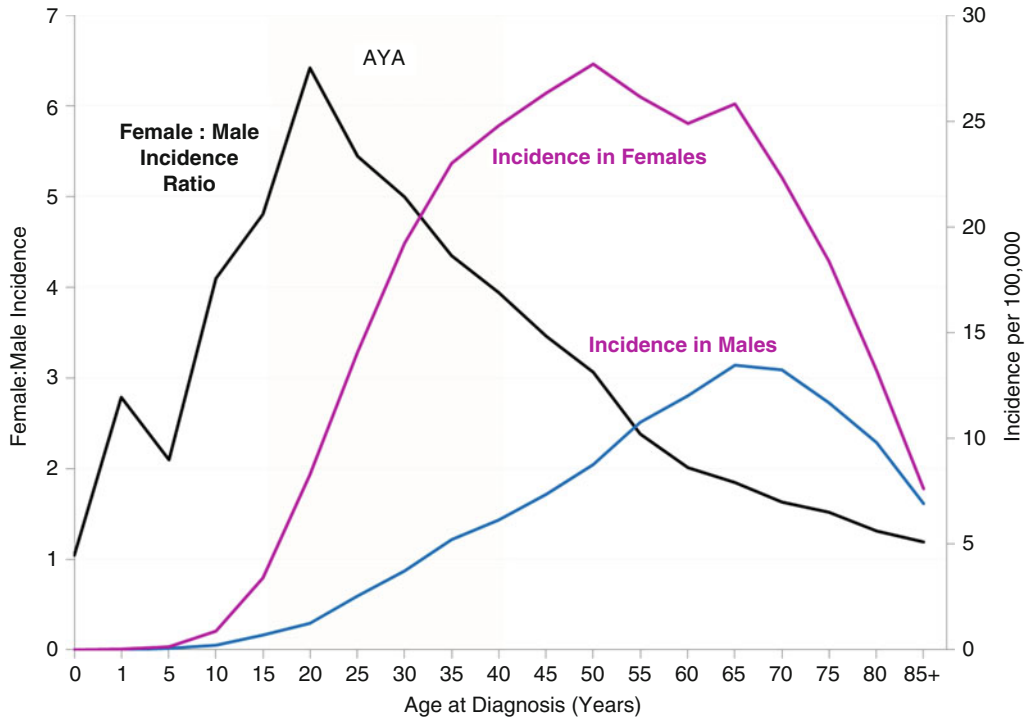

Fig. 9.2 Thyroid cancer female/male incidence ratio and incidence by age and sex, SEER18, 2000–2011

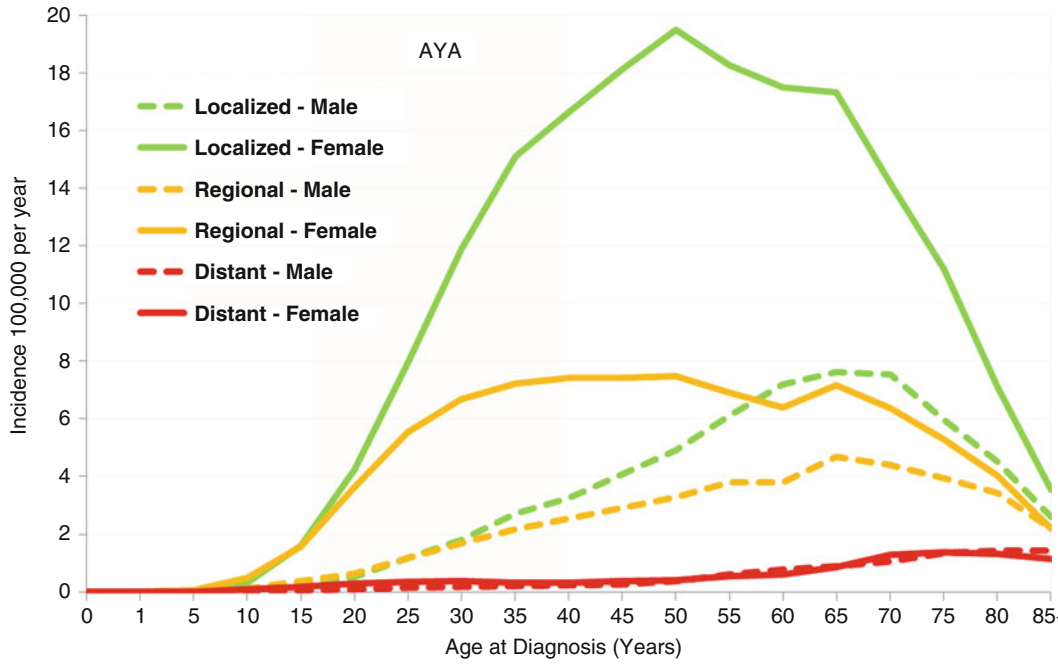

Fig. 9.3 Thyroid cancer incidence by age, sex, and extent of disease at diagnosis, SEER18, 2000–2011

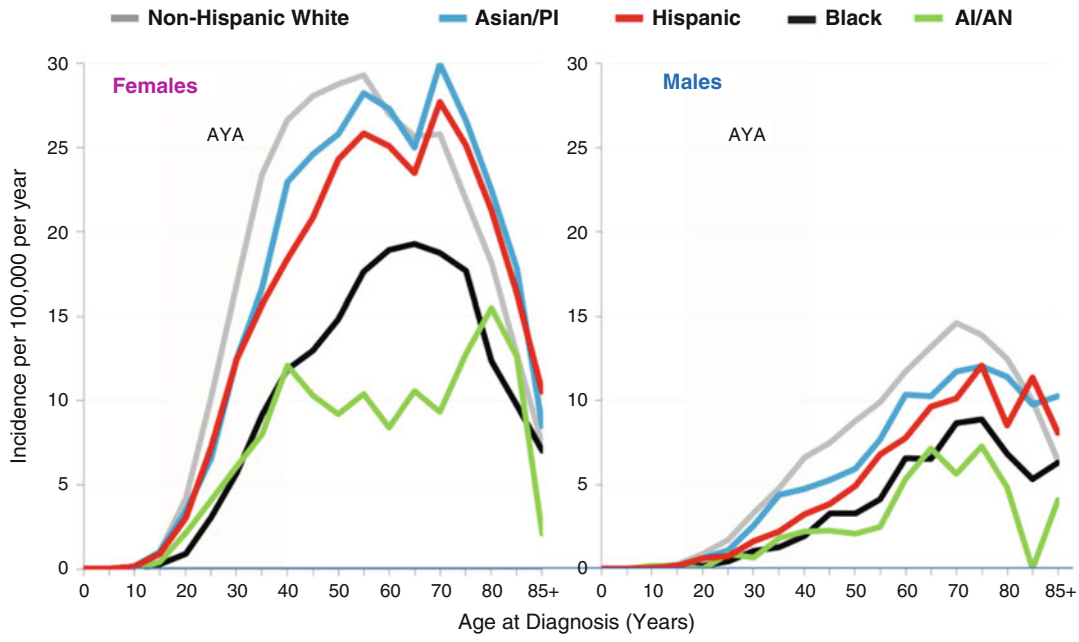

Fig. 9.4 Thyroid cancer incidence by age and race/ethnicity and sex, SEER18, 2000–2011. PI, Pacific Islander; AI/AN, American Indian/Alaska Naïve (native North Americans)

In both females and males, non-Hispanic whites had the highest incidence of thyroid cancer, and blacks and native North Americans had the lowest (Fig. 9.4). Hispanic AYA females had a higher relative incidence than other major races/ethnicities than in Hispanic AYA males, with the former more similar to non-Hispanic whites and Asians/Pacific Islanders and the latter similar to blacks and native North Americans.

9.2.3 Incidence Trends During 1976–2011

The incidence of thyroid cancer increased in females and males and primarily in AYAs (Fig. 9.5). In AYA females, the increase began in the early 1990s and was greater than in AYA males. In AYA males, the increase was more recent, primarily since 2000.

Whereas there was no consistent change in incidence of AYAs with distant disease at diagnosis, the incidence of regional and localized disease increased, with localized disease accounting quantitatively for most of the overall increase (Fig. 9.6).

9.2.4 Survival During 2000–2011

Including those with distant metastases at diagnosis, AYAs had the best 5-year thyroid cancer-specific survival, 99.9 % for localized disease, 99.8 % for regional disease, and 97.7 % for distant disease. In AYAs <30 years of age at diagnosis, the 5-year thyroid cancer-specific survival was >98.6 % for those with distant metastases at diagnosis. For AYAs of all ages, the rate was >99.8 % for regional and localized disease. In AYAs with distant metastases at diagnosis, males had a worse 5-year thyroid cancer-specific survival than did females, with the worse outcome, 92 % in males 35-29 years of age. Overall all stages, male and female AYAs had the same survival rate. Not until age 65 did males have a worse outcome, albeit by just a few percent (Fig. 9.7).

9.2.5 Survival Trends During 1976–2011

The 5-year thyroid cancer-specific survival has been near or at 100 % in AYAs since 1976. Only in patients over 40 years of age was the survival

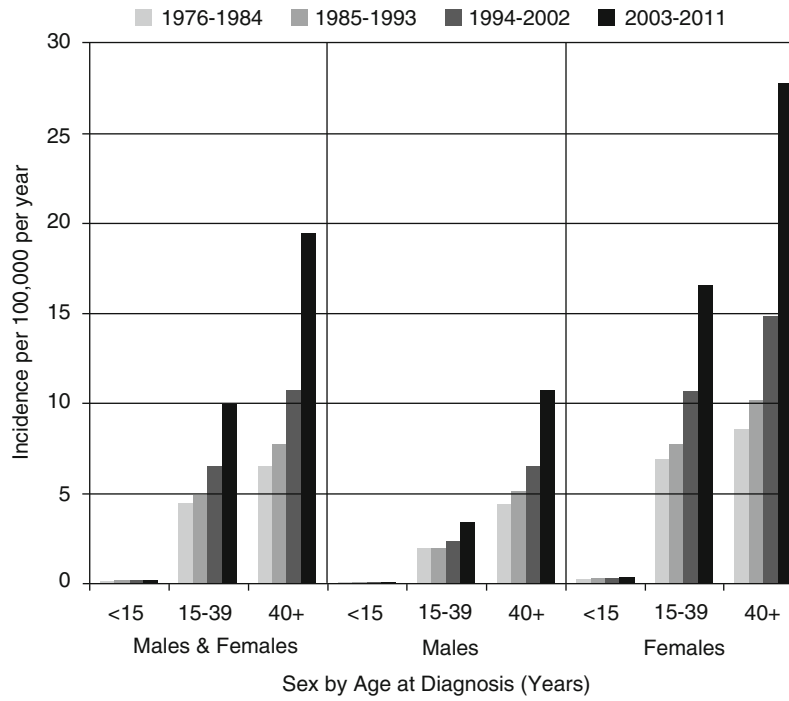

Fig. 9.5 Thyroid cancer incidence by age, race/ethnicity, and sex, SEER18, 2000–2011

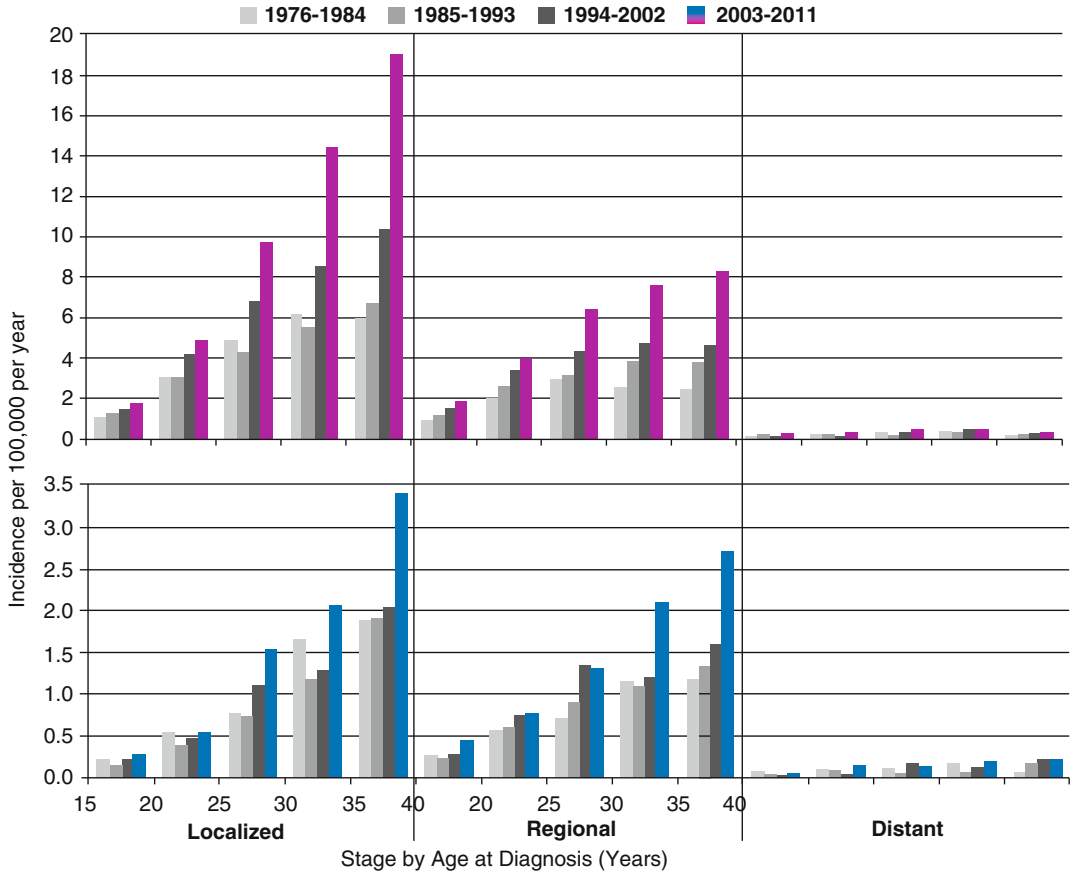

Fig. 9.6 Thyroid cancer incidence by age, race/ethnicity, sex, and extent of disease at diagnosis, SEER18, 2000–2011

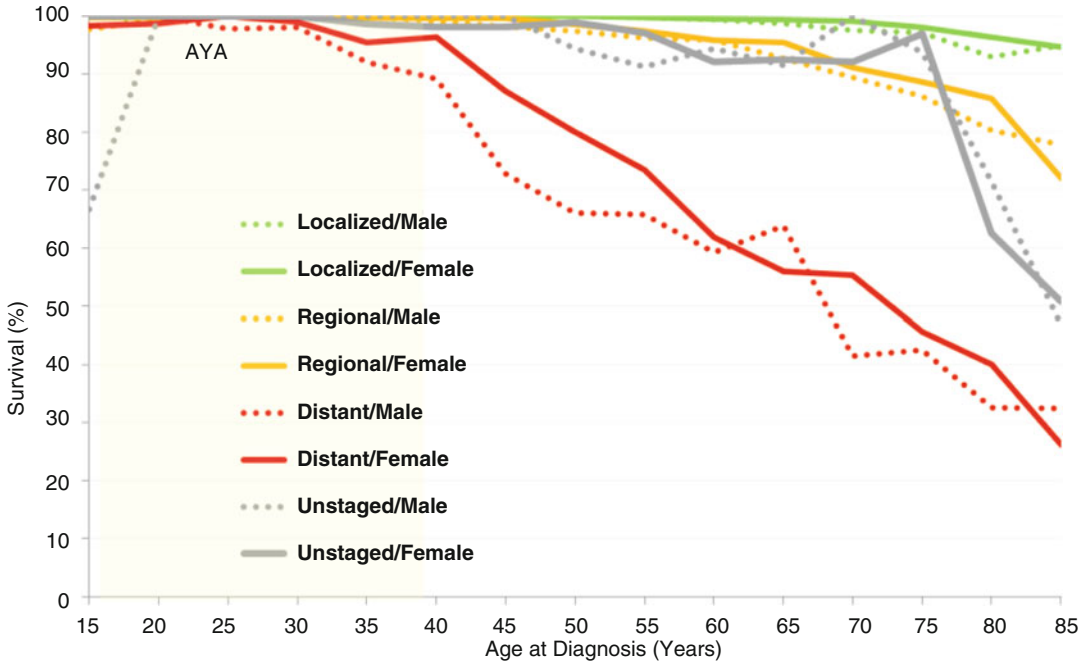

Fig. 9.7 Thyroid cancer survival by age, sex and extent of disease at diagnosis, SEER18, 2000–2011

significantly <100 %, and it improved during 1976–2010, from 89 to 96 % in males and from 91 to 98 % in females (Fig. 9.8).

9.2.6 Death Rates and Mortality Trends During 2000–2011 and Comparison with Incidence Trends

The thyroid cancer death rate was miniscule compared with the incidence rate up to the age of 55 (Fig. 9.9). In AYAs, the death rate (Fig. 9.9, inset) was 0.7–0.8 % of the incidence rate (Fig. 9.9, main chart) in 20–34-year-olds and 1.3 % in 35–39-year-olds. Among AYA females, one thyroid cancer death was recorded for each 560 new cases; in AYA males, one death occurred for each 123 new cases.

The striking increase in new cases of "thyroid cancer" since 1990 has not affected the mortality rate of thyroid cancer, either over all ages (left panel) or in AYAs specifically (right panel). The disassociation is more dramatic in females than males. Of three major explanations, (1) the expected increase in the death rate has not yet occurred and will do so in the future, (2) current therapy is completely curative, and (3) the excess cases are overdiagnosed (nonlife threatening, not "cancer"), and therapy is not necessary, the latter is most likely.

The striking increase in new cases of "thyroid cancer" since 1990 did not affect the incidence of metastatic disease at diagnosis, in either females (Fig. 9.11, left panel) or males (Fig. 9.11, right panel), which is most likely due to overdiagnosis. This "epidemic" has not included regional disease which indicates that more therapy, either more surgery, node dissections, and/or radiotherapy, was administered unnecessarily to those men and women who were overdiagnosed.

Of all the cancers in AYAs, thyroid cancer has had the greatest increase in incidence relative to the change in mortality rate (Fig. 9.12). During the past decade, AYAs have had greater increase in the incidence of thyroid than any other cancer except kidney cancer and average of 5 % per year or nearly 50 % during the decade, whereas deaths from thyroid cancer in the age group did not substantively change. The difference between the

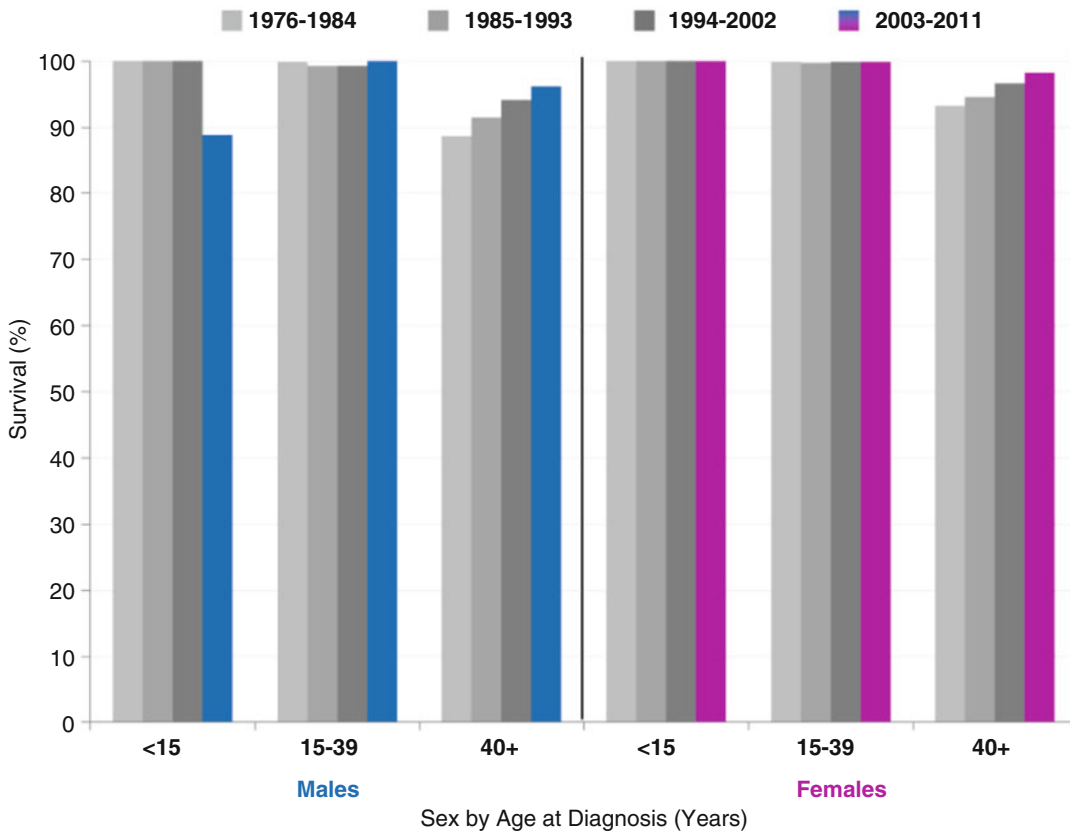

Fig. 9.8 Five-year thyroid-specific cancer survival trends by age and sex, 1976–2011, by 9-calendar year intervals, SEER18

average annual percent changes (AAPCs) among 15–39-year-olds in comparison with the AAPC of the death rate was greater for thyroid cancer than any other cancer.

9.2.7 Overdiagnosis

Overdiagnosis of thyroid cancer is more problematic for AYAs than for either younger or older person and more than any other cancer. The problem has been observed in the USA [8], Canada [9], Australia [10], and South Korea [11]. The increase in incidence of thyroid cancer and lack of change in thyroid cancer mortality in Figs. 9.10 and 9.11 suggest that two of every three AYAs with thyroid cancer in the USA are being overdiagnosed, the highest rate of overdiagnosis of any cancer. The cause has been attributed to the increased availability and use of more sensitive imaging techniques such as ultrasound, CT scanning, and MRI scanning [12] that detect subclinical nodules and that appear to pathologists as cancer but that do not affect the patient in her or his lifetime. Virtually all persons diagnosed with thyroid cancer are treated: roughly two thirds undergo radical thyroidectomy, and one third undergo subtotal thyroidectomy. The tumors being excised are getting smaller – at one center, the proportion of patients undergoing surgery for a tumor measuring less than 1 cm in diameter increased from 14% in 1995 to 56% 10 years later [11]. Despite guidelines in South Korea recommending against evaluation and surgery for tumors less than 0.5 cm in diameter, one quarter of surgical patients now have tumors that fall into this category. Thyroid cancer surgery has substantial consequences for patients. Most must

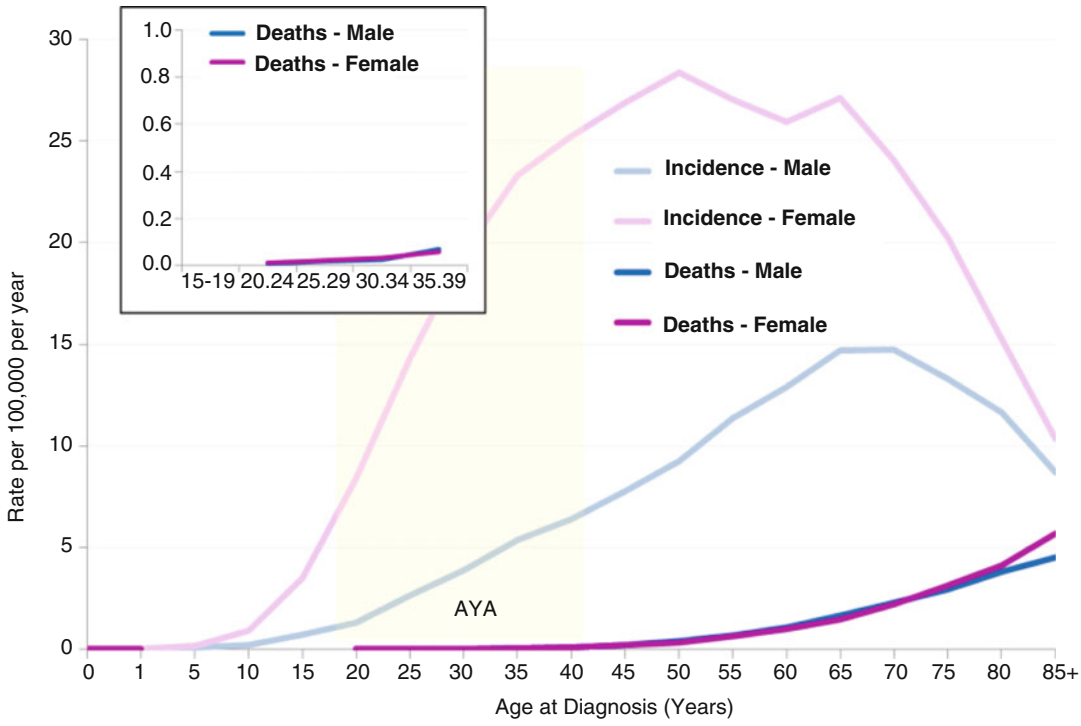

Fig. 9.9 Thyroid cancer incidence and death rates by sex and age, 2000–2011

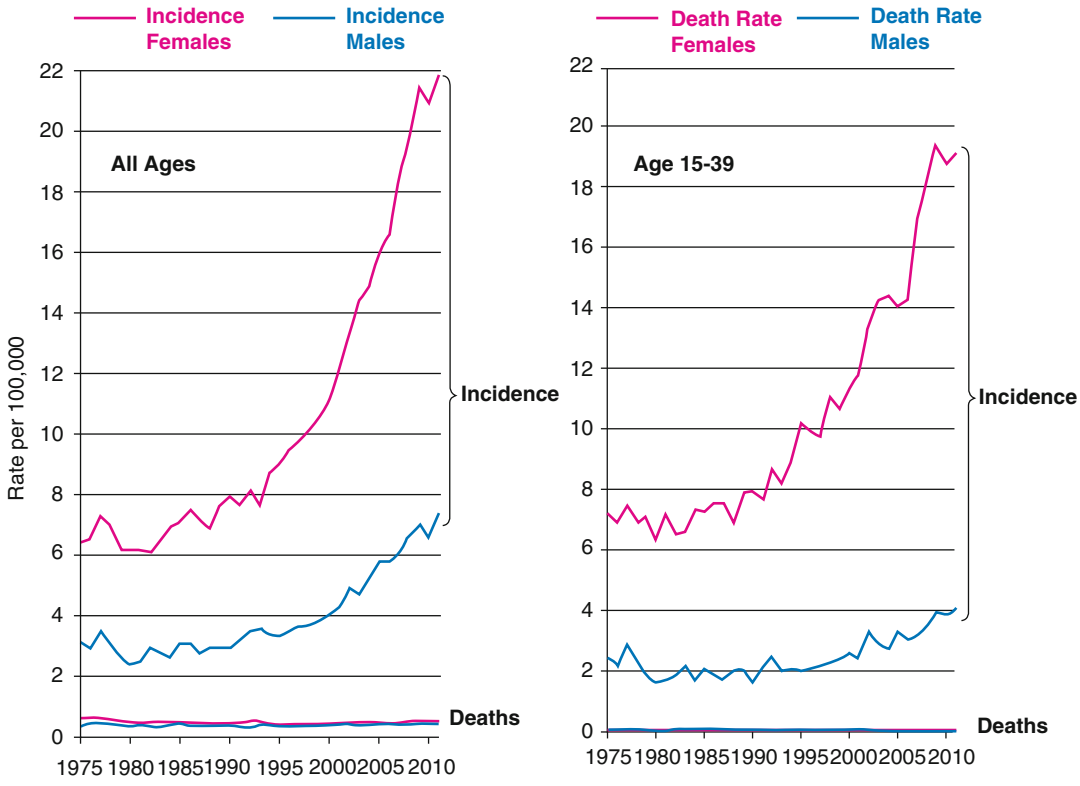

Fig. 9.10 Annual incidence of and deaths from thyroid cancer since 1975 in SEER regions, all ages (*left panel*) and AYAs (*right panel*)

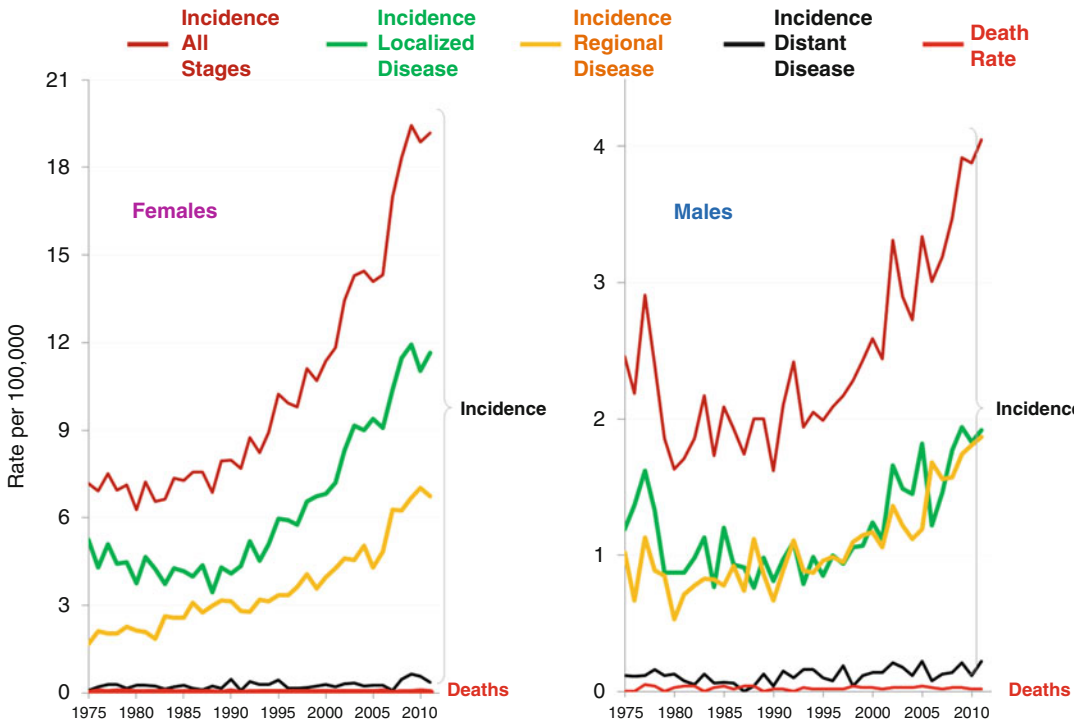

Fig. 9.11 Annual incidence of thyroid cancer overall and by stage and of thyroid cancer deaths among 15–39-year-olds since 1975 in SEER regions by sex

receive lifelong thyroid replacement therapy, and a few have complications from the procedure. An analysis of insurance claims for more than 15,000 Koreans who underwent surgery showed that 11 % had hypoparathyroidism and 2 % had vocal cord paralysis [11]. As of 2015, there is still little to no evidence that this extraordinary problem of a high rate of unnecessary therapy and associated compromise of health-related quality life has been addressed.

In the USA, the evolution of overdiagnosis of thyroid cancer accounts for a substantial proportion of the increase in incidence of invasive cancer in AYA females. When thyroid cancer is excluded, the statistically significant increase in incidence during 2000–2012 is eliminated (Fig. 9.13).

Also, the inclusion of such cases artificially increases the survival rate of a cohort because the cases per se cause no deaths. Among females, who have a much higher proportion of thyroid cancer than males, one third (32 %) of the improvement in survival of AYAs with cancer during 2000–2008 was due to thyroid cancer and its overdiagnosis (Fig. 9.14).

9.3 Differentiated Thyroid Carcinoma

9.3.1 Etiology/Pathology

Differentiated thyroid carcinoma (DTC) is the most commonly encountered thyroid cancer in childhood, with PTC representing about 80 % and FTC being roughly 20 % of malignancies that arise from the follicular epithelium [13–15]. The diagnosis of PTC and FTC is based upon unique histopathological features, and there are subtypes of each, including follicular cell, tall cell, diffuse sclerosing, columnar cell, and encapsulated variants in PTC. Variants of FTC include Hürthle cell (oncocytic), clear cell, and insular carcinoma. Certain tumor subtypes, such as the

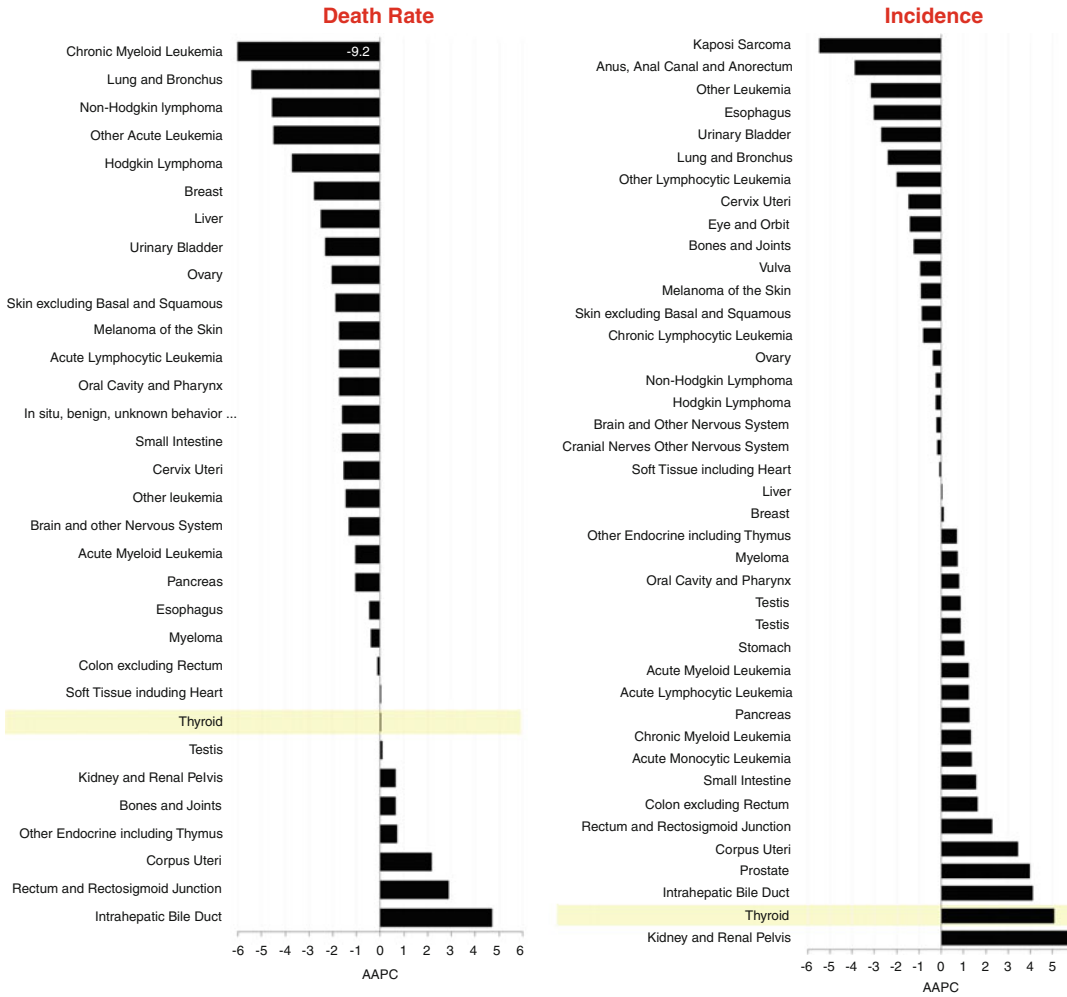

Fig. 9.12 Average annual % change (AAPC) in age-adjusted death rate (*left panel*) and incidence (*right* panel) in 15- to 39-year-olds by type of cancer, 2000–2011, USA

follicular and diffuse sclerosing variants of PTC, are more common in children and young adults as compared to older individuals [16]. Furthermore, as compared to the classical type found in older individuals, childhood PTC, particularly in patients less than 10 years of age, (1) may be unencapsulated and widely invasive throughout the gland and (2) may have a follicular and solid architecture with unique nuclear features and abundant psammoma bodies [17].

Despite the fact that PTC and FTC are both derived from the follicular epithelium and are treated in a similar fashion, there are some key differences in clinical behavior, specifically the risk and pattern of metastases. PTC is more likely to metastasize through lymphatic channels to regional neck lymph nodes. Hematogenous metastases, primarily to the lung, occur less frequently and typically only when locally metastatic disease is also present. FTC, on the other hand, is more prone to hematogenous metastases (affecting predominantly the lungs and bones); they metastasize less often to regional lymph nodes. Furthermore, PTC is more likely to be multifocal and bilateral [7]; FTC, in contrast, is usually a unifocal tumor.

It is a well-known phenomenon that the outcome of pediatric PCT is independent of strong

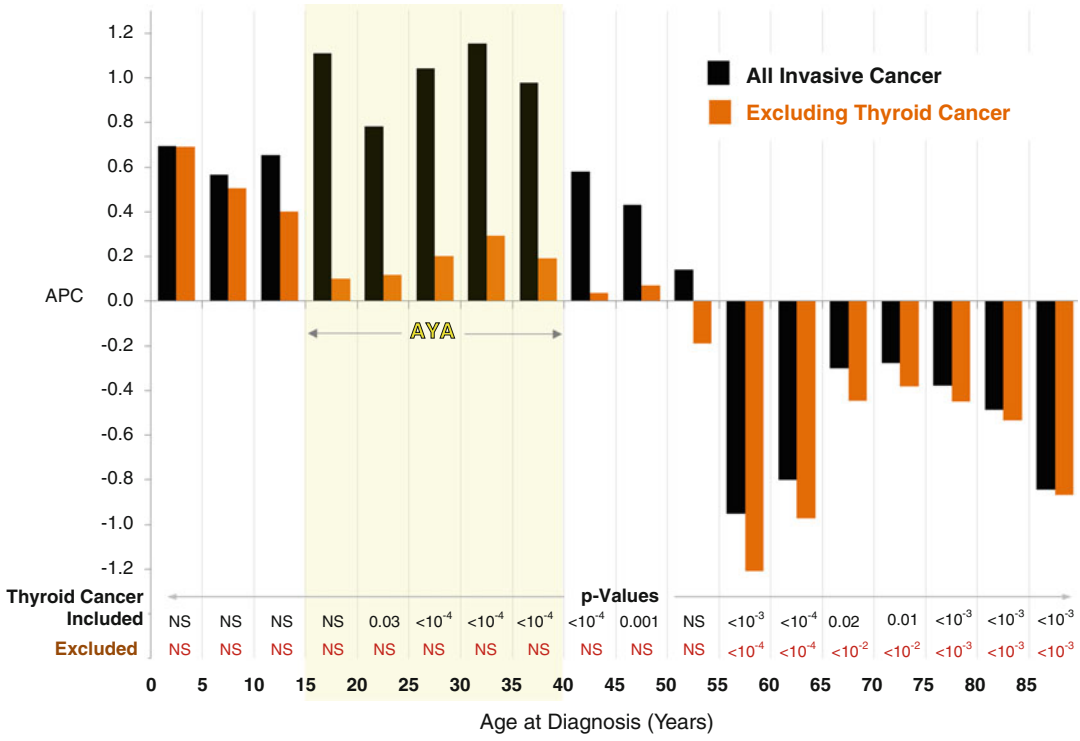

Fig. 9.13 Annual % change (APC) in incidence of invasive cancer in females by age with and without thyroid cancer, SEER18, 2000–2012

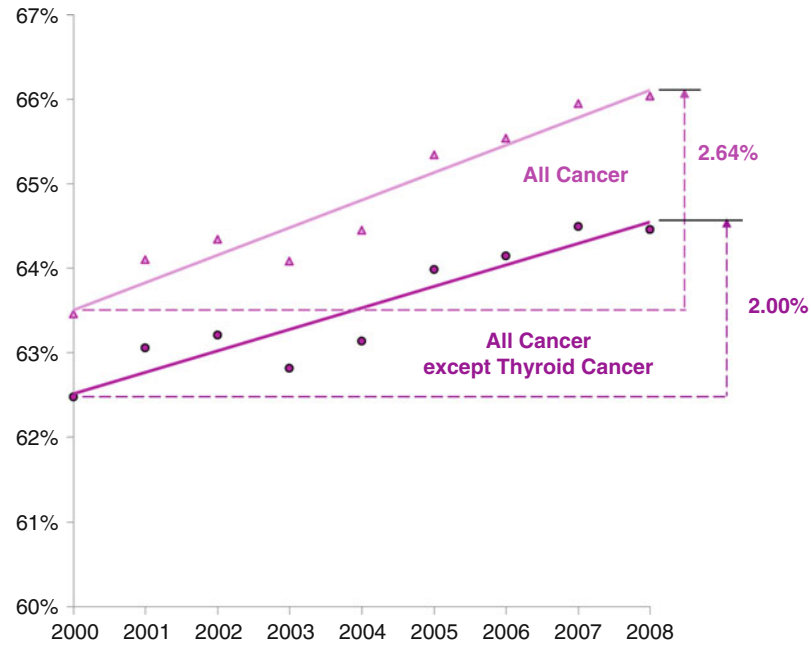

Fig. 9.14 Five-year relative survival of females with cancer, age of 15–39 years, by year of diagnosis, 2000–2008, with and without thyroid cancer, SEER

prognostic factors of adults, such as low- versus high-risk histological subtype, extrathyroid local invasion into soft tissue of the neck, presence of distant metastases, site of distant metastatic spread, occurrence of relapse, and type of surgery [4, 18]. Interestingly, a review of 120 papillary carcinomas, in patients younger than 20 years, has evaluated in a multivariate analysis risk factors for disease-free-survival and has revealed that initial nodal manifestation was the most significant risk factor. The amount of thyroid excision and the use of radioiodine therapy did not correlate to the final outcome [19].

The major established environmental risk factor for the development of benign and malignant thyroid neoplasms, particularly PTC, is radiation exposure to the head and neck [20, 21]. Children, particularly those less than age 5 years, are much more sensitive to the tumorigenic effects of irradiation [21, 22]; this may in part be due to the higher rate of thyroid cell replication in children as compared to adults [16, 23, 24]. Since children are no longer treated with radiation for benign conditions, such as thymic enlargement, tonsillar hypertrophy, or acne, there are now fewer thyroid cancer patients with this well-established risk factor; however, the use of external beam radiotherapy to treat malignancies (especially Hodgkin's disease) remains a significant risk for the development of thyroid carcinoma, even for many years after therapy is complete [25]. A specific paragraph has been dedicated to this subject. Although there are some conflicting data, it appears that cases of radiation-induced thyroid carcinoma are not significantly different in clinical behavior as compared to sporadic nonradiation-induced tumors [25, 26].

Internal ionizing radiation, such as that which occurred with the large environmental exposure to radioactive iodine from the Chernobyl nuclear accident, is another well-documented risk for the development of PTC, particularly in children less than 10 years of age at the time of exposure [27, 28]. Recent evidence suggests that the thyroid gland in younger children is better equipped to transport iodine as compared to older children [24]. Assuming that the mean radiation exposure per gram of thyroid tissue is inversely related to the age of the individual at exposure, it would make sense why the youngest children are most at risk for developing PTC after accidents such as Chernobyl. With an increased use of computed tomography scans in pediatric patients, there is an estimated risk of malignancy as high as one fatal cancer per 1,000 CT scans performed on children [29]

Researchers are beginning to unravel the molecular and genetic basis of the differentiated thyroid carcinomas. One of the major early somatic events that is associated with the development of papillary thyroid carcinoma is a chromosomal rearrangement linking the promoter region of an unrelated gene(s) (named PTC) to the carboxyl terminus of the RET (rearranged during transfection) proto-oncogene [16, 23, 28]. This occurs either because of a simple inversion of a segment of chromosome 10 (where RET resides) or a translocation of RET to a different chromosome. The RET/PTC rearrangement produces a chimeric oncogene, resulting in a constitutively activated form of the RET receptor tyrosine kinase (i.e., activation in the absence of ligand), thereby promoting tumorigenesis. Although it is believed that RET/PTC rearrangements may be critical for the development of pediatric- and radiation-induced PTC [30–36], some recent reports have challenged these conclusions [37].

Other important genes and gene products implicated in thyroid tumorigenesis and biological behavior include RAS and BRAF (important for intracellular signaling pathways; BRAF is implicated in PTC only), rearrangement of the TRK proto-oncogene (akin to RET but found in only a minority of PTCs), MET overexpression (mostly in PTCs), the p53 tumor suppressor gene (specifically involved in anaplastic thyroid cancer), and Pax8PPARγ1 translocations (follicular adenomas and follicular thyroid carcinomas only) [16, 23, 38, 39].

Approximately 3–5 % of patients with PTC have a family history of the disease [16, 40]. Having a positive family history may portend a worse prognosis, given that these cases appear to have more aggressive disease and shorter disease-free intervals after initial treatment [40, 41]. As

of yet, the genetic basis for dominantly inherited non-MTC has not been elucidated. Other familial tumor syndromes in which there is an increased risk of DTC include familial adenomatous polyposis (Gardner syndrome), Cowden disease, and the Carney complex [16].

9.3.2 Diagnosis and Clinical Presentation

In childhood, DTC usually presents as an asymptomatic neck mass [42, 43]. Occasionally, the diagnosis may be made incidentally after the discovery of pulmonary nodules on a chest radiograph. In any individual younger than 20 years of age presenting with a solitary thyroid nodule, there is a higher likelihood of malignancy [14, 44]. The overall prevalence of thyroid carcinoma is about 20–25 % of thyroid nodules in children, compared to 5 % in adults [14, 16, 44, 45]. Symptomatic thyroid cancers (i.e., those associated with hoarseness, dysphagia, or cough, thus suggesting more locally advanced disease) are rare in young individuals. Uncommonly, thyroid carcinoma arises ectopically in a thyroglossal duct remnant or cyst. Arguably, this would be an unusual presentation of childhood thyroid carcinoma, but it must be kept in mind for patients presenting with a midline mass in the region of the hyoid. Finally, although most patients are euthyroid at the time of diagnosis, rare cases of differentiated follicular thyroid carcinomas can present as a functioning nodule associated with a suppressed thyroid-stimulating hormone (TSH) or frank thyrotoxicosis.

In children and young adults, it is not unusual for thyroid carcinoma to present only with cervical lymph adenopathy, and locally metastatic disease is indeed present at diagnosis in the majority of pediatric PTC cases [43, 47, 48]. In addition, children more often have disseminated disease at diagnosis, with lung metastases identified in up to 20 % of cases [17, 47, 49]. Metastases to other sites, such as the bone and brain, are rare. In the presence of a thyroid or laterocervical nodule in the neck of a child or an adolescent, the first diagnostic step is a thorough clinical neck examination, with clinical assessment of the site of the nodule (thyroid vs. node vs. others) and its characteristics (site, size, consistency and mobility), and direct or indirect evaluation of laryngeal or esophageal involvement by the neoplasm through the evaluation of their functional alteration (dysphonia and dysphagia). In a patient presenting with a painless thyroid nodule, the first subsequent procedure should be a high-quality neck ultrasound (US; together with fine-needle aspiration and biopsy, FNAB), which assists greatly with surgical planning [50]. In young patients, FNAB has not been utilized extensively, and the scanty studies reported are often in disagreement. Nevertheless, a meta-analysis certified FNA as a sensitive diagnostic test and a useful tool in diagnosing malignancy in pediatric thyroid [51]. The procedure should only be performed by experienced physicians and cytologists. US is useful in determining the size and appearance of the lesion, assessing for other nodules, ensuring the accuracy of FNA, and looking for evidence of metastatic lymphadenopathy. For these reasons, US should be considered even when the diagnosis of thyroid carcinoma is already known. Ultrasound characteristics suggestive of malignancy include indistinct margins, microcalcifications, and variable echotexture [52–54]. However, it should not be understated that the utility of ultrasound is greatly dependent upon the expertise of the ultrasonographer, particularly when it comes to identifying metastatic lymphadenopathy.

There remains some controversy about the definitive management of thyroid nodules in children. For example, biopsy (often using US guidance) is the recommended initial procedure in adults and can easily be accomplished in mature adolescents and young adults [46, 52, 55]. Although FNAB can also be easily performed in younger children, conscious sedation may be required. On the other hand, many experts feel that the initial diagnostic step should be surgery (i.e., lobectomy and isthmusectomy), given the higher likelihood that a thyroid nodule in a child, particularly when accompanied by palpable lymphadenopathy, is a carcinoma. Although this is a reasonable approach, it is our feeling that a

preoperative FNAB (and subsequent pathologic diagnosis) allows for better operative planning and minimizes the need for a second surgery, particularly in children who present with a single thyroid nodule only.

Baseline thyroid function tests should also be obtained at presentation. Nuclear imaging studies using radioactive iodine or technetium pertechnetate are not very useful in the initial evaluation of these patients, except in those with a low TSH, because even benign thyroid nodules will be "cold" on nuclear imaging. In DTC, tumor cells typically retain the ability to produce the thyroid-specific glycoprotein, thyroglobulin (TG). Measuring TG is not routinely recommended in the initial evaluation of a thyroid neoplasm, because elevated TG levels are identified in a variety of benign thyroid processes, thereby lowering the specificity of this diagnostic test. Once a diagnosis of thyroid carcinoma is established, however, a baseline TG may be useful for follow-up. After a clinicopathological diagnosis of carcinoma, in the radical therapeutic approach, that follows conventionally the adult care with total thyroidectomy, lymphadenectomy, and radioiodine treatment of thyroid remnants, a "microstaging" (aimed at the detection of the subclinical neoplasm, for instance, by CT or MRI) is performed. A "macrostaging" (aimed at the detection of the clinically evident neoplastic burden) instead is considered adequate in the conservative approach that will be later described, considering as relevant only the grossly evident diffusion of the tumor [56].

9.3.3 Management

The initial care of adults with DTC is guided by consensus guidelines that can help the practitioner manage these patients [55]. However, it cannot be emphasized enough that established recommendations always need to be individualized for each patient, especially when dealing with children, adolescents, and young adults. It is imperative to note that no prospective clinical trials with randomized questions have been undertaken in children to determine the optimal therapeutic approach.

Assuming that a diagnosis of PTC is made preoperatively, the initial procedure can be chosen between a radical and a conservative approach.

9.3.3.1 Radical Therapeutic Approach

At the thyroid level, the "radical surgical approach" consists of a total thyroidectomy independently of the grossly detectable extension of disease. The subtotal thyroidectomy differs from the total thyroidectomy because a rim of normal thyroid tissue is left, and subsequently siderated by RAI therapy if showing more than 5 % of total activity. At the lymph node level, in the "radical surgical approach," a lymphadenectomy is carried out in patients with evidence of lymph node metastases in the lateral or central compartment region. All motor and sensory nerves, as well as the sternocleidomastoid muscle and internal jugular vein, are preserved unless invaded by tumor [56]. According to some authors, radical thyroidectomy is supported by three points:

1. Radical surgery removes all thyroid tissue potentially at risk of containing multiple neoplastic foci, in the same lobe or contralaterally, again potentially at risk of developing local relapses or metastases [57, 58].
2. The presence of physiological thyroid tissue does not allow the use of thyroglobulin dosage, in an efficacious way, as a marker of tumor relapse [59]. The absence of thyroid tissue allows the use, in an efficacious way, of radioiodine therapy in the treatment of metastatic foci, especially in the lungs.
3. Normal thyroid tissue, in fact, is much more efficient in concentrating radioiodine with respect to tumor, and a small percentage (2 %) of physiological tissue is enough to concentrate the iodinated drug and hide the metastases. Therefore, according to some authors, total thyroidectomy makes it easier to use total body scan in diagnosing metastases, especially those arising in lungs that are rarely appreciated by chest imaging at an early stage [49, 60].

9.3.3.2 Radioactive Iodine Therapy

Patients treated with the aim of obtaining the eradication of all clinical and subclinical neoplastic foci undergo surgery followed by metabolic ablation of thyroid remnants evaluated by routine postsurgical RAI scan. Around 6 weeks from surgery, in hypothyroidism (which means without administering L-thyroxin at substitutive doses), a dose of I123 is administered according to the weight of the child. If there is local residual parenchyma:

- With ≤5–10 ng/ml: TSH-suppressive L-thyroxin is prescribed and follow-up is begun.
- With >10 ng/ml: metabolic ablation of remnants with I131 is prescribed.
- This procedure consists of administering a fixed dose of 30 mCi or a weight-dependent dose of 1 mCi/kg. Subsequent follow-up has to include whole bone scan evaluation again.
- In case of metastases as seen on radio scan, the dose can be a 100 mCi fixed one or a weight-dependent one up to 2 mCi/kg.

Some considerations are needed also in case of metastatic disease and persistent thyroglobulin detectable levels after radioiodine therapy. An interesting report of such a situation describing a cohort of 20 children from Belarus developing PTC with pulmonary metastases revealed that also after stopping RAI therapy because of the high 131I dose already administered, the majority of those children continued to show a "spontaneous" thyroglobulin decrement without progression of lung metastases, thus further documenting the favorable course also of metastatic disease in children [61].

9.3.4 Hormonal Manipulation (Thyroid-Stimulating Hormone Suppression)

Functioning of the thyroid is dependent on TSH, whose synthesis and release depend on thyroid-releasing hormone (TRH), produced in the hypothalamus and secreted into the pituitary [62, 63]. The increase of TRH or TSH results in hypertrophy and hyperplasia of thyroid cells, increased trapping of iodine, and increased synthesis of thyroid hormones. Exogenous thyroid hormone or increased thyroid hormone synthesis inhibits TSH production. The use of thyroid hormone (L-thyroxin; commercially available) for the suppression of TSH secretion is adopted frequently to control differentiated thyroid cancers and their metastases growth. It is also known that the majority of thyroid cold nodules depend on TSH for their growth.

Optimal L-thyroxin dose is the minimum that can suppress TSH (<0.3 mcU/ml) and is approximately 2–2.5 μ/kg/day. These dosages are easy to be assumed by children, without inducing hyperthyroidism. For all the patients, the indication is to give L-thyroxin at a dose between 1.5 and 3 μ/kg/day according to the age and weight of the patients to reach a value for TSH less than 0.3 uU/ml. Suppressive hormonotherapy has the aim to control hidden microfoci of residual tumor and prevent overt metastases.

9.3.5 Follow-Up

Total body scan is repeated after 6–12 months from the metabolic treatment, and the therapeutic dose can be repeated in case of persistence of disease. The goal of this strategy is to obtain a negative scan and a thyroglobulin with an undeterminable value.

9.3.6 Postoperative Complications and Their Treatment

Subsequently to radical surgery, high percentages of permanent postoperative complications are documented. After total thyroidectomy, permanent hypoparathyroidism and recurrent laryngeal nerve paralysis often occur, while after neck dissection, spinal accessory nerve paralysis is the major complication. In addition, iatrogenic effects of RAI therapy are reported. Postoperative complications are high in almost all pediatric series, especially after total thyroidectomy and

also if performed by pediatric surgeons or by neck surgeons devoted to thyroid surgery. Hypoparathyroidism accounts for 0–36 % [5, 64, 65] and recurrent nerve palsy from 0 to 28 % [18, 66]. Age below 16 years is at risk of being accompanied by major complications. In children, recurrent nerves are at major risk of being injured, and parathyroid glands are very small, often hidden into the thyroid parenchyma, difficult to recognize and with a light vascularization. These complications can be very severe in developing age. Any calcium/phosphorus balance alteration can reflect in alteration of the body mass and in possible later consequences on the harmonic body growth. All these issues suggest that the management of children with thyroid carcinoma should be performed in selected centers.

9.3.7 Conservative Therapeutic Approach

Conservative surgery at the thyroid level, the "conservative surgical approach," is defined as the removal of only the thyroid lobe involved by the clinically detectable disease and isthmus (hemithyroidectomy). At the lymph node level, the "conservative surgical approach" consists of a selective neck dissection of only the clinically involved node levels, with preservation of the internal jugular vein, the sternocleidomastoid muscle, the spinal accessory nerve, and the greater auricular nerve. The selective neck dissection approach has a curative intent. To lower the risk of locoregional recurrence and reoperation, at our institution, we routinely perform the selective neck dissection of the metastatic levels plus the dissection of the two free stations immediately before and after the involved ones. Along these lines, the "berry picking" technique is disregarded [4, 5]. The arguments in favor of hemithyroidectomy are:

- PCT in children and adolescents are a particular and different disease with a different genetic and molecular pattern and a different course from adults when unfavorable features are matched homogeneously [67].
- Mortality for PCT in children is close to zero in all series, in spite of a presentation with a greater amount of extrathyroid extension and a bigger number of lymph nodal metastases and lung dissemination than adults.
- The presence of microscopic dissemination into the thyroid and lymph nodes is the rule and does not impair prognosis.
- Vascular invasion is also frequent (a third of cases) and does not influence prognosis, at variance with adult series.
- The chance of dedifferentiation of microscopic disease over the years is only theoretical.

More aggressive procedures, especially if applied in children under 16 years of age, are closely related to a morbidity increase (permanent hypoparathyroidism and recurrent nerve palsy) [68].

9.3.7.1 Hormonal Manipulation (Thyroid-Stimulating Hormone Suppression)

In the conservative approach, this therapeutic tool becomes a mainstay of treatment following surgery. Owing to the high sensitivity of pediatric PCT to hormonal manipulation, the suppression of TSH secretion is adopted to control hidden microfoci of residual tumor and prevent overt metastases. As after radical surgery, optimal L-thyroxin dose is the minimum that can suppress TSH (<0.3 mcU/ml) and is approximately 2–2.5 μ/kg/day. These dosages are easy to be assumed by children, without inducing hyperthyroidism. For all the patients, the indication is to give L-thyroxin at a dose between 1.5 and 3 μ/kg/day according to the age and weight of the patients to reach a value for TSH less than 0.3 uU/ml.

9.3.8 Radioactive Iodine Therapy

There is no indication to use this tool as first-line treatment if applying the conservative treatment approach.

9.3.8.1 Follow-Up

After a conservative treatment, the routine RAI scan after surgery is no longer requested. L-thyroxin at TSH-suppressive doses (2–2.5 μg/kg/day) is given. An optimal follow-up should include clinical examination, yearly chest radiograph, and serum tests for fT3, fT4, and TSH and thyroglobulin every 6 months during the first 2 years and then yearly. Thyroid ultrasound scans should be performed for the first 5 years only, twice in the first year and then yearly. In these instances, the normal value for thyroglobulin is considered as the result obtained a month after surgery that is in the range of 0–5 ng/ml. Cardiac function and bone metabolism markers were checked with an appropriate follow-up [4, 5].

A recent report on an Italian series of 260 DTC in children outlines the possibilities of differentiated treatment approach according to clinical presentation [69]. The authors conducted an Italian multicentric retrospective analysis on pediatric patients suffering from DTC between 2000 and 2014. Surgical treatment was applied according to clinical staging: conservative surgery (lobectomy associated to isthmusectomy) was to be performed in patients with a tumor <2 cm and neoplasm limited to one lobe, no lymph node involvement, and absence of distant metastasis. All the other patients were treated by radical surgery. Total thyroidectomy was performed in 236 (90.8 %) patients and hemithyroidectomy in 24 including 1 presenting with lymph node metastases. Postsurgical complications, all after radical surgery, occurred in 55 patients (21.2 % of the total series and 23 % of the total thyroidectomized ones): 37 (14.2 %) had transient hypocalcemia, 11 (4.2 %) permanent hypocalcaemia, and 7 (2.7 %) laryngeal nerve injury with vocal cord palsy (five, ipsilateral; two, bilateral requiring urgent tracheostomy in one case). To date, after a median follow-up of 5.8 years (range, 114 years), all patients were alive; 30 patients (11.5 %) had relapse, in average after 1.7 years: 29 after radical surgery with 6 thyroid bed relapses despite total thyroidectomy and 1 after conservative surgery (in this case, lymph node metastases were present at diagnosis and relapse was lymph nodal). This series again showed that in a selected patient group, non-radical thyroid surgery was feasible, safe, and prognostically favorable.

9.3.9 Postradiation Thyroid Neoplasms

As above affirmed, the thyroid gland is particularly vulnerable to the carcinogenic action of ionizing radiation, and any treatment involving >50 cGy to the thyroid should be viewed with concern. Exposure to 100–700 cGy in the first 34 years of life has been associated with a 17 % incidence of thyroid cancer 1,030 years later [70]. Studies following the Chernobyl reactor disaster provide evidence of a dose-response relationship and a predominance of papillary thyroid carcinoma in children exposed to radiation [71, 72]. For individuals given radiotherapy for malignant disease in childhood, the risk of thyroid cancer remains significant for several decades afterward [73–75]. Up to 2,025 Gy, the risk is higher; the higher the dose of radiation to the thyroid gland [76], the more the related risk tends to decline, an effect attributed to cell killing rather than transformation [77]. The latency period between radiation exposure and thyroid cancer varied from 5 to 35+ years [78, 79].

Radiation treatment is known to be the main pathogenic cause behind thyroid cancer, although a genetic component capable of reinforcing the carcinogenic potential of radiotherapy should not be underestimated. Some papers [79] attribute chemotherapy a role in the pathogenesis of thyroid cancer too but only if the radiotherapy dose to the thyroid was less than 20 Gy. The strength of the association between thyroid cancer and radiation decreased with increasing age at exposure [73]. Hodgkin's lymphoma is associated with a raised risk of thyroid cancer compared with other cancers in childhood: this risk is persistent even after adjustment for radiation dose and age at irradiation [77]. This is possibly attributable to close surveillance for thyroid abnormalities during long-term follow-up, but it

is known that several solid cancers aggregate in family members of patients with Hodgkin's lymphoma [80, 81].

Papillary cancer is the main histological type of radiation-associated thyroid cancer (RAD cancers); there is a higher frequency of multifocal tumors, and the prevalence of lymph node metastasis is higher [74, 82]. The management strategies for RAD carcinoma in adolescent and young adult remain to be debated. In general, the radical approach utilizing radical surgery (thyroidectomy plus lymph node dissection) followed by radioiodine therapy and TSH suppression aims for control of both macro- and microscopic diseases. However, considering potential long-term sequelae of this treatment and considering the previous treatment administered in patients with malignancy during childhood and adolescence, a more conservative approach might also be considered in selected patients as for primary tumors but even with more concern about late effects. In the perspective of the excellent overall survival with both approaches [83, 84] in each patient the advantes and disadvanteges of each treatment option must be weighted. A careful neck assessment before surgery is mandatory especially if the patient was given radiotherapy at young age; again a cardiorespiratory evaluation for patients previously treated with cardiotoxic drugs and radiotherapy involving the lungs and heart is deemed moreover if the physician plans radiometabolic therapy given the risks of pulmonary fibrosis.

While it is pointless to risk severe morbidity when treating an indolent disease, a conservative surgical approach demands a good compliance with a long-term follow-up, which is always worthwhile for patients with a history of radiotherapy.

Despite patients who received radiation have at the time of the diagnosis more extensive thyroid carcinoma, the prognosis is similar to patients without a history of irradiation. The aggressive behavior of RAD thyroid cancer is associated with an elevate recurrence rate, but no influence on the mortality rate has been described [85, 86].

9.3.10 RAI Late Effects

Early and usually transient side effects of 131I therapy may include nausea, vomiting, sialoadenitis, xerostomia, loss of taste, thyroiditis (if a sizable thyroid remnant remains after surgery), and, rarely, bone marrow suppression (leukopenia and thrombocytopenia). The long-term consequences of 131I therapy in children remain an area of concern, particularly in individuals who receive high cumulative doses in early childhood [87]. Much remains to be learned about possible late effects, which can include infertility (particularly in men), permanent damage to the salivary glands resulting in chronic xerostomia or salivary duct stones, excessive dental caries, reduced taste, pulmonary fibrosis (in those with diffuse pulmonary metastases), and the possibility of the development of other cancers (stomach, bladder, colon, salivary gland, breast, and leukemia) after very high cumulative doses of 131I [56]. A recent retrospective review on 1,078 children and adolescents with PTC treated in the Belarusian population during the years 1990 reported an overall survival of 96.9 % with a median follow-up longer than 16 years. It is to be outlined that only one patient died from advanced disease, while the other 20 died for other causes and, importantly, one for pulmonary fibrosis after radioiodine courses, one for liver cirrhosis, and one for myxedema due to inadequate iodine intake [88]. Therefore, caution should be exercised when giving multiple repeat doses of 131I to children and young adults, particularly in those patients whose disease is more indolent and does not require such aggressive therapy.

9.3.11 Therapy at Relapse

Similarly, at relapse, the options in treating the patient again can follow a radical or a conservative approach [56].

9.3.11.1 Radical Approach

In cases of local, nodal, or distant relapse following the radical approach, the same guidelines as at diagnosis are followed.

9.3.11.2 Conservative Approach

Surgery

In case of local or lymph nodal relapse, the conservative therapeutic approach follows the rules of the beginning, which is to say that all the macroscopic disease only should be excised. In addition to the resection of local relapse in the soft tissue of the thyroid bed, completion thyroidectomy in case of contralateral relapse, and further nodal dissection, in case of radiologically evident distant metastases, it will be necessary to complete the thyroidectomy, even in the absence of thyroid neoplastic involvement, to allow the use of RAI therapy for the treatment of distant metastases.

Hormonal manipulation (thyroid-stimulating hormone suppression)

The administration of L-thyroxin should be continued according to the guidelines already expressed.

Radioactive Iodine Therapy

RAI therapy after complete thyroidectomy should be used only in cases of radiologically evident metastases, which are found prevalently in lungs followed by bone. In our experience, this condition is to be considered absolutely exceptional if metastases are not determined with the use of total body RAI scan in the diagnostic phase.

9.4 Medullary Thyroid Carcinoma

9.4.1 Epidemiology

In children and young adults, MTC is an uncommon disease with an incidence of less than one case/million/year [2]. It accounts for approximately 7–10% of all thyroid malignancies. Shortly after the discovery that MTC represents a unique thyroid cancer, it was recognized that the tumor occurred either sporadically or in a hereditary form as a component of the type 2 multiple endocrine neoplasia (MEN) syndromes, MEN2A, MEN2B, and the related syndrome, familial MTC (FMTC). Five-year survival rates for MTC are between 90 and 95% in the pediatric and young adult population [2]. In patients not diagnosed early, incurable yet indolent disease is often the norm.

9.4.2 Etiology/Pathology

Even though MTC is a unique endocrine neoplasm with several distinguishing features, it was not recognized as a distinct clinical entity until 1959 [89]. During embryogenesis, progenitor C cells stream from the neural crest and populate several endocrine organs, including the pituitary, the thyroid, the pancreatic islet cells, the adrenal medulla, and the enterochromaffin system of the gut. In mammals, the neural crest-derived C cells become entrapped in the upper portion of the lateral thyroid complex as it develops during embryogenesis. The greatest concentration of these parafollicular C cells is at the intersection between the upper one third and lower two thirds of the thyroid cephalad-caudal central axis. It is these cells that give rise to MTC. Therefore, although MTC is recognized as a thyroid tumor, it is more properly characterized as a malignancy of neural crest origin.

Sporadic MTC rarely occurs in children and young adults. Therefore, it is more appropriately characterized as a genetic disease when it affects this age group. Almost all children with MTC are afflicted with one of the three hereditary cancer syndromes: multiple endocrine neoplasia type 2a (MEN2A) or type 2b (MEN2B) and familial MTC (FMTC). In addition to MTC, 50% of patients with MEN2A and MEN2B develop pheochromocytomas, and up to 20% of MEN2A patients develop hyperparathyroidism [90]. Patients with MEN2A may also develop a pruritic cutaneous lesion on the upper back, termed "cutaneous lichen amyloidosis" [91], and some kindreds can have associated Hirschsprung's disease [92]. All patients with MEN2B develop a generalized ganglioneuromatosis, manifested most obviously by the presence of oral mucosal

neuromas, and a characteristic facial appearance and marfanoid body habitus. Patients with FMTC only develop MTC.

MTC occurs in virtually all patients with these familial endocrinopathies, and it is the most common cause of death in affected individuals. The development of MTC in this setting is particularly relevant in children because, with current methods of diagnosis and treatment, MTC is one of the few malignancies that can be prevented or cured before it becomes clinically relevant.

Over 10 years ago, it was found that characteristic missense mutations in the RET proto-oncogene caused MEN2A, MEN2B, and FMTC [93–95]. RET encodes for a tyrosine kinase receptor that is important for the differentiation of neural crest-derived tissues. These point mutations cause activation of intracellular signaling pathways in the absence of ligand. In patients with MEN2A, mutations are located mostly in the extracellular cysteine-rich domain of the RET proto-oncogene, usually in exon 10 (codons 609, 611, 618, or 620) or exon 11 (codon 634). In almost all cases, there is a family history of MEN2A-associated neoplasms. In patients with MEN2B, which occurs as a de novo mutation in over half the cases, the mutation is almost exclusively in exon 16 (a change from methionine to threonine at codon 918), located in the intracellular tyrosine kinase domain of the gene. In patients with FMTC, the RET mutations are found in codons similar to MEN2A, or less often, in exon 13 (codons 768, 790, and 791), exon 14 (codon 804), or exon 15 (codon 891). There is a correlation between genotype and phenotype in that patients with MTC, pheochromocytomas, and hyperparathyroidism almost always have mutations in codon 634, whereas patients with MTC and pheochromocytomas, but not hyperparathyroidism, most often have mutations in codon 618, 620, or 634. RET mutation is involved in almost 80 % of patients carrying sporadic MTC. Sporadic cases are virtually absent in childhood and adolescence. Investigators recently discovered that 1,880 % of sporadic MTCs lacking somatic RET mutations have somatic mutations of HRAS, KRAS, or rarely NRAS [96–98].

On gross examination, MTC is whitish tan and located in the upper pole(s) of the thyroid lobe. Larger tumors often become calcified. In patients with sporadic tumors, only one thyroid lobe is involved. In patients with heritable disease, the MTC is virtually always bilateral and multicentric and located at the junction of the upper one third and lower two thirds of the thyroid lobes. Therefore, the finding of a multifocal MTC in any patient should raise concern for an underlying RET mutation. On microscopic examination, the tumor cells have a spindle-shaped appearance, and with special staining, one sees material with histological properties of amyloid. Also, in patients with the familial forms of MTC, clusters of C cells (C-cell hyperplasia) are also routinely identified pathologically. This C-cell hyperplasia is believed to be one of the initial stages in the development and progression of MTC [99].

The biological aggressiveness of MTC depends on the hereditary setting in which it develops. In patients with MEN2B, the MTC progresses rapidly and thyroidectomy, regardless of the age at which it is performed, is rarely curative. In patients with FMTC, however, the MTC progresses slowly, and it is uncommon for patients to die from this malignancy. In patients with MEN2A, the MTC is somewhat capricious; it usually follows an indolent course, but in some patients, it may progress rapidly. The reasons for this variable biological behavior of MTC in these various clinical entities are unknown. It is also difficult to assess the behavior of MTC in sporadic compared to familial cases.

9.4.3 Diagnosis and Clinical Presentation

The MTC cells have great biosynthetic activity and secrete calcitonin (CTN) and carcinoembryonic antigen (CEA), both of which are excellent tumor markers for the disease. CTN, in particular, provides a high degree of diagnostic sensitivity, specifically in the long-term follow-up of MTC. Occasionally, MTC can lose its ability to produce CTN, which is usually indicative of a more aggressive tumor and hence, a poorer prog-

nosis. Intravenous calcium and pentagastrin are potent CTN secretagogues that stimulate production of the hormone within minutes of injection. Measurement of basal and stimulated plasma CTN levels is especially useful in the evaluation of patients following thyroidectomy. Elevated levels postoperatively indicate the presence of metastatic MTC, even though it may not be evident clinically. Furthermore, a preoperative diagnosis can also be made by measuring basal or stimulated levels of plasma CTN. Considering the rarity of MTC and the possibility of false-positive results, preoperative measurement of CTN in children presenting with nodular thyroid disease is not performed routinely. However, in kindred members of MEN2A, MEN2B, or FMTC families who present with a thyroid nodule, the diagnosis of MTC must be excluded, and measuring plasma CTN levels in this setting may be useful.

Similar to DTC, MTC usually presents as a firm, painless neck mass without associated abnormalities. However, in those who have very high plasma CTN levels, diarrhea and/or flushing may be present. The tumor has spread usually beyond the thyroid gland by the time it becomes clinically apparent. Therefore, most patients presenting with a palpable MTC already have metastases to regional cervical nodes at diagnosis [92]. The overall approach to the evaluation of a child suspected to have MTC is similar to the assessment of PTC and FTC, including the use of US and FNA. One major difference, however, rests in our ability to diagnosis MTC (in the context of a positive family history and a known RET mutation) in advance of clinical disease (i.e., a palpable thyroid nodule). As genetic testing becomes more widely utilized in families with MEN2A and FMTC, more children and young adults are presenting with C-cell hyperplasia or microscopic MTC that is detected early only because genetic testing was undertaken.

9.4.4 Management

The identification of RET proto-oncogene mutations as the cause for hereditary MTC has provided the opportunity for direct DNA analysis in clinically normal individuals at risk for having inherited a mutated allele, thus permitting identification at a young age of those destined to develop MTC. This technology has revolutionized the surgical management in this group of patients, since these children can now have prophylactic thyroidectomy before they develop a thyroid malignancy [100].

Any child or young adult diagnosed with MTC should have a total thyroidectomy with resection of lymph nodes in the central zone of the neck (an anatomical region bounded above and below by the hyoid bone and the sternal notch and laterally by the carotid arteries). If nodal metastases are evident grossly, the lymph node dissection should be extended to the lateral neck(s). Children from kindred with MEN2A, MEN2B, or FMTC found by direct DNA screening to have inherited a mutated REt allele should also have a total thyroidectomy. Resection of lymph nodes in the central zone of the neck is required in MEN2B patients, but can be performed selectively in MEN2A and FMTC patients, specifically those undergoing prophylactic thyroidectomy, as long as the preoperative evaluation is favorable. There are however two schools of thought regarding the use of preoperative studies in the management of lymph node compartments at thyroidectomy. Some endocrinologists and surgeons consider preoperative US of primary importance in detecting lymph node metastases and do not advocate compartment dissection if US of the neck is negative. Others argue that elective dissection of US normal ipsilateral central and ipsilateral lateral neck compartments is indicated in patients with elevated basal serum Ctn levels between 20 and 50 pg/mL. Also, elective dissection of an US normal contralateral lateral neck compartment is indicated when the basal serum Ctn level is greater than 200 pg/mL [101].

The timing of prophylactic thyroidectomy remains an area of debate, and recommendations are based upon the earliest ages at which children with a particular mutation present with clinically relevant disease. Currently, RET proto-oncogene mutations are stratified into one of three/four levels [101, 102] that will probably change according to new ATA guidelines. The current level D category should be changed to a new category,

"highest risk" (HST) that includes patients with MEN2B and the RET codon M918T mutation. The current level C category should be changed to a new category, "high risk" (H), that includes patients with MEN2A and RET codon C634 mutations [103]. The current level A and B categories should be combined into a new category "moderate risk" (MOD) that includes patients with hereditary MTC and RET codon mutations other than M918T and C634. Children in the ATAHST category with a RET codon M918T mutation should have a thyroidectomy in the first year of life, perhaps even in the first months of life. In the absence of suspicious lymph nodes, the performance of a central neck dissection should be based on whether the parathyroid glands can be identified and left in situ or autotransplanted. The surgeon and pediatrician caring for the patient, in consultation with the child's parents, should decide the timing of thyroidectomy [104]. It is the usual practice in MEN2A kindred (level 2) to perform total thyroidectomy by 5 years of age, whereas in MEN2B patients (level 3), surgery is recommended within the first 6–12 months of life. Children with level 1 mutations (codons 609, 768, 790, 791, 804, and 891) have the lowest risk for the development of aggressive MTC, and the timing of thyroidectomy in these cases remains controversial [90].

In patients with MTC and/or MEN2, it is critically important that the presence of a pheochromocytoma be excluded prior to thyroidectomy, since severe complications and even death due to excessive catecholamine release may occur during anesthesia induction or during the operative procedure. The most useful way to screen for this is via plasma metanephrines, particularly in young children, in whom timed urine collections may be difficult. If identified, the pheochromocytoma(s) should be resected, usually laparoscopically, prior to thyroidectomy. As with any case of pheochromocytoma, surgery should proceed only after appropriate alpha (and beta) blockade.

In patients with sporadic or heritable MTC and no evidence of hyperparathyroidism, every effort should be made to preserve parathyroid gland function at the time of thyroidectomy. If there is any question about parathyroid gland viability during the procedure, parathyroid tissue is typically grafted into a sternocleidomastoid muscle. If this procedure is performed carefully, it virtually assures that the patient will have normal parathyroid function in the postoperative period. In patients with MEN2A and hyperparathyroidism, a total parathyroidectomy with autotransplantation of parathyroid gland tissue to the nondominant forearm is the procedure of choice. Some surgeons prefer to perform a radical subtotal 3½ gland parathyroidectomy in these cases. However, in combination with a total thyroidectomy, this procedure is associated with a greater risk of permanent postoperative hypoparathyroidism. If there is no evidence of hyperparathyroidism and the patient has a RET codon 634 mutation, which is commonly associated with hyperparathyroidism, parathyroid tissue is grafted to the nondominant forearm. It is critically important that parathyroid function be preserved in all of these patients, especially in young children, since permanent hypoparathyroidism can be a difficult problem to manage.

Children who have thyroidectomy performed prior to the time that the disease is evident clinically have an excellent chance of being cured. Patients are cured infrequently if the disease progresses beyond the thyroid gland. In these cases, patients may have microscopic disease (detectable only via tumor markers) and be asymptomatic for years. However, the tumors tend to grow progressively and can metastasize to mediastinal lymph nodes, lung, liver, and/or bone. Metastases are often vascular, and hepatic metastases may be confused with hemangiomas on imaging studies. The management of patients with metastatic disease presents a major challenge because the tumors are not sensitive to standard chemotherapeutic regimens, which usually incorporate the agent dacarbazine (DTIC), nor are they very sensitive to conventional doses of external beam radiotherapy. Unlike DTC, the use of RAI in MTC is not beneficial or indicated.

The long-term follow-up of children and young adults diagnosed with MTC involves monitoring CTN and CEA levels, obtaining US and other imaging studies as indicated by tumor

markers, and screening routinely for the other endocrine manifestations of MEN2A and MEN2B, noting that these typically have their onset in adulthood. The lifelong management of heritable MTC also includes appropriate genetic counseling, and it is ideal to involve a genetic counselor at the outset to assist these children and their families in understanding this dominantly inherited disease.

9.4.5 Other Treatment Modalities for Persistent or Recurrent Disease

Traditional chemotherapeutics in patients with progressive MTC have limited efficacy. Full response to cytotoxic therapy is rare and partial. The only hope for systemic therapy in patients with metastatic MTC lies in the exploitation of knowledge of the mechanisms and pathways that regulate its growth and spread of MTC. The targeted development of receptor tyrosine kinase inhibitors (TKIs) has allowed to see some effects to halt the growth of progressive disease. Vandetanib is a once-daily oral inhibitor with action against RET, vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor receptor. It has been shown to give significant advantages in terms of progression-free survival, objective response rate, rate ($P=0.001$), and biochemical response [105]. Selecting patients based on target gene expression, vandetanib was shown to be well tolerated and highly active for children and adolescents with MEN2B and locally advanced or metastatic MTC [106].

Cabozantinib is an oral inhibitor of multiple receptor tyrosine kinases including RET and VEGFR2 that has shown more responses than placebo in a phase 3 trial [107].

Other TKIs that target RET and various VEGFR subtypes in phase II trials include sorafenib, sunitinib, pazopanib, and motesanib and also show clinical benefit for patients with progressive MTC. The tyrosine kinase agents have many side effects. The most commonly reported adverse drug reactions (25 % or greater) were diarrhea, stomatitis, palmarplantar erythrodysesthesia syndrome, decreased weight, decreased appetite, nausea, fatigue, hypertension, abdominal pain, and constipation. Other investigational therapies include the use of tumor vaccines, radioimmunotherapy, and radiolabeled octreotide.

It is likely that a combination of agents that attack the RET tyrosine kinase and multiple downstream targets will improve the effectiveness.

New agents are needed for definitive treatment of metastatic disease. Further studies are needed to best understand the genotype/phenotype relationship in patients with genetic mutations leading to MTC and to further elucidate the role of key pathways to enable the design of novel therapies.

Many of these questions are best addressed in the setting of a clinical trial or in the hands of a physician with extensive experience in this area of specialty. In the absence of curative nonsurgical methods, surgical management of these patients to completely extirpate or debulk the disease remains paramount in the management of MTC [108].

9.4.6 Late Effects

If the initial surgical procedure is successful, patients are cured of MTC and have normal serum calcium levels and phonation. If the recurrent laryngeal nerves or the external branches of the superior laryngeal nerve are damaged, patients may be hoarse following surgery and require reconstruction procedures of the vocal cords. Patients who develop permanent hypoparathyroidism will require lifelong vitamin D and oral calcium preparations to maintain eucalcemia.

Conclusion

Nowadays, the existence of two therapeutic approaches, that is radical versus conservative therapy, is still an area of great controversy [68, 109–111]. Nonetheless, we think that both options should be considered whenever treating a child or adolescent with a non-med-

ullary thyroid carcinoma. Not least, permanent posttreatment complications of both surgery and RAI therapy should be taken into account, with all the damage in the quality of life and the economic costs that are implied. Our hope is that in the future, the conservative approach will be considered in the suitable cases, with a decrease of overtreatment of a type of cancer that still shows an about 100 % OS independently of stage, occurrence of relapse, and type of approach applied.

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Malignant Melanoma in the Adolescent and Young Adult (AYA) Population

10

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Abstract

Incidence of melanoma in the adolescent and young adult (AYA) population is rapidly increasing. AYA melanoma is genetically similar to that of adults with a similarly adverse prognosis in patients with advanced disease. Management of AYA patients requires attention to several unique features in this patient population including historically low rates of clinical trial participation and lack of suitable psychosocial support services - factors which affect may access to treatment and possibly impact upon survival. In this chapter, we review recent data regarding changing incidence trends and management of melanoma in the AYA population.

10.1 Introduction

The incidence of malignant melanoma in adults is rising especially in older men [1]. Largely driven by increased recreational exposure to ultraviolet (UV) radiation, the incidence of invasive cutaneous melanoma in the adolescent and young adult (AYA) population (aged 15–39 years) is also rising, particularly in females. From 1973 to 2004, the age-adjusted annual incidence of melanoma in men aged 15–39 years increased from 4.7 to 7.7 cases per 100,000 men compared to 5.5–13.9 cases per 100,000 women in the same time period [2]. The past decade has witnessed a dramatic transformation in our understanding of the genetic drivers of melanoma as well as the mechanisms of immune regulation in this disease. These discoveries have translated into new therapies with unprecedented clinical results. However, development of these therapies for

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pediatric and AYA melanoma has lagged behind, and their toxicity and activity profile in these populations has not yet been defined. In this chapter, we review the epidemiology, etiology, risk factors, clinical presentation, and staging of AYA melanoma. We will briefly review recent advances in surgical and nonsurgical therapy and conclude by discussing potential advances in the near future.

10.2 Epidemiology

10.2.1 Trends in Incidence by Gender

In 2014, melanoma accounted for 4.6% of incident cancer diagnoses and 1.7% of cancer deaths in adults – fifth in incidence behind prostate, breast, lung, and colorectal malignancies and ahead of lymphomas and bladder and renal malignancies. However, in the pediatric and AYA population, melanoma is an uncommon malignancy – accounting for 6% of malignancies in adolescents aged 15–19 [1].

Both *in situ* and *invasive* melanomas have similar age-dependent incidences – continuously increasing with age until reaching a peak between the ages of 80 and 85 and then declining (Fig. 10.1, *top left panel*). At all ages, the incidence of *invasive* melanoma is greater than the incidence of *in situ* disease although the reporting of the latter may make this an underestimate. The rate of increase as a function of age is greatest during adolescence and exponential from age 25–30 to age 60–70. When examined by sex, the incidence of *invasive* melanoma is similar in male and female patients up to age 14. Between ages 15 and 49, female patients have a greater incidence, but after age 50, this trend dramatically reverses with a consistently greater incidence of *invasive* melanoma among men that increases with age (Fig. 10.1, *top right panel*).

In the AYA population, the incidence of both *invasive* and *in situ* melanoma of the face, scalp, and neck was similar in females and males (Fig. 10.1, *bottom left panel*). However, the incidence of both *invasive* and *in situ* melanoma of the sun-exposed areas including the trunk, thigh, shoulders, and extremities was far more frequent in females than males (Fig. 10.1, *bottom right panel*).

10.2.2 Trends in Incidence of In Situ and Invasive Disease

In older adults, *in situ* melanoma occurred most frequently in the head and arms (Fig. 10.2, *left panel*). In AYA subjects, however, the predominant sites of *in situ* melanoma were the trunk, hip, and legs, and the least involved sites were the face, scalp, neck, and eye (Fig. 10.2, *left panel*). The predilection for intermittently sun-exposed areas in AYAs versus chronically sun-exposed areas in older persons implies that chronic solar exposure is *not* the primary mechanism of in situ melanoma in AYAs. These data are also in line with the rarity of the histologic subtype of lentigo malignant melanoma in AYA.

In AYA and persons up to the age of 80, the most frequent site of *invasive* melanoma was the trunk, and the least involved site was the scalp and neck. In AYA subjects, the hip and legs were the second most common sites of invasive melanoma. In older persons, the shoulder and arms were the second most common body sites (Fig. 10.2, *right panel*).

10.2.3 Trends in Incidence by Race/Ethnicity

At any age (except in children <10 years), non-Hispanic white individuals have a higher incidence of *in situ* (Fig. 10.3, *top left panel*) and *invasive* (Fig. 10.3, *top right panel*) melanoma than any other race or ethnicity, while blacks and Asian/Pacific Islanders had the lowest incidence. The vast majority (90%) of melanoma diagnosed in the United States occurs in non-Hispanic white individuals.

In non-Hispanic whites, the trunk was the body site of greatest incidence in AYAs (Fig. 10.3, *bottom left panel*) and older adults up to the age of 80. In Hispanics, the trunk, hip, and legs were the body sites of greatest incidence in AYAs (inset) and middle-aged adults (Fig. 10.3, *bottom right panel*).

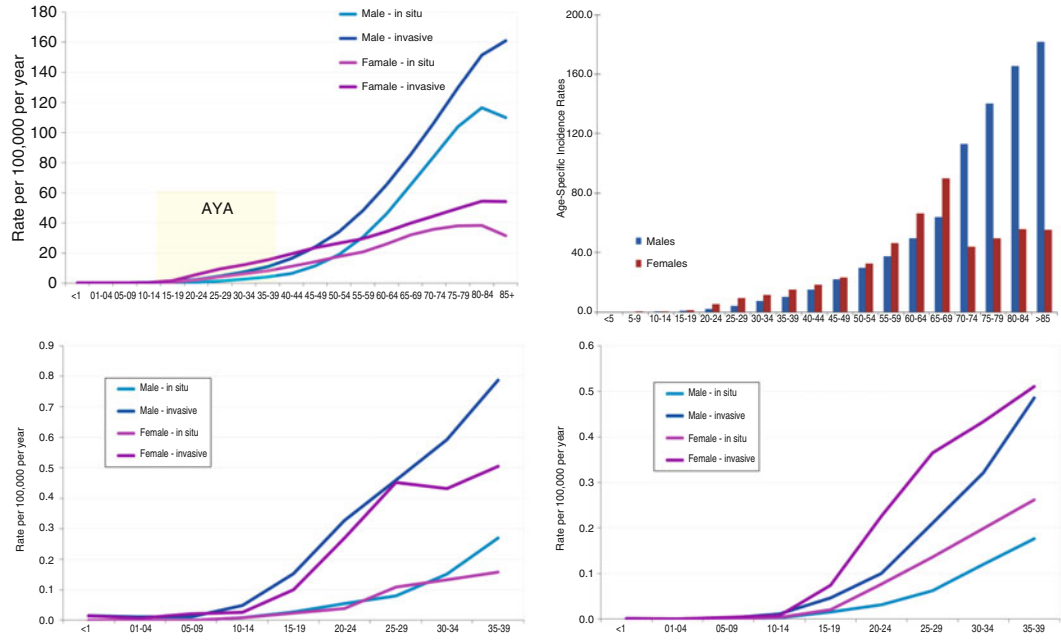

Fig. 10.1 Age-dependent incidence of melanoma. Age-dependent incidence of in-situ and invasive melanoma (*top left*). Age-dependent incidence of melanoma by sex (*top right*). Age-dependent incidence of AYA melanoma in face/scalp/neck (*bottom left*). Age-dependent incidence of AYA melanoma in sun-exposed trunk/thighs/shoulders/extremities (*bottom right*)

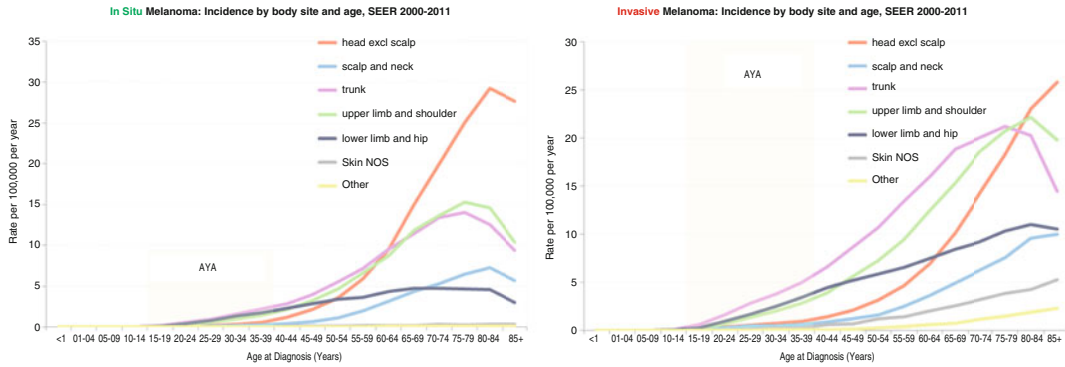

Fig. 10.2 Age-Dependent Incidence of Melanoma By Body Site and Age, SEER 2000-2011. In-situ Melanoma (*left panel*), Invasive Melanoma (*right panel*)

10.2.4 Trends in Mortality

Five-year melanoma-specific survival with in situ disease exceeded 99 % at all ages, while survival with invasive disease (stages I–IV) was lower but exceeded 85 % at all ages (Fig. 10.4, *top left panel*). Females had a survival advantage over males across all ages (Fig. 10.4, *top left panel*). Younger patients with invasive disease had greater 5-year melanoma-specific survival than older patients (Fig. 10.4, *top right panel*). Unsurprisingly, survival was worse in patients with no identifiable primary lesion (Fig. 10.4, *bottom left panel*). Five-year melanoma-specific survival of *invasive* melanoma was worse at all ages in blacks and Asians/Pacific Islander than in other major races/ethnicities, a difference that persisted irrespective of sex (Fig. 10.4, *bottom right panel*).

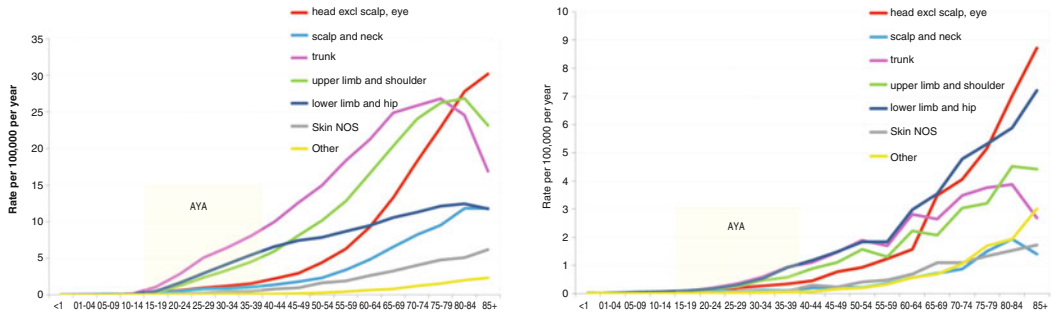

Fig. 10.3 Age-Dependent Incidence of Melanoma By Body Site in Non-Hispanic Whites (*left panel*). Age-Dependent Incidence of Melanoma By Body Site in Hispanic Whites (*right panel*)

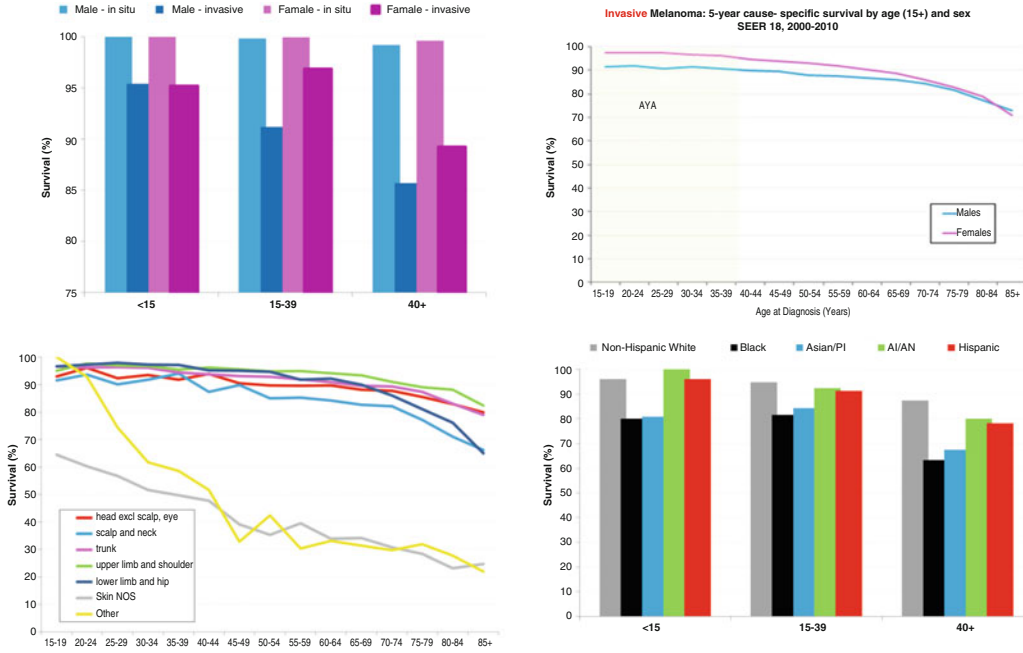

Fig. 10.4 5-Year Melanoma-Specific Survival (SEER 18, 2000-2010). 5-Year Melanoma-Specific Survival in AYA Groups (<15, 15-39, >40) (*top left*). Invasive Melanoma 5-Year Melanoma-Specific Survival by Age and Sex (*top right*). 5-Year Melanoma-Specific Survival By Primary Site (*bottom left*). 5-Year Melanoma-Specific Survival in AYA Groups (<15, 15-39, >40) by Race (*bottom right*)

10.3 Etiology and Risk Factors

10.3.1 Genetic Characterization

Early efforts to elucidate the genetic basis of cutaneous melanoma identified driver mutations involving several members of the MAPK pathway including *BRAF* (35–50 %) and *NRAS* (10–25 %) [3]. Next-generation high-throughput sequencing by The Cancer Genome Atlas (TCGA) has provided a comprehensive mutational landscape of cutaneous melanoma in adult melanoma and suggests that ~70 % of melanoma is associated with either *BRAF* or *NRAS* mutations (*BRAF* mutated 40–50 %; *NRAS* mutated 20–28 %) which directly result in activation of the MAPK pathway [4]. The vast majority of *BRAF* and *NRAS* mutations occur at sites of genomic instability (hot spots) and are *not associated with the typical* UV signature C→T transitions. Recent TCGA work suggests that *NF1* mutations occur in 14 % of melanomas and these are mutually exclusive with *BRAF*/*NRAS*

mutations [4, 5]. In contrast to *BRAF* and *NRAS*, *NF1* and several other genes (*ARID2*, *PPP6C*, *RAC1*, *SNX31*, *TACC1*, *STK19*, and *IDH1*) and the known melanoma tumor suppressors (*PTEN*, *p14ARF*, *p16INK4a*) are *commonly associated with* C→T or G→A transitions – providing a causative link between UV exposure and melanoma oncogenesis. These data support a reclassification of cutaneous melanoma on the basis of mutational events into *BRAF*-mutated, *RAS*-mutated, *NF1*-mutated, and *BRAF*/*RAS*/*NF1* wild-type ("triple wild-type") cohorts – the latter comprising a group of tumors with a variety of mutations in tumor suppressors (*PTEN*, *p14ARF*, *p16INK4a*) and candidate oncogenes (*ARID2*, *CKIT*, *PPP6C*, *RAC1*, *SNX31*, *TACC1*, *STK19*, and *IDH*).

TCGA data were derived exclusively from adult specimens – and very little was known about the mutational spectrum of pediatric melanomas until recently. A group at St. Jude Children's Research Hospital performed a detailed multiplatform characterization of three pediatric melanocytic lesions: "conventional" melanoma, spitzoid melanoma, and congenital nevus-derived melanoma [6]. In "conventional" melanoma, authors noted a high somatic mutation burden (14.36 mutations per megabase) and a high percentage (>80 %) of C→T single-base mutations similar to the observations in adult melanoma. Most "conventional" melanoma patients had mutations in *BRAF* and *TERT* promoter, while approximately half had non-mutually exclusive *PTEN* copy number changes or loss of function mutations. Conversely, congenital nevus-derived melanomas were associated with *NRAS* mutations and lacked *TERT* promoter mutations. About 40 % of spitzoid melanomas had kinase fusions involving the *NTRK1*, *ROS*, *ALK*, *RET*, and *BRAF genes*.

These data suggest that pediatric "conventional" melanoma and adult cutaneous melanoma are similar diseases. Similar to adult melanoma, pediatric "conventional" melanoma is associated with a high somatic mutation load and high frequencies of activating *BRAF* mutations and *PTEN* alterations with resulting activation of MAPK and PI3K/AKT cellular signaling pathways. Spitzoid melanoma and congenital nevus-derived melanoma emerge as distinct clinicopathologic entities with characteristic molecular phenotypes. The high somatic mutation burden and presence of mutated *NRAS* in congenital nevus-derived melanoma contrast distinctly with the absence of *BRAF*/*NRAS* mutations and low somatic mutation burden of spitzoid melanoma. Notably, both the analyses of Bastian and the St Jude's group have identified novel kinase fusions in spitzoid melanoma that separates this group of lesions from other melanomas [7]. The kinase fusions observed are constitutively expressed and result in active oncogenes that drive malignant transformation. Further study is required to characterize the natural history of these unusual melanocytic lesions and confirm the above findings.

10.3.2 Inherited Susceptibility to Melanoma

10.3.2.1 High-Risk Loci: FAMMM, CDKN2A/CDK4 Mutations, and Xeroderma Pigmentosum

Early studies of genetic predisposition in melanoma did not distinguish clustered sporadic cases from inherited single-locus predisposition. Linkage analysis of Utah and Texas familial melanoma kindreds identified a melanoma susceptibility locus on chromosome 9p21 [8]. Concurrently, the phenotype of the familial syndrome was clarified [proband with variable number (10–100) of nevi, dysplastic features including junctional hyperplasia, and increased risk of melanoma and pancreatic malignancies], and the syndrome was termed familial atypical mole-malignant melanoma syndrome (FAMMM) or dysplastic nevus syndrome (DNS). Multiple affected first- or second-degree relatives suggested an autosomal dominant inheritance with high penetrance but variable expression.

Subsequently, investigators mapped the CDKN2A gene to this locus and established that CDKN2A encodes two proteins, p16 and p14ARF, that are transcribed in alternate reading frames through alternative first exons [9]. The p16 protein product binds to and inhibits CDK4 that, together with cyclin D, regulates G1/S phase transition during mitosis. The p14ARF protein inhibits mdm2 and promotes p53/p21

activation that inhibits CDK1/CDK2 complexes. Both p16 and p14ARF thus function as tumor suppressors, and their loss results in unrestricted cell cycle progression. CDKN2A mutations are associated with 20–57 % of hereditary melanoma and 1.3 % of sporadic melanoma, while CDK4 mutations are detected in 2–3 % of familial cohorts and only very rarely in sporadic melanoma [10–12]. Studies have reported diverse estimates of the lifetime risk of melanoma with CDKN2A mutations – ranging from 58 % in Europe to 91 % in Australia. A Genes, Environment, and Melanoma Study (GEMS) report evaluated 3,626 CDKN2A mutation carriers from Australia, Canada, the United States, and Italy and reported a lifetime risk of 14 % by age 50 years, 24 % by age 70 years, and 28 % by age 80 years [13].

Xeroderma pigmentosum (XP) is an autosomal recessive disease in which defective nucleotide excision repair (NER) results in an accumulation of UV-mediated DNA damage in epidermal cells. XP patients have an increased risk of all cutaneous malignancies including melanoma, basal cell carcinoma, and squamous cell carcinoma. Given the rarity (1 in 250,000) and severity (<50 % of patients survive past age 20), XP does not significantly impact melanoma incidence at the population level. Since CDKN2A/CDK4 mutations do not account for all hereditary cases of melanoma coupled with the rarity of XP, it is likely that other as yet unidentified genes are implicated in inherited predisposition to melanoma.

10.3.2.2 Moderate- to Low-Risk Loci

A variety of other genes have been associated with an increased risk of melanoma: MC1R, BRCA2, Rb, MITF (E318K) variant, and 1p22 locus. Melanocortin-1 receptor (MC1R), a G-protein-coupled receptor located on the surface of melanocytes, regulates relative levels of eumelanin and pheomelanin production by melanocytes. As eumelanin protects skin from UV radiation more than pheomelanin does, MC1R allelic variants have divergent risks of melanoma with odds ratios ranging from 1.42 (p.R163Q) to 2.45 (p.I155T) [14]. Patients with mutated BRCA2 and the MITF E318K variant have a twofold increased risk of developing melanoma [15–17]. The increased risk of melanoma in patients with Rb mutations is uncertain, and the melanoma susceptibility locus on chromosome 1p22 has yet to be identified [18, 19].

10.3.3 Risk Factors for Developing Melanoma

As discussed above, the risk of developing melanoma is an aggregate of genetic and environmental factors with UV exposure being the single greatest environmental risk factor. UV exposure is inversely proportional to latitude – being greatest at the equatorial belt (latitude 0°). The link between geography and melanoma incidence was first elucidated by Herbert Lancaster, who evaluated melanoma mortality in populations of European extraction residing at varying latitudes from the equator [20]. Lancaster reported greater mortality among individuals residing in tropical and subtropical Australian states compared to those living in temperate climes; a greater mortality was noted even within countries among subjects living at higher altitudes compared to those living at lower altitudes. These findings have since been replicated in other populations and provide a compelling implication of UV exposure (especially childhood sun UV exposure) in melanoma tumorigenesis [21–23]. Recreational UV exposure (outdoor and indoor tanning) further increases melanoma risk – especially after ten tanning sessions [24]. Recognizing these risks, the Society of Behavioral Medicine has issued a position statement banning indoor tanning for minors that has resulted in legislation to this effect in 11 states [25]. Beyond UV exposure, other risk factors include a personal history of prior melanoma, typical/atypical nevi, and systemic immunosuppression.

10.3.4 Risk Assessment and Screening Strategies

Some of these risk factors have variably been aggregated into several risk prediction models including Australia's Victorian Melanoma Service (Emily's Melanoma Risk Calculator) and National Cancer Institute (Melanoma Risk Assessment Tool) [26, 27]. These tools allow practitioners to individualize risk and consider specific interventions such as complete skin surveillance and/or participation in prevention trials in patients deemed high risk.

Survival of melanoma is strongly associated with thickness and level of invasion through the skin, and early detection appears to identify groups of patients for whom cure may be achieved with surgical excision alone. Despite compelling data regarding risk stratification and high lifetime risk of invasive disease in high-risk individuals, the US Preventive Services Task Force (USPSTF) and Cancer Council Australia have not adopted recommendations for population screening strategies to date, citing insufficient evidence that screening reduces mortality. Recent data, however, suggests otherwise. Investigators conducted an observational study at the Lawrence Livermore National Laboratory that incorporated awareness and targeted screening over a 26-year period (1969–1996). Albeit neither randomized nor controlled, targeted screening was associated with declining incidence of melanomas >0.75 mm, and no melanoma-specific deaths were noted during the screening period [28]. Germany has funded a screening study that was initially pursued in the State of Schleswig-Holstein, in which general practitioners and dermatologists were trained in an 8 h session to perform a standardized whole-body examination. Between July 2003 and June 2004, 360,288 men and women aged >20 were screened by general practitioners or dermatologists trained in this fashion. Age-standardized melanoma mortality declined by 47 % (men) and 49 % (women) by 2008/2009 compared to similar prescreening statistics [29]. These results have prompted similar trials in several large integrated hospital systems in the United States – reports from which are eagerly awaited.

Consensus society guidelines recommend genetic counseling for patients with a suggestive family pedigree to discuss the risks and benefits of genetic testing. CDKN2A testing can be considered in several instances:

- Melanoma diagnoses among multiple first-degree family members. An Australian series of 131 probands with a family history of melanoma reported a 15.1 % incidence of CDKN2A mutations when in families with three or more cases of melanoma among first-degree relatives [30].
- Multiple primary melanomas (MPM). Patients with two or more primaries are more likely to have CDKN2A mutations than patients with a single primary melanoma. GEMS Study Group report suggested a CDKN2A mutation rate of 3 % in patients with MPM, although other reports have suggested that this might be higher especially in patients with greater than two melanomas [13, 31].
- Melanomas in association with other primary malignancies. Besides melanoma, CDKN2A mutations are associated with the development of other malignancies with lifetime relative risk estimates ranging from 40.4 (Wilms tumor), 7.4 (pancreatic cancer), 1.9 (colorectal cancer, brain cancer), to 1.4 (lung cancer) [32].

Patients with a defined mutation such as CDKN2A/CDK4 are recommended to undergo close surveillance and receive education regarding primary prevention with sunscreen and avoiding unnecessary UV exposure. Given the attendant risk of pancreatic cancer, pancreatic cancer surveillance is recommended in patients with CDKN2A mutations and/or family history of CDKN2A-associated melanoma/pancreatic cancer. In patients in whom no germline gene mutation is detected or in those who have a

moderate- to low-risk locus, experts advocate education regarding risk reduction and recommend routine surveillance. Although the data from the Lawrence Livermore National Laboratory and Schleswig-Holstein studies are highly suggestive, there is a need for more rigorous or randomized data to allow the USPSTF to develop recommendations for universal screening of adults at this time, and the incidence of melanoma below 20–35 may make recommendations for the AYA group more difficult even then.

10.4 Clinical Presentation

Although certain predisposing factors, such as a familial history of melanoma, multiple dysplastic nevi [33], large congenital nevi [34], and an impaired immune system, increase one's risk of developing melanoma earlier in life – for the majority of AYA with melanoma – no preexisting factor can be found. As in adults, those AYA with fair skin, blue or green eyes, red or blonde hair, and propensity to sunburn (Fitzpatrick skin phenotypes I–II) are at a higher risk for melanoma [35].

Because of a low index of suspicion, the diagnosis of melanoma may sometimes be delayed among younger patients [36]. The diagnosis of melanocytic tumors in AYA is further complicated because of the higher likelihood of lesions with spitzoid morphology to occur in this age group. Spitzoid lesions, which can be benign (e.g., Spitz nevus), borderline (atypical Spitz tumor), or frankly malignant (spitzoid melanoma), more commonly affect younger individuals and sometimes can create diagnostic uncertainty regarding their proper classification [37].

The clinical presentation of melanoma in AYA is similar to those in adults. The most common complaints in AYA with early lesions are a change in the size and color of a pigmented lesion. Other signs and symptoms may be bleeding, itching, pain, or ulceration that represent manifestations of later disease. Spitzoid melanoma presents as a papule, nodule, or less often a plaque that may often be amelanotic [38].

10.5 Staging

In cutaneous melanoma, four factors (primary tumor thickness, ulceration, mitotic rate, and lymph node tumor burden) independently predict the risk of locoregional relapse and mortality. These factors are delineated in the revised 2009 classification on the staging and prognosis of cutaneous melanoma copublished by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) [39].

Primary tumor thickness (measured in mm) is the single most powerful factor predictive of 5- and 10-year survival rates, which decline commensurate with the thickness of the tumor. Tumor ulceration is an adverse factor associated with poorer survival and factored into the a/b substages of the "T" category; ulceration of any given "T" substage (designated "b") has a risk of relapse and/or death that approximates the next higher "T" substage (T1, T2, T3, and T4).

Mitotic rate (number of mitoses per square millimeter observed) in the primary tumor is an adverse prognostic factor that has been recognized for some time, but was factored into the AJCC staging system only in the last edition. Mitotic activity subclassifies lesions into nonmitogenic potential (0 mitoses/mm^2), low mitogenic potential (1–2 mitoses/mm^2), and high mitogenic potential ($\geq$3 mitoses/mm^2). In the 2009 AJCC/UICC staging manual, high mitotic rate (as defined as $\geq$1 mitoses/mm^2) was incorporated into the substaging of T1 lesions only – where this finding was used to assign patients to T1b, much as ulceration does. Recent evidence suggests that mitotic rate is a reliable adverse prognostic factor and may have a greater value than ulceration in early melanomas [40]. The grading of a lesion for mitotic rate and the role of mitotic activity in lesions over T1 micro-stage will be a factor to have clarified in the 8th edition of the AJCC/UICC staging manual, which is being developed over the next year.

The risk of lymph node involvement increases with tumor thickness by approximately 2–5 % for Breslow's depth $\leq$1.00 mm and reaches 34 % for

T4 lesions. Lymph node involvement is staged based on number (N1, one node; N2, two to three nodes; and N3, four or more nodes, the presence of tumor satellites surrounding the primary, or in-transit disease in the proximal lymphatics) and is subdivided according to the extent (a, micrometastases; b, macro-metastases). Unlike micrometastases, which are clinically non-palpable and diagnosed only after pathological evaluation of the wide excision and sentinel lymph node biopsy (with a cutoff of 0.1 mm to be considered positive), macro-metastases refer to clinically palpable regional lymph nodes. Sub-0.1 mm involvement ("submicrometastases") after sentinel lymph node evaluation is considered by some to be negative as such patients in some series have had similar rates of relapse and mortality as patients with sentinel lymph node-negative disease [41]. However, the long interval that is required to reach maturity and definitive conclusions qualifies the assessment of these questions, and the AJCC Subcommittee for the 7th edition chose to delineate the presence of even a single tumor cell as positive.

In evaluating the systemic burden of disease, the site(s) of distant metastases has greater prognostic import than the number of metastatic sites. Patients with distant skin, subcutaneous, and/or lymph node metastases have what has been classified as M1a disease – with improved 1-year survival rates (62 %) compared to patients with pulmonary (M1b, 53 %) and extrapulmonary visceral metastases (M1c, 33 %). Patients with elevated serum lactate dehydrogenase (LDH) enzyme levels have poor outcomes that are similar to patients with non-lung visceral metastases and are therefore staged M1c.

10.6 Surgical Therapy

10.6.1 Resection

In the absence of guidelines regarding the surgical resection of melanomas in pediatric and AYA patients, management has defaulted to standards used to treat adults. Ideally, suspicious-appearing pigmented cutaneous lesions should be biopsied: either with a punch biopsy of the lesion including its deepest portion or with an excisional biopsy that includes a 1–2 mm rim of normal skin. Initial biopsies should be oriented parallel to long axis for extremity lesions or parallel to Langer's lines of stress for truncal lesions thinking ahead to the definitive wide local excision (WLE) required should diagnosis of melanoma be confirmed. Such forethought facilitates subsequent surgical closure and minimizes skin grafting requirements. Deep punch or excisional biopsies are recommended over superficial shave biopsies for several reasons:

- Shave biopsies tend to underestimate or incompletely assess Breslow's thickness.
- Shave biopsies tend to leave residual tumor at the radial and/or deep margins.
- Post-biopsy scarring can obscure identification of residual melanoma in subsequent resection specimens.

Once pathological confirmation is obtained, definitive surgical management involves WLE with consideration of regional lymph node staging for a subset of deeper tumors. Definitive WLE involves an excision down to deep fascia with a width of peri-lesional normal tissue ranging from 1 cm (<2 mm T1–T2 melanomas) to 2 cm (>2.01 mm T3–T4 melanomas) [42]. Although some have argued for larger (3 cm) margins for patients with thick (T4) melanomas, no correlation between greater margin width and lower local/regional recurrence rates has been demonstrated [43, 44].

There is an absence of high-quality data from randomized trials to guide the management of melanoma in situ (MIS) lesions. A 5 mm margin was recommended by a National Institutes of Health (NIH) consensus statement in 1992 [45] and the WHO prior to that.

Mohs microsurgery (MMS) has gained popularity, especially in the management of lesions in locations where primary closure is hard to achieve (face, head and neck, distal upper extremity) and for large superficial lesions (lentigo maligna). Although retrospective data suggests

that MMS has good outcomes, it has not been prospectively compared to WLE [46]. Further, although suitable for local control, MMS does not obviate the need for regional staging with sentinel lymph node (SLN) biopsy.

10.6.2 Lymph Node Staging

Regional lymph nodes are the most common (and often initial) site of melanoma metastases. For decades, surgical oncologists debated the rationale of removing clinically negative lymph nodes – essentially aiming to identify a group of patients with concurrent high risk of regional metastases but low risk of distant metastases. In 1979, Balch CM and colleagues reported on the 3-year risk of regional metastases with resected primary melanoma: 0% (<0.76 mm), 25% (0.6–1.50 mm), 51% (1.50–3.99 mm), and 62% (>4 mm) [47]. These results led many surgeons to advocate for elective lymph node dissections (LND) in all patients – with significant attendant morbidity as only 15–20% of patients have regional lymph node involvement. The Intergroup Melanoma Surgical Trial was a randomized study of upfront elective LND versus observation in intermediate-thickness melanomas (1.0–4.0 mm). Although overall survival at 10 years was not significantly different in either group, patients with ulcerated and/or T1–T2 (1.0–2.0 mm) melanomas especially benefited from upfront LND – suggesting that these patients had a substantial risk of regional disease with no occult metastases [48]. In 1992, Donald Morton and Alistair Cochran demonstrated that sentinel lymph nodes (SLN) could be reliably mapped using a minimally invasive technique that utilized colloid dye and lymphoscintigraphy with intradermal injection of 99mTc-sulfur colloid or 99mTc-human serum albumin [49].

SLN assessment is reliable and of prognostic value to the patient and managing physicians. False-negative rates are low (<10%), although greater tumor depth and non-extremity primary sites are associated with higher false-negative rates [50]. SLN status is highly prognostic – SLN negativity is associated with significant increases in disease-specific survival [51]. SLN biopsy was compared to observation in 2001 patients with intermediate (defined as 1.2–3.5 mm) and thick (defined as >3.5 mm) melanomas in the Multicenter Selective Lymphadenectomy Trial (MSLT-I). The initial report of this trial consisted of the 5-year outcomes in the intermediate cohort. Compared to observation, patients who underwent SLNB had improved time to relapse, but melanoma-specific survival was similar in both groups. Patients with positive SLN treated with immediate lymphadenectomy had an improved survival although this was a subset analysis and not the primary endpoint [52]. Recently, final results of the MSLT-I consisting of 10-year outcomes in the intermediate-thickness melanomas were reported [53]. Previously noted survival benefits in intermediate-thickness melanoma with positive SLN who underwent immediate LND compared to patients on observation treated with LND at time of clinical recurrence were upheld. Notably, thick melanomas that underwent LND guided by SLN biopsy had improved 10-year disease-free survival, but not melanoma-specific survival – suggesting that thick melanomas had a higher risk of occult distant metastases than intermediate melanomas.

The risk of identifying a positive sentinel node is directly correlated with the thickness of primary melanoma. Even thin melanomas (≤1.50 mm) carry a substantial risk of SLN involvement – ranging from 2.9% (≤1.00 mm) to 7.1% (1.01–1.50 mm) [54]. Bleicher et al. observed a higher incidence of SLN involvement in patients aged <44 years compared to older patients [54]. Ultimately, this underscores the need to consider SLN evaluation in all patients with Breslow's depth >1.00 mm and in selected candidates with thinner melanomas who have other adverse prognostic factors or incomplete biopsies.

Unlike cutaneous melanomas and pediatric "conventional" melanomas, in which SLN involvement is commensurate to risk of distant metastases and eventual mortality, Spitzoid melanomas in the AYA have a high incidence of nodal involvement but a generally low risk of subsequent systemic spread. Lallas et al. conducted a systematic review of 24 trials that evaluated SLN biopsy in 541 patients with

atypical Spitz tumors [55]. Two hundred and thirty-eight patients underwent wide excision alone, while 303 patients had SLN evaluation in addition to wide excision; SLN was negative in 184 (61 %) patients and positive in 119 (31 %) patients. Of the latter, 97 (97/119, 82 %) underwent completion LN dissection, and 18 (18/97, 19 %) had 1 or more positive LN. Five patients had regional recurrence, while six patients died from metastatic disease – of whom one fifth and one sixth, respectively, had a positive SLN but no subsequent completion LN dissection. Ninety nine percent of all patients were alive at a median follow-up of 59 months. Separately, other authors have reported that the age at diagnosis may affect the likelihood of SLN involvement – with a lower risk of SLN involvement in patients younger than 10 years of age [56]. These studies illustrate the unique biology of spitzoid melanomas, which have a high incidence of nodal disease but subsequent lack of dissemination beyond LN, and underscore the controversial nature of SLN evaluation in this disease.

10.7 Nonsurgical Therapy

10.7.1 Adjuvant Therapy in High-Risk Resected Disease

10.7.1.1 Adjuvant High-Dose IFN (HDI)

Early reports of the antitumor efficacy of cytokines (IFN-α, IL-2, IL-7, and IL-21) in a variety of tumor types resulted in a series of studies that evaluated IFN-α in advanced melanoma. Results were promising: occasional durable responses and complete responses, albeit of low frequency. Attempting to forestall the epidemic of advanced disease, investigators evaluated IFN-α in a plethora of adjuvant trials. These studies tested multiple subtypes (IFN-α2a, IFN-α2b, and IFN-α2c) at various dosages (low dose, ≤3 MU/dose; intermediate dose, 5–10 MU/dose; and high dose, ≥10 MU/dose) and schedules (induction, maintenance, and induction/maintenance) in an effort to define the most efficacious subtype, dose, and schedule and are summarized in Table 10.1 [57–75].

Two systematic reviews [76, 77], two meta-analyses [78, 79], and a patient data analysis [80] have collectively concluded that IFN-α-based adjuvant therapy improves risk of relapse with a lesser impact on overall survival in high-risk resected melanoma. Mocellin and colleagues reviewed 18 trials of adjuvant IFN-α compared to observation (or any other therapy) in a Cochrane Database Review and concluded that adjuvant IFN-α administered to stage II-III patients improves disease-free survival by 17 % (hazard ratio, 0.83; 95 % confidence interval, 0.78–0.87; *p*-value significant) and overall survival by 9 % (hazard ratio, 0.91; 95 % confidence interval, 0.85–0.97; *p*-value significant) [77]. The absolute survival benefit with adjuvant IFN-α is estimated at 3 %, which favorably compares to other diseases: 1.2–6.9 % (polychemotherapy, breast cancer), 3.9–5.4 % (cisplatin-based chemotherapy, non-small cell lung cancer), and 5–7 % (cisplatin-based chemotherapy, transitional cell bladder cancer) [81–83].

Subset analyses from ECOG E1684 which suggested that relapse risk reduction occurred relatively early provided a biological rationale to test truncated dosing schedules. The considerable toxicity (23 % grade 3 fatigue), difficulty with completion (~50 % of treated patients), and attendant costs associated with full 12 months of HDI therapy buttressed the desire among investigators to assess whether a truncated treatment course provided equivalent benefit with less toxicity [84]. This hypothesis has been evaluated in three prospective randomized trials: Hellenic He13A/98 [62], ECOG E1697 [64], and an Oxford phase II study [85]. ECOG E1697 compared HDI induction to observation but closed for futility after 1,150 patients of a planned 1,420 patients were enrolled. At ASCO in 2011, investigators reported absence of a significant improvement in either relapse risk or 5-year survival for the 1-month induction schedule compared to observation alone in stage IIA or greater disease. Both Hellenic He13A/98 and the Oxford phase II study compared induction only to induction/maintenance – although the Hellenic He13A/98 study used a non-inferiority design and a reduced dosage induction (IV 15 MU/m^2, 5 days a week for 4 weeks) and maintenance

Table 10.1 Phase III studies of adjuvant IFN-α in high-risk resected melanoma

Study reference	Patients eligible for analysis	Stage	IFN type	Dose and schedule – treatment arm	Median follow-up at reporting (years)	DFS/RFS	OS	% node positive
High dose								
NCCTG 83-7052 [57]	262	II–III (T2–4N0M0 or TanyN+M0)	IFN-α2a vs. observation	IM 20 MU/m^2 3 days a week for 4 months	6.1	HR: 1.20 (HDI vs. observation) (NS)	HR: 1.11 (HDI vs. observation) (NS)	61
ECOG E1684 [58]	287	II–III (T4N0M0 or TanyN+M0)	IFN-α2b vs. observation	Induction: IV 20 MU/m^2 5 days a week for 4 weeks Maintenance: SC 10 MU/m^2 3 days a week for 48 weeks	12.6	HR: 1.38 (HDI vs. observation) (S)	HR: 1.22 (HDI vs. observation) (S at 6.9 years but NS at 12.6 years)	89
ECOG E1690 [59]	642		IFN-α2b – high dose vs. low dose vs. observation	High dose: Induction: IV 20 MU/m^2 5 days a week for 4 weeks Maintenance: SC 10 MU/m^2 3 days a week for 48 weeks	4.3	HR: 1.28 (HDI vs. observation) (S)	HR: 1.0 (HDI vs. observation) (NS)	74
				Low dose: SC 3 MU/m^2 2 days a week for 2 years		1.19 (LDI vs. observation) (NS)	1.04 (LDI vs. observation) (NS)	
						RFS: 44 % (HDI) vs. 40 % (LDI) vs. 35 % (observation)	OS: 52 % (HDI) vs. 53 % (LDI) vs. 55 % (observation)	
ECOG E1694 [60]	774		IFN-α2b vs. GMK vaccine	Induction: IV 20 MU/m^2 5 days a week for 4 weeks Maintenance: SC 10 MU/m^2 3 days a week for 48 weeks	2.1	HR: 1.49 (HDI vs. GMK) (S)	HR: 1.38 (HDI vs. GMK) (S)	77
						RFS: 25 % (HDI) vs. 39 % (GMK)	OS: 78 % (HDI) vs. 73 % (GMK)	

ECOG E2696 [61]	107	II–IV	GMK vaccination with concurrent HDI (arm A) vs. GMK vaccination with HDI beginning D28 (arm B) vs. GMK vaccination alone (arm C)	Induction: IV 20 MU/m^2 5 days a week for 4 weeks Maintenance: SC 10 MU/m^2 3 days a week for 48 weeks GMK vaccination: GM2-KLH/QS-21 on D1, 8, 15, 22 then weeks 12, 24, 36	2.4	HR: 1.75 (C vs. A) (S) 1.96 (C vs. B) (S) RFS: not reached (A) vs. 30.72 months (B) vs. 14.85 months (C)	HR: not reported OS: not reached (A, B, or C)	Not reported
Hellenic He13A/98 [62]	364	IIB–C/III (T3/4N0M0 or TanyN+M0)	Modified IFN-α2b induction only (arm A) vs. modified IFN-α2b induction and maintenance (arm B) Non-inferiority design	Modified induction: IV 15 MU/m^2 5 days a week for 4 weeks Modified maintenance: SC 10 MU 3 days a week for 48 weeks	5.3	Median RFS: 24.1 months (arm A) vs. 27.9 (arm B) (NS, primary non-inferiority endpoint met)	Median OS: 64.4 months (arm A) vs. 65.3 (arm B) (NS)	58
Italian Melanoma Intergroup [63]	330	III (TanyN1–3 M0)	Intensified IFN-α2b (IHDI) every other month vs. IFN-α2b for 1 year	IHDI: IV 20 MU/m^2 5 days a week for 4 weeks every other month for 4 cycles Standard HDI: IV 20 MU/m^2 5 days a week for 4 weeks → then → SC 10 MU/m^2 3 days a week for 48 weeks	5.0	Median RFS: 47.9 months (IHDI) vs. 35.6 months (HDI) (NS) 5 year RFS: 45.8 % (IHDI) vs. 44.3 % (HDI)	Median OS: 88.7 months 5 year OS: 60.1 % (IHDI) vs. 82.6 % (HDI) (NS)	100
E1697 [64]	1,150 (1,420 planned enrollment)	IIB–C/III (T2–4N0M0 or TanyN1a/2aM0)	Induction HDI vs. observation	Induction only: IV 20 MU/m^2 5 days a week for 4 weeks	Not reported	Median RFS: 6.8 years (HDI induction) vs. 7.3 years (observation) (NS)	5 year OS: 82 % (HDI induction) vs. 85 % (observation) (NS)	19

(continued)

Table 10.1 (continued)

Study reference	Patients eligible for analysis	Stage	IFN type	Dose and schedule – treatment arm	Median follow-up at reporting (years)	DFS/RFS	OS	% node positive
Intermediate dose								
EORTC 18952 [65]	1,388	II–III (T4N0M0 or TanyN+M0)	IFN-α2b for 1 year vs. 2 years vs. observation	Induction: IV 10 MU 5 days a week for 4 weeks Maintenance: SC 10 MU 3 days a week for 1 year *or* SC 5 MU 3 days a week for 2 years	4.7	DMFI: HR: 0.93 (13 month vs. observation) (NS) 0.83 (25 month vs. observation) (S)	DMFS: HR: 0.95 (13 month vs. observation) (NS) 0.85 (25 month vs. observation) (NS)	74
EORTC 18991 [66]	1,256	III (TanyN+M0)	Peg-IFN vs. observation	Induction: SC 6 μg/kg/week for 8 weeks Maintenance: SC 3 μg/kg/week for 5 years	7.6	34.8 months (IFN) vs. 25.6 months (observation); S	Not reported	100
Nordic IFN [67]	855	IIB-IIIB (T4N0M0 or TanyN1–2 M0)	IFN-α2b for 1 year vs. 2 years vs. observation	SC 10 MU 5 days a week for 4 weeks then SC 10 MU 3 days a week for 1 year (B) versus SC 10 MU 5 days a week for 4 weeks then SC 10 MU 3 days a week for 2 years (C) versus observation (A)	6.0	23.2 months (A) vs. 37.8 months (B) vs. 28.6 months (C) IFN vs. observation and IFN 1 year vs. observation (S); IFN 2 year vs. observation (NS)	56.1 months (A) vs. 72.1 months (B) vs. 64.3 months (C) (NS)	81
Low dose								
Austrian Melanoma Cooperative Group (AMCG) [68]	311	II (T2-4N0M0)	IFN-α2a vs. observation	SC 3 MU 7 days a week for 3 weeks, then SC 3 MU 3 days a week for 1 year	3.4	RFS/DMFS not reported Rate of relapse: (24.0 % LDI vs. 36.3 % observation)	Not reported	0
French Melanoma Cooperative Group (FCGM) [69]	499	II (T2–4N0M0)	IFN-α2a vs. observation	SC 3 MU 3 days a week for 18 months	>3	HR: 0.74 (LDI vs. observation) (S)	HR: 0.70 (LDI vs. observation) (S)	0

WHO Melanoma Program Trial 16 [70]	444	III (TanyN+M0)	IFN-α2a vs. observation	SC 3 MU 3 days a week for 36 months	7.3	NS	NS	100
Scottish Melanoma Cooperative Group [71]	96	II–III (T3–4N0M0 or TanyN+M0)	IFN-α2a vs. observation	SC 3 MU 3 days a week for 6 months	>6	NS	NS	Not reported
EORTC 18871/ DKG 80-1 [72]	728	II–III (T3–4N0M0 or TanyN+M0)	IFN-α2b vs. IFN-γ vs. ISCADOR M® vs. observation	IFN-α2b: SC 1 MU every other day for 12 months IFN-γ: SC 0.2 mg every other day for 12 months	8.2	NS	NS	58
UKCCCR/AIM HIGH [73]	674	II–III (T3–4N0M0 or TanyN+M0)	IFN-α2a vs. observation	SC 3 MU 3 days a week for 24 months	3.1	NS	NS	Not reported
DeCOG [74]	840	III (T3anyN+M0)	IFN-α2a	SC 3 MU 3 days a week for 18 months (A) vs. 5 years (B)	4.3	5 year DMFS 81.9 %(A) vs. 79.7 % (B) (NS)	5 year OS 85.9 %(A) vs. 84.9 % (B) (NS)	Not reported
DeCOG [75]	444	III (TanyN+M0)	IFN-α2a	SC 3 MU 3 days a week for 24 months (A) vs. SC 3 MU 3 days a week for 24 months + DTIC 850 mg/m^2 every 4–8 weeks for 24 months (B) vs. observation (C)	3.9	HR: 0.69 (A) vs. 1.01 (B) vs. 1.0 (C)	HR: 0.62 (A) vs. 0.96 (B) vs. 1.0 (C)	100 %

Key: *NS* not significant, *S* significant, *HR* hazard ratio, *DFS* disease-free survival, *OS* overall survival

(SC 10 MU, 3 days a week for 48 weeks) doses. Overall and relapse-free survival was greater with the 1-year duration of therapy in both studies, although these differences were not statistically significant in the Greek study, and was of borderline significance for survival in Oxford study where the subjects often had higher-risk stage IIIB disease.

The antipodal question of whether more is better has been raised – and given the toxicity associated with HDI, trials seeking to answer this question have utilized either lower doses of HDI (ECOG E1690, WHO 16, EORTC 18952, Nordic IFN trial) or pegylated IFN (EORTC 18991). ECOG E1690, WHO 16, and EORTC 18952 were largely negative – although EORTC 18952 reported a survival benefit on subset analysis for patients with low-stage (IIB/IIC) disease, suggesting that lower tumor burden was associated with response to IFN [65]. Both the Nordic IFN and EORTC 18991 trials concluded that adjuvant IFN given for 2 years (IFN-α2b and pegylated IFN respectively) improved risk of relapse with no overall survival benefit despite an extended duration of therapy [66, 67]. Post-hoc analyses in EORTC 18991 suggested an unexpected relapse/survival benefit for patients with ulcerated primaries and/or microscopic nodal metastases. This has prompted a prospective evaluation of Peg-IFN in this select group of patients with ulcerated primaries and nodal disease, using a new schedule of 2 years of Peg-IFN. EORTC 18081 is a phase III trial currently in accrual in which 1,200 patients with ulcerated node-negative (T2b–T4b N0M0) melanoma are randomized to adjuvant pegylated IFN given for 2 years or observation.

These studies restricted enrollment to patients aged 18 years or greater. Retrospective reports of small numbers of pediatric patients treated with HDI at the Hospital for Sick Children, St. Jude Children's Research Hospital, and the University of Michigan suggest that pediatric patients can safely be treated with standard adjuvant doses of HDI [86–88]. With improved understanding of the similarity in biology between pediatric and adult melanoma, it is reasonable to consider extending these options to pediatric patients – ideally in the context of a clinical trial. ECOG E1609 which recently completed accrual was a forerunner in this regard as it permitted accrual of patients as young as 10 years of age.

10.7.1.2 Other Adjuvant Therapies: Vaccines, Chemotherapy, and Radiotherapy

Cancer vaccines utilizing a variety of antigen(s) and/or cell(s) – including whole cell/cell lysate, dendritic cell (DC), peptide, ganglioside, and DNA vaccines – have been extensively evaluated in both resected and advanced melanoma with disappointing results [89]. Recently, two large phase III vaccine studies of lineage antigen (MAGE-A3 with AS15 adjuvant) in resected stage III B/C melanoma and intralesional velimogene aliplasmid (Allovectin-7®) in recurrent stage III/IV melanoma both failed to meet their primary efficacy endpoints. No further evaluation of Allovectin is planned, although the benefits of the MAGEA3 vaccine are pending further evaluation among patients with a favorable gene expression profile. Intralesional talimogene laherparepvec (T-VEC) – an oncolytic virus created by reengineering HSV-1 to facilitate antigen presentation and secrete GM-CSF – represents a novel approach in the vaccine arena. Positive results were reported recently in a phase III trial (OPTiM) of T-VEC against GM-CSF alone in patients with low-volume primarily cutaneous advanced disease [90]. Further evaluation is pending in the advanced and neoadjuvant settings.

Adjuvant chemotherapy has been evaluated in several phase III trials, none of which demonstrated significant improvement in relapse-free and overall survival. Combinations of immunotherapy and chemotherapy – termed biochemotherapy (BCT) – have improved response rates without changing survival of resectable high-risk stage IIIB or stage IV patients at the expense of greater toxicity. A recent phase III Southwest Oncology Group (SWOG) study – S0008 – of BCT (cisplatin, vinblastine, DTIC, IL-2, and IFN-α2b) compared to HDI reported 23 % reduction in relapse (HR, 0.77) with no change in overall survival [91]. A phase II 3-arm Asian study compared temozolomide/cisplatin chemotherapy to HDI and observation in high-risk resected mucosal melanoma [92]. Authors reported improvements in relapse/overall survival with

both temozolomide/cisplatin and HDI although chemotherapy appeared superior to HDI in both relapse/overall survival terms – suggesting that biological differences in acral/mucosal vs. cutaneous melanoma may result in differential responses to adjuvant chemotherapy.

Given the high likelihood of disseminated disease at recurrence, the role of radiotherapy is limited to patients who either refuse or whose performance status precludes consideration of HDI or a clinical trial. ANZMTG – a phase III study of 250 patients with high-risk disease who were randomized to either observation or regional nodal basin RT (48 Gy in 20 fractions) following surgery with adequate margins – reported that RT significantly reduced risk of locoregional recurrence with no impact on survival [93]. Clinicopathologic features that predisposed to local recurrence included:

- Cervical lymph node location
- Involvement of four or more nodes
- Extracapsular lymph node extension
- Bulky disease (exceeding 3 cm in size)

The inhibitory antibody targeting the immune checkpoint CTLA-4 and known as ipilimumab is being evaluated in the adjuvant setting in both Europe and the United States. EORTC 18071 compared ipilimumab 10 mg/kg to placebo in 951 patients with stage IIIA–C melanoma patients post-resection [94]. A minimum threshold of 1 mm was used to specify risk defined by LN involvement. 45 % had IIIB disease, while 20 and 35 % had IIIA and IIIC disease, respectively. Investigators reported a 25 % reduction in risk of relapse (hazard ratio, 0.75; 95 % confidence interval, 0.64–0.90) – associated with a 9.0 month (26.1 vs. 17.1 months) improvement in time to relapse compared to placebo. Benefit appeared greatest in patients with stage IIIC disease or ulcerated primaries. At a median follow-up of 2.74 years, survival data are not sufficiently mature to be reported. Toxicities observed were consistent with studies of ipilimumab in advanced disease – with 54 % grade 3/4 events including 7 % grade 3/4 colitis and 5 % grade 3/4 hypophysitis. Unfortunately, five treatment-related deaths (three, colitis; one, myocarditis; one, Guillain-Barré syndrome and multiorgan failure) were observed. Notably, 40 % of patients discontinued ipilimumab prior to initiation of maintenance phase (compared to 4 % of patients receiving placebo), suggesting that induction phase accounted for the majority of observed benefit. ECOG intergroup trial E1609 is an open-label randomized phase III trial comparing ipilimumab at two dose levels (3 mg/kg and 10 mg/kg) to HDI in 1,673 patients. Accrual is complete and initial results are expected in 2016. Compared to EORTC 18071, ECOG E1609 enrolled a higher-risk cohort (stages IIIB/IIIC/IV resected) and specified a primary endpoint of relapse-free and overall survival, where EORTC 18071 specified only relapse-free survival. ECOG E1609 will clarify whether ipilimumab truly improves either relapse-free or overall survival over the reference standard HDI or whether benefit can be achieved at a potentially lower dose of 3 mg/kg.

10.7.2 Advanced Disease

Prior to the advent of efficacious targeted and immunotherapies, patients were treated with high-dose IL-2 or chemotherapy. High-dose IL-2 (HD IL-2) was associated with response and disease stabilization in 15–20 % of treated patients; complete responses although rare (4–5 %) were durable [95, 96].

Over the past decade, scientific advances have transformed our understanding of melanoma biology – yielding insights into driver mutations that activate MAPK pathway and mechanisms by which tumors inhibit T-cell activation. Consequently, approaches targeting the MAPK pathway (BRAF/MEK inhibitors) and immune checkpoints (CTLA-4/PD-1/PD-L1 inhibitors) have had resounding success. Between 2011 and present, the US Food and Drug Administration (FDA) has approved seven new agents including BRAF inhibitors (vemurafenib and dabrafenib), MEK inhibitors (trametinib and cobimetinib), CTLA-4 (ipilimumab), and PD-1-blocking antibodies (pembrolizumab and nivolumab). The regulatory studies supporting this unprecedented rush of approvals are summarized in Tables 10.2 and 10.3 [97–118].

Table 10.2 Regulatory studies of targeted therapy agents in advanced melanoma

Agent (trade name, sponsors)	Study reference	Disease type (no. of evaluable patients)	Study design and endpoints	Dose and schedule	ORR (%) (all analyses significant)	PFS and OS (all analyses significant)
BRAF inhibitors						
Vemurafenib (Zelboraf®, Plexxikon, and Roche-Genentech)	BRIM3 [97, 98]	First-line *BRAF* V600-mutant melanoma (675 evaluable)	Randomized open-label phase III trial in first-line *BRAF* V600-mutant melanoma of vemurafenib vs. dacarbazine (1:1 randomization)	Vemurafenib 960 mg twice daily till progression	Vemurafenib vs. dacarbazine:	Vemurafenib vs. dacarbazine:
		Treated/stable brain metastases % unknown		Dacarbazine: 1,000 mg/m^2 q3 weekly till progression	57 % vs. 9 %	Median OS 13.6 vs. 9.7 months
		M1c 65 %	Primary: OS and PFS			HR, 0.37 (95 % CI, 0.26–0.55)
		BRAF mutational status centrally assessed (V600E initially reported, later V600E and V600K data reported)	Secondary: RR			Vemurafenib vs. dacarbazine:
						Median PFS 6.9 vs. 1.6 months
Dabrafenib (Tafinlar®, GlaxoSmithKline)	BREAK-3 [99, 100]	First-line *BRAF* V600E- and V600K-mutant melanoma (250 evaluable)	Randomized open-label phase III trial in first-line *BRAF* V600E- and V600K-mutant melanoma of vemurafenib vs. dacarbazine (3:1 randomization)	Dabrafenib 150 mg twice daily till progression	Dabrafenib vs. Dacarbazine:	Dabrafenib vs. Dacarbazine PFS (investigator assessed):
		Treated/stable brain metastases % unknown		Dacarbazine 1,000 mg/m^2 q3 weekly till progression	50 % vs. 6 %	Median PFS 5.1 vs. 2.7 months
						HR, 0.30 (95 % CI, 0.18–0.51)
			Primary: PFS (investigator assessed)			Dabrafenib vs. Dacarbazine PFS (independent assessed):
			Secondary: PFS (independent), OS, RR			Median PFS 6.7 vs. 2.9 months
		M1c 66 %				HR, 0.35 (95 % CI, 0.20–0.61)
						Dabrafenib vs. dacarbazine OS:
						Median OS 20.0 vs. 15.6 months
						HR 0.77 (0.52–1.13)

Encorafenib (LGX818, Array BioPharma and Novartis)	N/A	N/A	N/A	N/A	N/A	N/A
MEK inhibitors						
Trametinib (Mekinist®, GlaxoSmithKline)	METRIC [101]	First-/second-line *BRAF* V600E- and V600K-mutant melanoma (322 evaluable – 273 included in efficacy analysis) Treated/stable brain metastases 3.4 % M1c 64 % Prior chemotherapy 34 % Prior chemotherapy allowed (34 % received), prior *BRAF*/*MEK* inhibitors or ipilimumab excluded	Randomized open-label phase III trial in First-/second-line *BRAF* V600E- and V600K-mutant melanoma of trametinib vs. chemotherapy with either dacarbazine or paclitaxel (2:1 randomization) Primary: PFS (investigator assessed) Secondary: PFS (independent), OS, RR	Trametinib 2 mg once daily till progression Chemotherapy Dacarbazine 1,000 mg/m^2 q3 weekly till progression *OR* Paclitaxel 175 mg/m^2 q3 weekly till progression	Trametinib vs. chemotherapy: 22 % vs. 8 %	Trametinib vs. chemotherapy PFS (investigator assessed): Median PFS 4.8 vs. 1.5 months HR 0.45 (95 % CI, 0.33–0.63) Trametinib vs. chemotherapy PFS (independent assessed): HR, 0.42 (95 % CI, 0.29–0.59) Trametinib vs. chemotherapy survival: 6 month survival rate: 81 % vs. 67 % HR, 0.54 (95 % CI, 0.32–0.92)

(continued)

Table 10.2 (continued)

Agent (trade name, sponsors)	Study reference	Disease type (no. of evaluable patients)	Study design and endpoints	Dose and schedule	ORR (%) (all analyses significant)	PFS and OS (all analyses significant)
Cobimetinib (Exelixis and Roche-Genentech)	N/A	N/A	N/A	N/A	N/A	N/A
Binimetinib (MEK162, Array BioPharma and Novartis)	NEMO (NCT01763164) [102]	First-/second-line *NRAS Q61*-mutant melanoma (393 planned) Treated/stable brain metastases allowed Prior immunotherapy allowed, prior BRAF/MEK inhibitors excluded	Randomized open-label phase III trial in first-/second-line NRAS Q61-mutant melanoma of binimetinib vs. dacarbazine (2:1 randomization) Primary: PFS Secondary: OS, ORR (including DCR)	Binimetinib 45 mg twice daily till progression Dacarbazine 1,000 mg/m^2 q3 weekly till progression	Pending	Pending
Combinations of BRAF/MEK inhibitors						
Dabrafenib (Tafinlar®, GlaxoSmithKline) + Trametinib (Mekinist®, GlaxoSmithKline)	COMBI-d [103]	First-line *BRAF* V600E- or V600K-mutant melanoma (423 evaluable) Treated/stable brain metastases allowed (% not reported)	Randomized double-blind phase III trial in first-line *BRAF* V600E- or V600K-mutant melanoma of dabrafenib and trametinib vs. dabrafenib and placebo (1:1 randomization) Primary: PFS (investigator assessed) Secondary: PFS (independent), OS, RR	Dabrafenib 150 mg twice daily till progression Trametinib 2 mg daily till progression	Dabrafenib and trametinib vs. dabrafenib and placebo: 67 % vs. 51 % *V600E* 68 % vs. 53 % *V600K* 61 % vs. 40 %	Dabrafenib and trametinib vs. dabrafenib and placebo PFS (investigator assessed): Median PFS 9.3 vs. 8.8 months HR, 0.75 (95 % CI, 0.57–0.99) Dabrafenib and trametinib vs. dabrafenib and placebo PFS (independent assessed): Median PFS 9.3 vs. 7.6 months HR, 0.73 (95 % CI, 0.56–0.96) Dabrafenib and trametinib vs. dabrafenib and placebo survival: 6 month survival rate: 93 % vs. 85 %

		M1c 66 %				HR, 0.63 (95 % CI, 0.42–0.94)
		BRAF mutation: V600E (85 %), V600K (*15* %)				
Dabrafenib (Tafinlar®, GlaxoSmithKline) + Trametinib (Mekinist®, GlaxoSmithKline)	COMBI-v [104]	First-line *BRAF* V600E- or V600K-mutant melanoma (704 evaluable)	Randomized open-label phase III trial in first-line *BRAF* V600E- or V600K-mutant melanoma of dabrafenib and trametinib vs. vemurafenib (1:1 randomization)	Dabrafenib 150 mg twice daily till progression	Dabrafenib and trametinib vs. vemurafenib:	Dabrafenib and trametinib vs. vemurafenib PFS (investigator assessed):
					64 % vs. 51 %	Median PFS 11.4 vs. 7.3 months
						HR 0.56 (95 % CI, 0.46–0.69)
						Dabrafenib and trametinib vs. vemurafenib survival:
					V600E 64 % vs. 52 %	Median OS not reached vs. 17.2 months
			Primary: PFS (investigator assessed)	Trametinib 2 mg daily till progression	*V600K* 65 % vs. 44 %	12-month survival rate: 72 % vs. 65 %
		Treated/stable brain metastases allowed (% not reported)		Vemurafenib 960 mg twice daily till progression		
		M1c 61 %	Secondary: OS, RR			
		BRAF mutation: V600E (90 %), V600K (10)				

(continued)

Table 10.2 (continued)

Agent (trade name, sponsors)	Study reference	Disease type (no. of evaluable patients)	Study design and endpoints	Dose and schedule	ORR (%) (all analyses significant)	PFS and OS (all analyses significant)
Vemurafenib (Zelboraf®, Plexxikon and Roche-Genentech) + cobimetinib (Exelixis and Roche-Genentech)	coBRIM [105]	First-line *BRAF* V600E- or V600K-mutant melanoma (495 evaluable)	Randomized open-label phase III trial in first-line *BRAF* V600E- or V600K-mutant melanoma of vemurafenib and cobimetinib vs. vemurafenib and placebo (1:1 randomization)	Vemurafenib 960 mg twice daily till progression	Vemurafenib and cobimetinib vs. vemurafenib and placebo:	Vemurafenib and cobimetinib vs. vemurafenib and placebo PFS (investigator assessed):
				Cobimetinib 60 mg once daily for 21 days, followed by 7 days off	68 % vs. 45 %	Median PFS 9.9 vs. 6.2 months
		Treated/stable brain metastases 0.01 % (3 patients)	Primary: PFS (investigator assessed)			HR, 0.51 (95 % CI, 0.39–0.68)
						Vemurafenib and cobimetinib vs. vemurafenib and placebo PFS (independent assessed):
						Median PFS 11.3 vs. 6.0 months
						HR 0.60 (95 % CI, 0.45–0.79)
						Vemurafenib and cobimetinib vs. vemurafenib and placebo survival:
						9 month survival rate: 81 % vs. 73 %
		M1c 60 %	Secondary: PFS (independent), OS, RR			HR 0.65 (95 % CI, 0.42–1.00)
		BRAF mutation: V600E (69 %), V600K (11), other (20 %)				

Encorafenib (LGX818, Array BioPharma and Novartis) + binimetinib (MEK162, Array BioPharma and Novartis)	COLUMBUS (NCT01909453) [106]	First-/second-line *BRAF* V600E- or V600K-mutant melanoma (900 planned)	Randomized 2-part open-label phase III trial in first-/second-line *BRAF* V600E- or V600K-mutant melanoma of:	Encorafenib 450 mg (part 1) or 300 mg (part 2) daily till progression	Pending	Pending
				Binimetinib 45 mg twice daily till progression		
		Treated/stable brain metastases allowed	Part 1 Encorafenib and binimetinib vs. encorafenib vs. vemurafenib (1:1:1 randomization)	Vemurafenib 960 mg twice daily till progression		
			Part 2 Encorafenib and binimetinib vs. encorafenib (3:1 randomization)			
			Primary: PFS			
		Prior immunotherapy allowed, prior BRAF/MEK inhibitors excluded	Secondary: OS, ORR (including DCR)			

Key: *ORR* overall response rate, *PFS* progression-free survival, *OS* overall survival

Table 10.3 Regulatory studies of checkpoint inhibitors in advanced melanoma

Agent (trade name, sponsors)	Study reference	Disease type (no. of evaluable patients)	Study design and endpoints	Dose and schedule	ORR (%) (all analyses significant)	PFS and OS (all analyses significant)
CTLA-4 inhibitor						
Ipilimumab (Yervoy®, Bristol-Myers Squibb)	MDX010-20 [107, 108]	Relapsed/refractory melanoma (676 evaluable)	Randomized open-label phase III study of ipilimumab/gp100 vs. ipilimumab/placebo vs. gp100/placebo (3:1:1 randomization)	Ipilimumab 3 mg/kg q3 weeks ×4 doses	Ipilimumab/gp100 vs. ipilimumab vs. gp100:	OS vs. gp100:
		BRAF mutant (unknown)	Primary: initially ORR (RECIST), amended to OR (primarily ipilimumab/gp100 vs. gp100/placebo)	gp100 vaccine: 1 mg gp100:209–217 (210 M) peptide + 1 mg gp100:280–288 (288 V) peptide + Montanide ISA-51	ORR 10.9 % vs. 5.7 % vs. 1.5 %	Ipilimumab HR, 0.66 (95 % CI, 0.51–0.87)
		Treated/stable brain metastases (12 %)	Secondary: OS (between ipilimumab/placebo and gp100/placebo; and ipilimumab/placebo vs. ipilimumab/gp100), ORR, PFS			Ipilimumab/gp100 HR, 0.68 (95 % CI, 0.55–0.85)
						OS vs. ipilimumab:
						Ipilimumab/gp100 HR, 1.04 (95 % CI, 0.83–1.30)
						OS >2 years:
						Ipilimumab/gp100 (19 %) vs. ipilimumab/placebo (25 %) vs. gp100/placebo (17 %)
						OS >3 years:
						Ipilimumab/gp100 (15 %) vs. ipilimumab/placebo (25 %) vs. gp100/placebo (10 %)

	MDX010-24 [109, 110]	First-line melanoma (502 evaluable	Randomized double-blind phase III study of ipilimumab and dacarbazine vs. dacarbazine and placebo (1:1 randomization)	Ipilimumab 10 mg/kg q3 weeks ×4 doses	Ipilimumab and dacarbazine vs. dacarbazine and placebo:	Ipilimumab/dacarbazine vs. dacarbazine and placebo OS:
		BRAF mutant (unknown)	Primary: OS and ORR (RECIST)	AND	ORR 15.2 % vs. 10.3 %	HR, 0.72 (95 % CI, 0.59–0.87)
		Treated/stable brain metastases (0 %)	Secondary: PFS, PD-L1 expression	Dacarbazine 850 mg/m^2 or placebo q3 weeks till progression	Stable disease 18.0 % vs. 19.8 %	Ipilimumab/dacarbazine vs. dacarbazine and placebo survival:
						1 year: 47.3 % vs. 36.3 %
						2 year: 28.5 % vs. 17.9 %
						3 year: 20.8 % vs. 12.2 %
PD-1 inhibitor						
Pembrolizumab (Keytruda®, Merck Sharp & Dohme)	KEYNOTE-001 [111]	Relapsed/refractory melanoma (1,260 evaluable, 135 melanoma)	Non-randomized open-label phase I expansion trial of pembrolizumab in relapsed/refractory melanoma	Pembrolizumab doses evaluated:	10 mg/kg q2	Median PFS:
		BRAF mutant (19 %), wild type (69 %), and unknown (12 %)	Primary: safety, toxicity	10 mg/kg q2, 10 mg/kg q3 and 2 mg/kg q3	52 % (RECIST) and 56 % (irRC)	>7 months
		Treated/stable brain metastases (9 %)	Secondary: ORR (RECIST and irRC)		10 mg/kg q3	Median OS:
		Prior ipilimumab (36 %), BRAFi (7 %)			27 % (RECIST) and 27 % (irRC)	Not reported
		PD-L1 expression *not* required			2 mg/kg q3	
					25 % (RECIST) and 14 % (irRC)	

(continued)

Table 10.3 (continued)

Agent (trade name, sponsors)	Study reference	Disease type (no. of evaluable patients)	Study design and endpoints	Dose and schedule	ORR (%) (all analyses significant)	PFS and OS (all analyses significant)
	KEYNOTE-006 [112]	First- and second-line melanoma (834 evaluable)	Randomized open-label phase III trial of pembrolizumab (2 schemas) vs. ipilimumab in first-/second-line melanoma (1:1:1 randomization)	Pembrolizumab (2 schemas):	Q3W vs. Q2W vs. Ipi:	PFS at 6 months:
		BRAF mutant (38.5%)	Primary: PFS and OS (RECIST though irRC used for treatment management)	10 mg/kg q3 weeks (Q3W)	33.7% (Q3W) vs. 32.9% (Q2W) vs. 11.9% (Ipi)	47.3% (Q3W) vs. 46.4% (Q2W) vs. 26.5% (Ipi)
		Treated/stable brain metastases (10.1%)	Secondary: RR	10 mg/kg q2 weeks (Q2W)	Analysis by PD-L1 expression status:	OS at 12 months:
		PD-L1 expression evaluated by central testing (cutoff membranous PD-L1 staining 1%): positive 80.9%		Ipilimumab 3 mg/kg q3 weeks ×4 doses	Not reported	68.4% (Q3W) vs. 74.1% (Q2W) vs. 58.2% (Ipi)
						Analysis by PD-L1 status:
						Not reported
Nivolumab (Opdivo®, Bristol-Myers Squibb)	MDX1106-03, CheckMate-003 [113, 114]	Relapsed/refractory melanoma (296 evaluable, 107 melanoma)	Non-randomized open-label phase I expansion trial of nivolumab in relapsed/refractory melanoma	Nivolumab: 0.1, 0.3, 1, 3, or 10 mg/kg q2	All dose levels: 30.8%	Median PFS: 3.7 months (all dose levels)
		BRAF mutant (not reported, but 5% prior BRAF inhibitor therapy)	Primary: safety, toxicity		0.1 mg/kg: 35.3%	Median PFS by dose level (months)
		Treated/stable brain metastases (3%)	Secondary: ORR (RECIST and irRC)		0.3 mg/kg: 27.8%	0.1 mg/kg: 3.6
		PD-L1 expression *not* required			1 mg/kg: 31.4%	0.3 mg/kg: 1.9
					3 mg/kg: 41.2%	1 mg/kg: 9.1
					10 mg/kg: 20.0%	3 mg/kg: 9.7
						10 mg/kg: 3.7
						1- and 2-year PFS rate: 36% and 27%

	CheckMate-037 [115]	Second-line melanoma (405 evaluable)	Randomized open-label phase III trial of nivolumab vs. physician's choice chemotherapy (dacarbazine or carboplatin/paclitaxel) in second-line melanoma after progression on ipilimumab (2:1 randomization)	Nivolumab (N) 3 mg/kg q2 weeks	Nivolumab vs. POC (first 120 patients):	Nivolumab vs. POC median PFS:
		BRAF mutant (22%)	Primary: OS and ORR (RECIST)	Physician's choice chemotherapy (POC)	31.7% (N) vs. 10.6% (POC)	Not reported
		Treated/stable brain metastases (18%)	Secondary: PFS, PD-L1 expression	Dacarbazine (D) 1,000 mg/m^2 q3 weeks	Analysis by PD-L1 expression status:	Analysis by PD-L1 expression status:
		PD-L1 expression evaluated by central testing (cutoff cell surface PD-L1 staining 5%): positive 50%		Carboplatin AUC6 with paclitaxel 175 mg/m^2 q3 weeks	Not reported	reported

(continued)

Table 10.3 (continued)

Agent (trade name, sponsors)	Study reference	Disease type (no. of evaluable patients)	Study design and endpoints	Dose and schedule	ORR (%) (all analyses significant)	PFS and OS (all analyses significant)
	CheckMate-066 [116]	First-line BRAF wild-type melanoma (418 evaluable)	Randomized blinded placebo-controlled phase III trial of nivolumab vs. dacarbazine in first-line BRAF wild-type melanoma (1: 1 randomization)	Nivolumab (N) 3 mg/kg q2 weeks + matching placebo q3 weeks	Nivolumab vs. dacarbazine:	Nivolumab vs. dacarbazine median PFS:
		Treated/stable brain metastases (3.6 %)	Primary: OS	Dacarbazine (D) 1,000 mg/m^2 q3 weeks + matching placebo q2 weeks	40.0 % vs. 13.9 %	5.1 (N) vs. 2.2 (D) months
		PD-L1 expression evaluated by central testing (cutoff cell surface PD-L1 staining 5 %): positive 35.4 %	Secondary: PFS, ORR (RECIST), PD-L1 expression		Analysis by PD-L1 expression status:	Nivolumab vs. dacarbazine median OS:
					PD-L1 positive: 52.7 % (N) vs. 10.8 % (D)	Not reached (N) vs. 10.8 (D) months
					PD-L1 negative or indeterminate: 33.1 % (N) vs. 15.7 % (D)	Nivolumab vs. dacarbazine OS at 12 months:
						72.9 % (N) vs. 42.1 % (D)
						Analysis by PD-L1 status:
						PD-L1 positive: HR, 0.30 (95 % CI, 0.15–0.60)
						PD-L1 negative or indeterminate: HR, 0.48 (95 % CI, 0.32–0.71)
Combinations of CTLA-4/PD-1 inhibitors						
Ipilimumab (Yervoy®, Bristol-Myers Squibb) and nivolumab (Opdivo®, Bristol-Myers Squibb)	CheckMate-004 [117]	Relapsed/refractory melanoma (86 evaluable)	Non-randomized open-label phase IB expansion trial of ipilimumab and nivolumab combination in relapsed/refractory melanoma	Ipilimumab q3 weeks (4 doses) and nivolumab q3 weeks (8 doses) *then* ipilimumab and nivolumab q12 weeks (8 doses)	ORR:	OS and/or PFS:

		53 (62 %) concurrent and 33 (38 %) sequence treatment	Primary: safety toxicity	Cohorts 1–5 concurrent. Cohorts 6–7 sequenced with ipilimumab monotherapy prior to study entry, then	Cohort 1 21 %	Not reported
		BRAF mutant (unknown)	Secondary: ORR (RECIST and irRC)	nivolumab q2 weeks for up to 48 doses	Cohort 2 53 %	
		Treated/stable brain metastases (0 %)			Cohort 2a 40 %	
		PD-L1 expression evaluated by central testing (cutoff cell surface PD-L1 staining 5 %): positive 38 %		Cohort 1: ipilimumab 3 mg/kg and nivolumab 0.3 mg/kg	Cohort 3 50 %	
				Cohort 2: ipilimumab 3 mg/kg and nivolumab 1 mg/kg	All 40 %	
				Cohort 2a: ipilimumab 1 mg/kg and nivolumab 3 mg/kg		
				Cohort 3: ipilimumab 3 mg/kg and nivolumab 3 mg/kg		
				Cohort 4: ipilimumab 3 mg/kg and nivolumab 10 mg/kg		

(continued)

Table 10.3 (continued)

Agent (trade name, sponsors)	Study reference	Disease type (no. of evaluable patients)	Study design and endpoints	Dose and schedule	ORR (%) (all analyses significant)	PFS and OS (all analyses significant)
				Cohort 5: ipilimumab 10 mg/kg and nivolumab 10 mg/kg		
				Cohort 6 (sequenced): Ipilimumab prior dose and nivolumab 1 mg/kg		
				Cohort 7 (sequenced): Ipilimumab prior dose and nivolumab 3 mg/kg		
Ipilimumab (Yervoy®, Bristol-Myers Squibb) and nivolumab (Opdivo®, Bristol-Myers Squibb)	CheckMate-069 [118]	First-line melanoma (142 evaluable)	Randomized double-blind phase II trial in first-line melanoma of ipilimumab and nivolumab vs. ipilimumab and placebo (2:1 randomization)	Ipilimumab and nivolumab:	Ipilimumab and nivolumab vs. ipilimumab and placebo ORR:	Ipilimumab and nivolumab vs. ipilimumab and placebo median PFS:
		BRAF mutant (23%)	Primary: ORR (BRAF wild type)	Ipilimumab 3 mg/kg q3 weeks for 4 doses and nivolumab 1 mg/kg q3 weeks for 4 doses → nivolumab 3 mg/kg q2 weeks till progression	44% vs. 4% (BRAF wild type)	Not reached vs. 4.4 months (BRAF wild type)
		Treated/stable brain metastases (3%)	Secondary: PFS (BRAF wild type), ORR (BRAF mutant), PFS (BRAF mutant)	Ipilimumab and placebo:	12% vs. 1% (BRAF mutant)	8.5 vs. 2.7 months (BRAF mutant)
		PD-L1 expression evaluated by central testing (cutoff cell surface PD-L1 staining 5% – 118 available): 30%		Ipilimumab 3 mg/kg q3 weeks for 4 doses and placebo → placebo q2 weeks till progression		

Key: *ORR* overall response rate, *PFS* progression-free survival, *OS* overall survival; *CTLA-4* cytotoxic T-lymphocyte-associated protein 4, *PD-1* programmed cell death 1

Compared with chemotherapy in the first-line setting, BRAF inhibitors vemurafenib and dabrafenib significantly improve response rates (50–60 %) and progression-free and overall survival in melanomas with *BRAF* V600E or V600K mutations. Acquired resistance mediated by reactivation of the MAPK pathway typically develops after a median of 6–8 months. BRAF inhibitor use is associated with development of secondary cutaneous squamous cell cancers and keratoacanthomas in 15–30 % of patients secondary to paradoxical activation of the MAPK pathway in cells lacking the *BRAF* mutation. Adding a MEK inhibitor to a BRAF inhibitor delays emergence of acquired resistance to BRAF inhibitor monotherapy and reduces incidence of secondary cutaneous malignancies while prolonging duration of benefit. Studies of dabrafenib/trametinib and vemurafenib/cobimetinib combinations reported greater response rates (64–68 %) and prolonged progression-free survival (9–11 months) compared to BRAF inhibitor monotherapy. FDA has approved dabrafenib/trametinib combination, while Roche/Genentech's application for vemurafenib/cobimetinib combination is pending. Binimetinib (MEK162, Array BioPharma and Novartis) is a MEK1/2 inhibitor with activity in *NRAS*/*BRAF*-mutated melanoma [119]. Phase 3 trials of binimetinib monotherapy in *NRAS Q61*-mutant melanoma (NEMO, NCT01763164) and in combination with BRAF inhibitor encorafenib in *BRAF*-mutant melanoma (COLUMBUS, NCT01909453) are in accrual.

Unlike BRAF and MEK inhibitors that produce response rates of 50–60 % as single agents, CTLA-4 inhibitors – ipilimumab (10–15 %) and tremelimumab (6 %) – have lower response rates although these are often durable. Ipilimumab has demonstrated improved overall survival in the first- and second-line treatment settings compared against dacarbazine [109, 110] and gp100 vaccine [107, 108], respectively – with a 3-year survival rates of 22 % in a pooled analysis of 1,861 patients treated in 12 studies [120].

Agents targeting the PD-1 inhibitory checkpoint have reported high antitumor response rates approaching those of BRAF/MEK inhibitors – nivolumab (32–40 %) and pembrolizumab (34–50 %) – against multiple comparators in phase I studies [111, 113, 114]. Responses are more rapid than those with ipilimumab and appear to be similarly durable – although long-term survival data is lacking at this time.

Phase III studies of pembrolizumab (compared to ipilimumab) and nivolumab (compared to dacarbazine) in previously untreated patients reported improved progression-free survival and objective response rates with approximately 70 % of PD-1-treated patients alive at 12 months in both studies compared to 58.2 % (ipilimumab) or 42.1 % (dacarbazine) [112, 116]. Regulatory approval for first-line use in metastatic disease irrespective of BRAF/NRAS mutation status is expected – as has already occurred in the National Comprehensive Cancer Network (NCCN) guidelines.

Several questions remain about the optimal use of PD-1 inhibitors. Prior studies have shown that immunotherapy combinations have improved antitumor effects without dose-limiting toxicities – as seen when tremelimumab was combined with high-dose IFN in a phase II study [121]. An initial phase I study of ipilimumab/nivolumab reported significant increases in response rates over either agent singly, results of which were confirmed in a recent phase II study; these observations raise issues of how best CTLA-4 and PD-1 inhibitors should be combined and/or sequenced [117, 118]. Secondly, PD-L1 expression is not a useful predictive biomarker with either pembrolizumab or nivolumab. Given recent reports of the prognostic importance of CD8+ T-cell infiltrate and immunogenic neoantigens, models incorporating these (and other) factors may better reflect the complexities of the immune responses triggered by PD-1 inhibitors [122, 123].

Compared to chemotherapy and targeted therapy, immunotherapies are associated with unique response kinetics and durability. In contrast to responses using standard RECIST criteria, patterns observed with checkpoint inhibition can include long-term disease stabilization, initial disease increases, and subsequent decreases of target lesion(s) and/or appearance of new non-target lesions. To avoid underestimating benefit, immune-related response criteria (irRC) that take

into account total tumor volume and emphasize serial assessment have been developed [124]. However, the greater efficacy of anti-PD1 agents and of combined PD-1/CTLA-4 blockade may make irRC moot. The biology and immunology of the combinations of immunotherapy are of interest where anti-CTLA-4 blockade and anti-PD1 blockade have distinct nonoverlapping effects on T cells. CTLA-4 blockade induces T-cell proliferation, especially in transitional memory T cells (CD45RO+, CCR7-CD27+CD28+CD95+), while PD-1 blockade results in increased expression of NK-associated genes and augments CD8+ T-cell activation and cytolysis [125]. Combinatorial blockade augments the effects of single-checkpoint blockade with expression of additional potent chemokines involved in immune infiltration such as IL-8.

The phase III studies of BRAF and MEK inhibitors to date have excluded patients below 18 years of age. At this time, the use of these agents in the pediatric population remains investigational although efforts to characterize the pharmacokinetics and clinical activity of dabrafenib (NCT01677741) and binimetinib (NCT02285439) in pediatric cohorts are ongoing. Similarly, studies of the checkpoint inhibitors have not extended enrollment to pediatric patients. A report from the NCI Pediatric Oncology Branch experience suggests that ipilimumab (including doses up to 10 mg/kg) is safely administered in the pediatric setting with a similar efficacy and toxicity profile to that observed in adults [126]. Studies are underway to evaluate the safety and efficacy of pembrolizumab in advanced melanoma and PD-L1-positive tumors (KEYNOTE-051) and high-grade/intrinsic pontine gliomas (NCT02359565).

Despite this wealth of treatment options, the optimal sequence of immunotherapies (ipilimumab, nivolumab, pembrolizumab, and HD IL-2) and/or targeted therapies (BRAF/MEK inhibitors) has not been determined in randomized clinical trials. At this time, the primary considerations in managing patients with advanced disease are the presence/absence of targetable driver mutations (BRAF) and performance status. Patients with limited metastatic disease should be seen in consultation with experienced surgical oncologists to assess suitability for metastasectomy as this approach is associated with prolonged survival [127]. For patients with good performance status (regardless of presence/absence of driver mutation), immunotherapies are recommended upfront to maximize likelihood and duration of response. In patients with highly symptomatic or rapidly progressive disease, targeted therapy should be considered ahead of immunotherapy given the rapid response kinetics associated with targeted agents. Compared to single-agent therapy with BRAF, MEK, CTLA-4, or PD-1 inhibitors, BRAF/MEK combinations and CTLA-4/PD-1 combinations are associated with greater response rates and prolonged durations of response.

Conclusions

The incidence of invasive cutaneous melanoma is increasing in the population, especially among older men aged >60 and younger women aged 15–39 years. Increased understanding of the genetic heterogeneity in melanoma and the role of immune checkpoints in modulating the magnitude and nature of T-cell and other immune cell (MDSC, Treg) responses to melanoma has resulted in a bevy of treatment options with the capacity to achieve dramatic improvements in the survival of patients with advanced melanoma. Our understanding of the biology of melanoma and the impact of both immunomodulatory and targeted therapies in the AYA population has not paralleled the advances observed in adult melanoma.

Improving outcomes in AYA melanoma requires a multipronged approach and should begin with primary prevention designed to reduce recreational UV exposure through education, community outreach, and legislative efforts. Secondary prevention with population-based screening to detect noninvasive and highly curable disease early as well as genetic testing CDKN2A and others as outline in Section 10.3 of patients with suspicious pedigrees should be considered for implementation by suitably trained providers.

AYA patients with cancer have historically had high participation rates exceeding 60 % in clinical trials – accounting in large part for the tremendous success in improving mortality rates among pediatric leukemia, gonadal cancer, Hodgkin's and non-Hodgkin's lymphomas, neuroblastoma, and bone cancers between 1975 and the present [128]. However, only 2 % of patients aged 20–39 years of age are treated in clinical trials. Further, AYA patients have largely been excluded from the trials that have led to the development of new highly effective therapies targeting BRAF, MEK, and PD-1/CTLA-4 immune checkpoints in melanoma. Reversing this trend will require committed participation from multiple stakeholders including the pharmaceutical industry, academic institutions, and organizations such as the Children's Oncology Group (COG), treating physicians, patients, and their families to design and implement clinical trials of highly active agents and ensure rapid accrual. Such trials should incorporate elements designed to address the unique challenges of enrollment in this patient cohort: insurance status, low health literacy, perceived treatment burden, and procedural concerns. A comprehensive strategy targeting these aspects concurrently will almost certainly improve upon the gains in survival that have been noted in adult populations in this vulnerable patient cohort.

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Cancer of the Ovary, Uterus, and Cervix

11

Jubilee Brown and Jean Hurteau

11.1 Introduction

The epidemiology, biology, treatment, outcomes, and fertility considerations are unique to the adolescent or young adult (AYA) woman with a gynecologic cancer. These diseases represent a wide spectrum of disorders and warrant specific consideration.

In the past, discussion surrounding gynecologic cancers in the adolescent or young adult was restricted to germ cell tumors of the ovary, sex cord-stromal tumors of the ovary, and a handful of very rare disorders like embryonal rhabdomyosarcoma. The inclusion of women up to age 44 in this category, however, necessitates a broader discussion of other tumor types. Additional malignancies of the ovary, as well as malignancies of the uterine corpus, uterine cervix, vulva, and vagina, and gestational trophoblastic disease are integral to the understanding of cancer in the adolescent or young woman.

This chapter discusses the management of the most frequently encountered gynecologic malignancies in this population and provides practical guidelines for management. Population statistics are provided, strategies to maximize fertility are presented, and prevention strategies for the future are highlighted.

11.2 Malignancies of the Ovary

11.2.1 Epidemiology

11.2.1.1 Incidence

Ovarian malignancies are rare in AYAs; it has been estimated that only 3–17 % of ovarian malignancies occur in women younger than 40 years of age. There are fewer than 16 cases per million girls younger than 15 years of age, representing <2 % of malignancies in this age group [1]. However, this increases to 23.7 cases per million females age 15–29, and genital tract tumors account for 18 % of all invasive cancers in females 15 to 20 years of age [1, 2].

Figure 11.1 shows the incidence of ovarian cancer in the United States by age and histologic type. Germ cell tumors (GCTs) of the ovary peak in incidence between 15 and 20 years of age, carcinomas increase exponentially in incidence in AYAs (Fig. 11.1 inset), and stromal tumors peak in incidence in the middle of the AYA age range between 25 and 30 years (Fig. 11.2). GCTs of the ovary are the predominant histologic subtype in AYAs under age 25, after which age they decrease substantially to almost zero by age 40 (Fig. 11.2)

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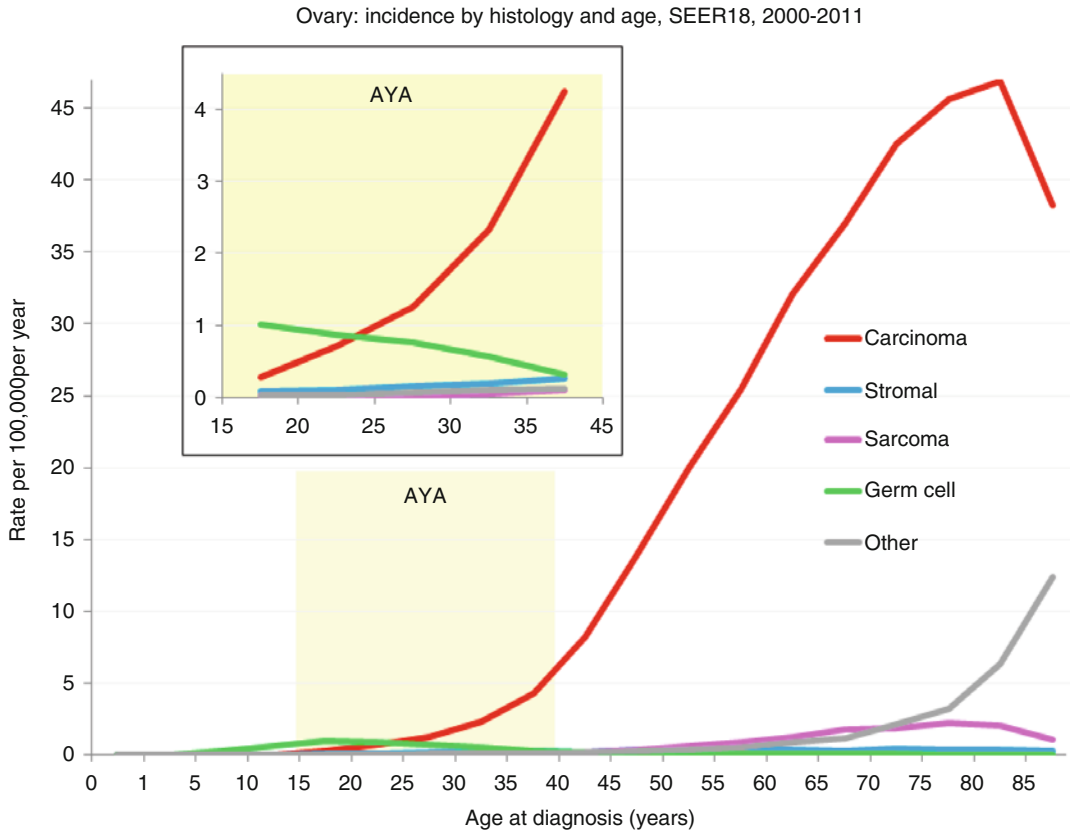

Fig. 11.1 Incidence of ovarian cancer, United States SEER 18 regions, 2000–2011, by histologic type

[3]. Young found that germ cell tumor accounted for 78 % of ovarian cancers in girls younger than 15 years, 54 % of ovarian cancers in adolescents between 15 and 19 years, and less than 50 % after age 20 [4, 5]. Others have confirmed these findings, with germ cell tumors comprising 61–68 % of ovarian cancers in the AYA population [6, 7].

In women with ovarian cancer over 15 years of age, the younger the patient, the more likely the disease is to be localized and therefore of earlier stage (Fig. 11.3). This may reflect the tendency for germ cell tumors to be present in younger females (Fig. 11.2), as these tumors tend to be detected at an earlier stage. As the disease type shifts away from germ cell tumors with increasing age, distant disease at diagnosis increases with age. By age 40, a woman is equally likely to have distant metastases at diagnosis as localized disease. As a result of young women having a favorable histologic subtype (GCTs) with early stage at diagnosis, the prognosis for AYA women with ovarian cancer is better than that for older woman with ovarian cancer. This is unlike most other types of cancer, in which older patients fare better than AYA patients.

Figure 11.4 depicts the incidence of ovarian cancer in the United States by age and race/ethnicity. In AYAs (inset), all major races/ethnicities except native North Americans have similar incidence rates as a function of age. The incidence of ovarian cancer in native North Americans was one-third to one-half of any other racial/ethnic group. Native North Americans had one-third to one-half of the incidence. In older women, non-Hispanic whites had the greatest incidence and Asians/Pacific Islander had the lowest incidence.

11.2.1.2 Incidence Trends

The incidence of ovarian cancer has been largely unchanged in AYA females in the United

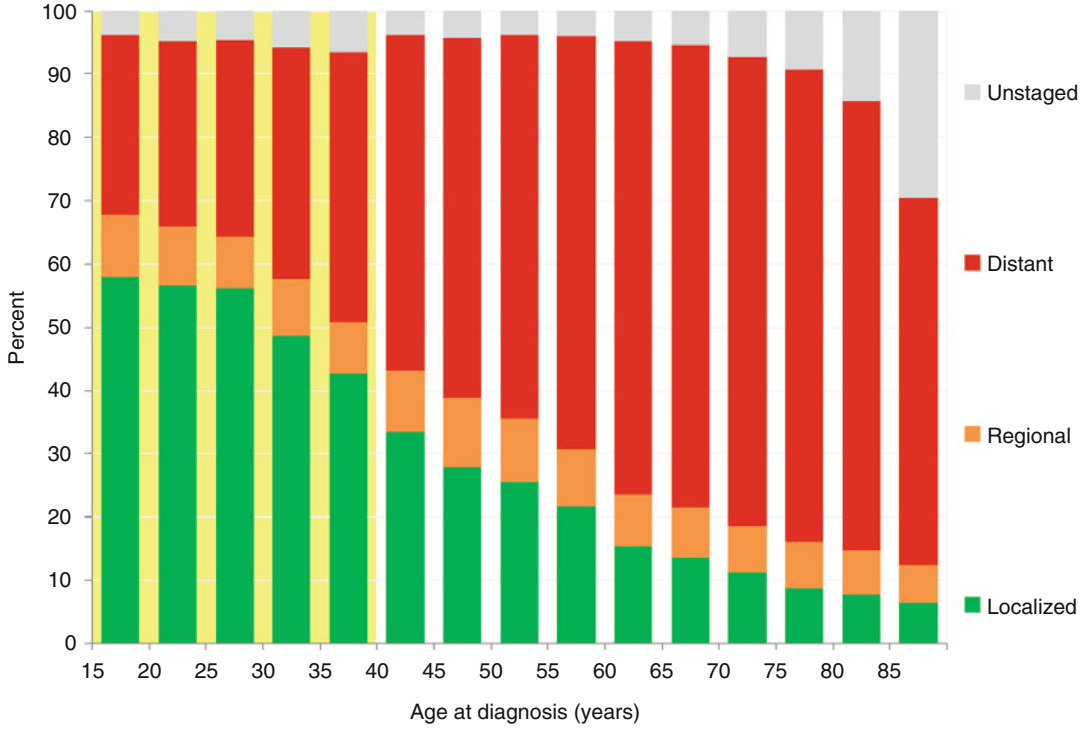

Fig. 11.2 Distribution of ovarian cancer, United States SEER 18 regions, 2000–2011, by histologic type and age

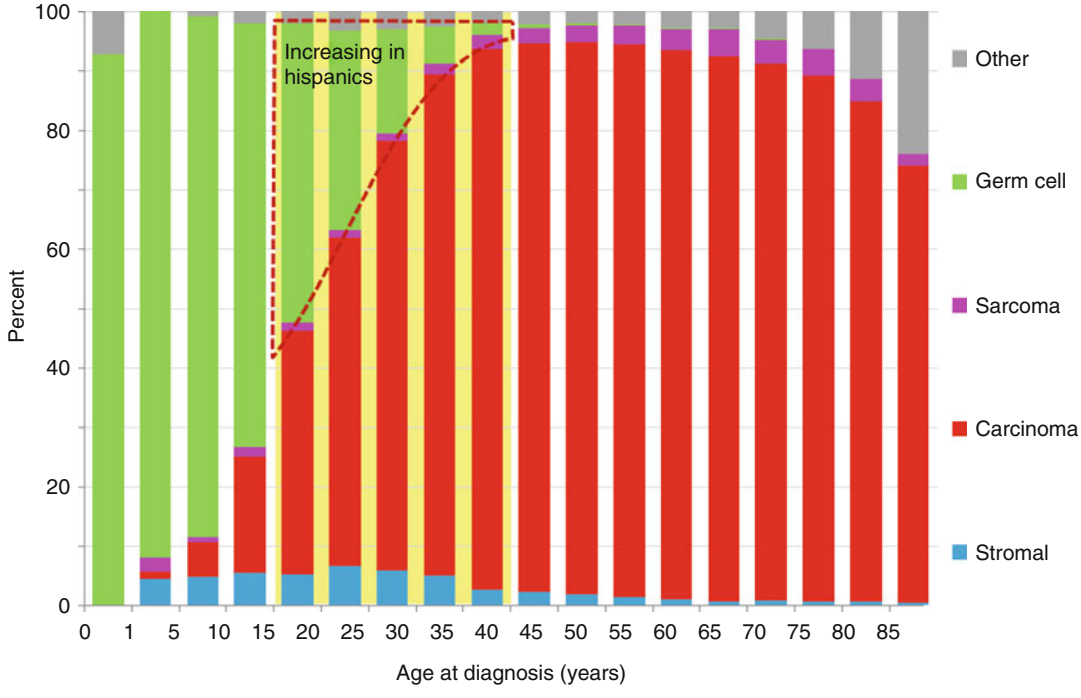

Fig. 11.3 Distribution of ovarian cancer by stage at diagnosis, United States SEER 18 regions, 2000–2011

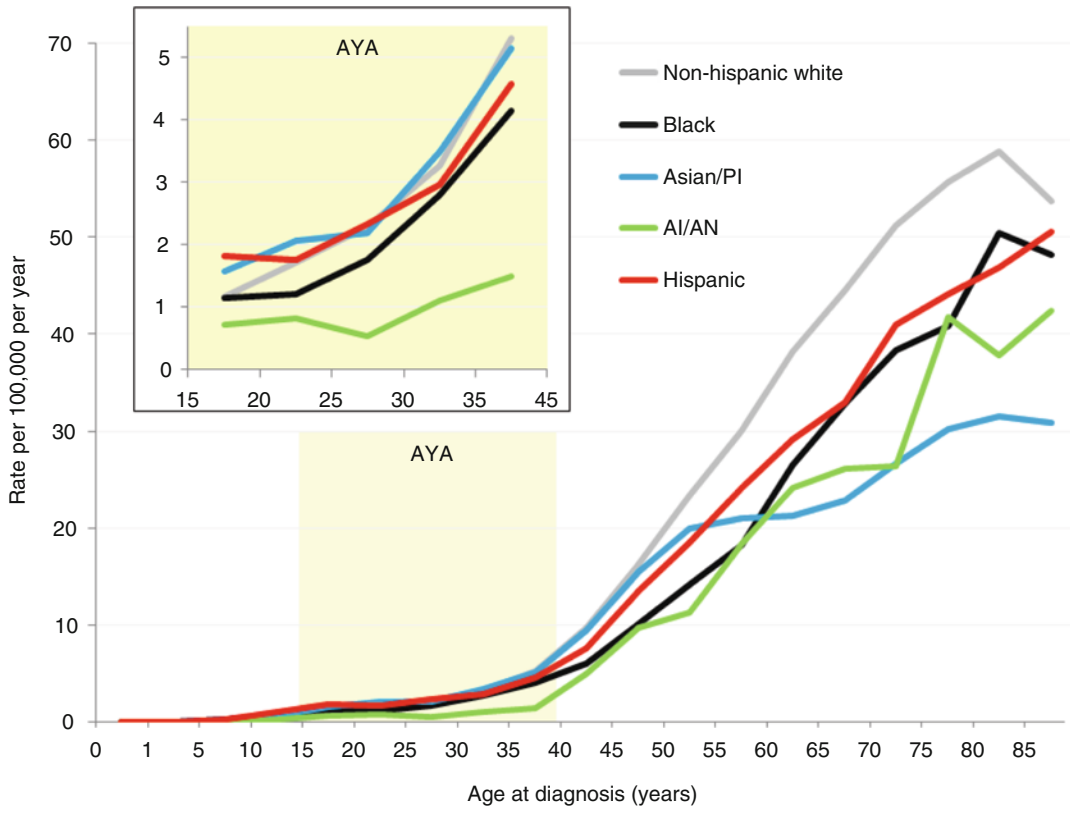

Fig. 11.4 Incidence of ovarian cancer, United States SEER 18 regions, 2000–2011, by age and race/ethnicity

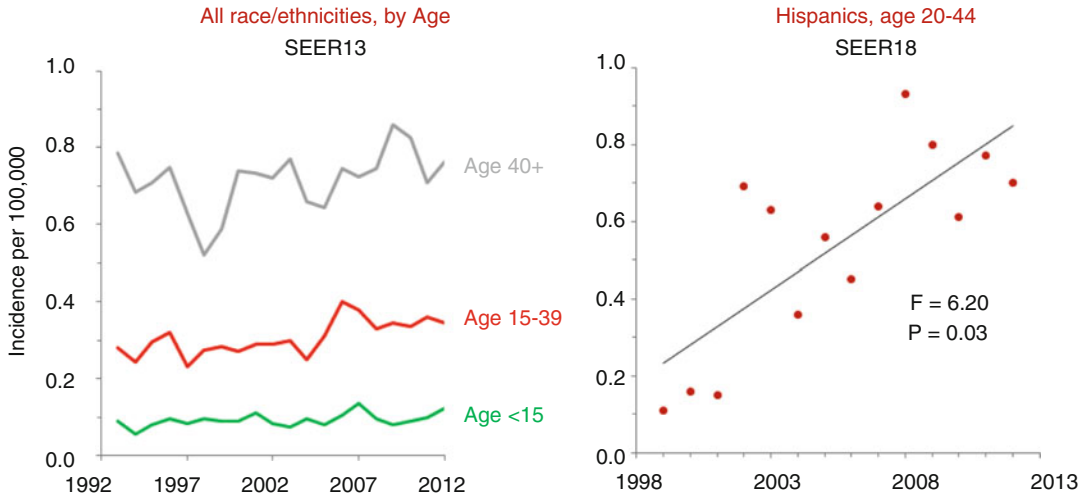

Fig. 11.5 Annual incidence of ovarian GCTs, United States SEER 9 regions, 1975–2011, by age

States since 1996 [4]. However, the incidence of GCT has increased slightly in premenopausal Asian women and substantially in premenopausal Hispanic women since 1973. In 20- to 44-year old Hispanic women, whose incidence can only be tracked in SEER since 1992, the diagnosis of ovarian GCTs is dramatically increasing, especially since the late 1990s

(Fig. 11.5). No other age or ethnic group demonstrates this trend. Potential explanations for this increase include improved reporting, disparate use of oral contraceptives, increasing obesity in this demographic, and delay of childbirth to an older age.

11.2.2 Pathology and Biology

There are multiple tissue types present in the normal ovary, including germ cells, stroma, and surface epithelium (Tables 11.1 and 11.2). Table 11.2 lists all the histologic types reported in at least ten AYA females (age 15–39) during 2000–2011 in the SEER 18 regions of the United States. Each of these can give rise to a set of distinctive tumors that can occur in pure or combined forms. The majority of ovarian malignancies involve germ cells. Epithelial and stromal tumors become more prevalent throughout the adolescent and young adult years.

11.2.2.1 Germ Cell Tumors

Germ cell tumors (GCTs) arise from germ cells present in the normal ovary. Benign GCTs are almost always teratomas. Malignant GCTs include dysgerminoma, immature teratoma, yolk sac tumors, embryonal carcinoma, polyembryoma, and nongestational choriocarcinoma and are derived from one or more types of primitive cells or malignant adult components of teratomas [9]. They often display heterogeneous histologic differentiation with multiple histologic subtypes within the same tumor mass. Based on trial enrollment in the Pediatric Intergroup, 60–70 % of patients present with stage I disease, while 25–30 % present with advanced-stage disease. The stage distribution of malignant ovarian GCT in girls older than 12 years was 36 % stage I, 8 % stage II, 46 % stage III, and 10 % stage IV. Most early-stage tumors are mixed GCTs, comprised of immature teratomas with elements of yolk sac tumor. Among 74 high-risk patients with stage III–IV disease, the most common histologies were yolk sac tumors (38.9 %), dysgerminomas (23.6 %), and mixed GCTs (23.6 %) [10, 11]. Upon gross inspection, most malignant ovarian GCTs are unilateral and large, with a median size of 16 cm, ranging from 7 to 40 cm [8].

Historically, a 3-grade system has been used to characterize immature teratomas, but a two-tier

Table 11.1 World Health Organization classification of tumors

I. Germ cell tumors (GCT)
A. Primitive GCT
1. Dysgerminoma
2. Endodermal sinus tumor (yolk sac tumor)
3. Embryonal carcinoma
4. Polyembryoma
5. Nongestational choriocarcinoma
6. Mixed GCT
B. Biphasic or triphasic teratoma
1. Immature teratoma (grades 1–3)
2. Mature teratoma
3. Solid
4. Cystic (dermoid)
5. Fetiform teratoma
C. Monodermal teratoma and somatic-type tumors
1. Thyroid (struma ovarii)
2. Carcinoid
3. Neuroectodermal
4. Carcinoma
5. Melanocyte
6. Sarcoma
7. Sebaceous
8. Pituitary type
9. Other
II. Sex cord-stromal tumors
A. Granulosa cell tumors (adult, juvenile)
B. Sertoli-Leydig cell tumors
C. Gynandroblastoma
D. Sex cord tumor with annular tubules (SCTAT)
E. Pure stromal tumors (fibroma, thecoma, fibrosarcoma)
F. Other stromal tumors (sclerosing stromal tumor, Signet ring stromal tumor)
G. Steroid cell tumors (stromal luteoma; Leydig cell tumor; steroid cell tumor, not otherwise specified)
III. Epithelial ovarian cancers
A. Serous
B. Mucinous
C. Clear cell
D. Endometrioid
E. Brenner
F. Mixed
G. Undifferentiated

Adapted from Tavassoli and Deville [8]

Table 11.2 Incidence of ovarian cancer by histologic type, 2000–2011 SEER18 with ≥10 cases in AYAs of age 15–39 years

Histology	Incidence per 100,000, age adjusted			Number in SEER18		
Age (years):	<15	15–39	40+	<15	15–39	40+
SEER population ($\times 10^6$):	102.5	174.0	226.6			
8,460/3: papillary serous cystadenocarcinoma		0.35	6.33	2	581	14,531
8,380/3: endometrioid carcinoma		0.34	2.61	0	573	5,961
9,080/3: teratoma, malignant, NOS	0.13	0.26	0.03	137	450	57
9,060/3: dysgerminoma	0.07	0.22	0.02	70	389	32
8,480/3: mucinous adenocarcinoma		0.20	0.83	3	342	1,913
8,441/3: serous cystadenocarcinoma, NOS		0.17	3.92	1	289	9,009
8,470/3: mucinous cystadenocarcinoma, NOS		0.13	0.42	4	229	970
8,310/3: clear cell adenocarcinoma, NOS		0.11	1.29	0	187	2,983
8,620/3: granulosa cell tumor, malignant		0.10	0.3	4	176	684
9,071/3: yolk sac tumor	0.05	0.09	0.01	48	166	15
8,010/3: carcinoma, NOS		0.09	1.86	0	160	4,444
8,140/3: adenocarcinoma, NOS		0.09	3.59	0	146	8,379
8,462/1: serous papillary cystic tumor, borderline malig.		0.07	0.12	0	127	257
9,085/3: mixed germ cell tumor	0.06	0.07	0.01	57	122	14
8,000/3: neoplasm, malignant		0.06	1.44	1	109	3,539
8,472/1: mucinous cystic tumor of borderline malig.		0.06	0.12	0	109	262
8,323/3: mixed cell adenocarcinoma		0.06	0.88	0	106	2,010
8,461/3: serous surface papillary carcinoma		0.06	1.20	0	103	2,749
8,010/2: carcinoma in situ, NOS		0.05	0.09	2	88	207
8,442/1: serous cystadenoma, borderline malignancy		0.04	0.08	0	72	170
8,041/3: small cell carcinoma, NOS	0.01	0.04	0.04	6	64	81
8,240/3: carcinoid tumor, malignant		0.04	0.09	1	61	197
8,631/3: Sertoli-Leydig cell tumor, poorly differentiated	0.01	0.02	0.02	7	36	45
8,260/3: papillary adenocarcinoma, NOS		0.02	0.55	0	28	1,271
8,070/3: squamous cell carcinoma, NOS		0.01	0.07	0	25	168
8,440/3: cystadenocarcinoma, NOS		0.01	0.15	0	24	354
8,471/3: papillary mucinous cystadenocarcinoma		0.01	0.05	0	24	125
8,634/3: Sertoli-Leydig, poor diff. w. heterologous		0.01	0	2	22	9
9,090/3: struma ovarii, malignant		0.01	0.02	0	22	34
8,950/3: Mullerian mixed tumor		0.01	0.38	0	20	876
9,064/3: germinoma	0.01	0.01	0	11	18	9
8,560/3: adenosquamous carcinoma		0.01	0.04	0	16	101
8,020/3: carcinoma, undifferentiated type, NOS		0.01	0.11	0	15	242
8,050/3: papillary carcinoma, NOS		0.01	0.15	0	12	352
8,255/3: adenocarcinoma with mixed subtypes		0.01	0.09	0	12	201
9,084/3: teratoma with malignant transformation		0.01	0.01	0	12	34
8,450/3: papillary cystadenocarcinoma, NOS		0.01	0.07	0	11	155
8,590/3: sex cord-gonadal stromal tumor, malig., NOS		0.01	0.01	1	11	20
9,081/3: teratocarcinoma		0.01	0	1	11	2
9,100/3: choriocarcinoma		0.01	0	2	11	7
8,246/3: neuroendocrine carcinoma		0.01	0.04	0	10	101
8,470/2: mucinous cystadenocarcinoma, noninvasive		0.01	0.01	0	10	14
8,980/3: carcinosarcoma, NOS		0.01	0.30	0	10	700

system has been proposed due to interobserver and intraobserver inconsistency with the 3-grade system [12]. Tumors should be sampled well (one block for each centimeter of the largest tumor diameter).

Investigators have identified molecular changes specific to GCTs, but clinical application is premature. Overexpression of specific microRNAs (miR 371Y373 and miR 302 clusters) appears to be present in all malignant ovarian GCTs and correlate with response [13]. These microRNAs may aid initial diagnosis and have utility in monitoring response to treatment. In addition, advanced dysgerminomas harbor KIT mutations, which may be a targetable mutation in some patients with advanced metastatic or recurrent disease [14].

Ovarian GCTs bear many histologic and biologic similarities to testicular GCTs (seminomas). However, testicular GCTs in males tend to arise several years after the development of puberty, while ovarian GCTs in females can occur anytime after birth and are much more common in preadolescents. Genetic analysis of ovarian GCTs that present in the second decade of life reveals isochromosome 12p, the characteristic cytogenetic abnormality found in testicular GCT [15–17]. Biologic studies from early cooperative pediatric GCT trials showed that such cytogenetic aberrations were age dependent. Chromosome I(12p) abnormality has been reported in tumors from pubertal and postpubertal males, but the most common abnormalities in prepubertal females in order of prevalence were gains of 1q, +14, +8, +12, +2, +3, and +7 [18].

Comparative genomic hybridization (CGH) has demonstrated recurrent deletions of 6q and 1p in childhood yolk sac tumors [19]. The most commonly detected region of loss was 6q25-6qter, a finding which is noted in several other human tumors, including ovarian, breast, and hepatocellular carcinoma. Multipotent imprinting analysis showed that gonadal and nongonadal GCTs are derived from primordial germ cells that have lost imprinting of small nuclear ribonucleoprotein N (SNRPN) gene and partial loss of H19 and IGF2 [20]. Cooperative pediatric GCT trials from Pediatric Oncology Group (POG)/Children's Cancer Group (CCG) and Maligne Keimzelltumoren (MAKEI) found that all pure teratomas had normal CGH patterns [21]. Although there were few ovarian GCT specimens in these studies, monoallelic expression of H19 and IGF2 was seen, suggesting no loss of imprinting. Further studies are needed in adolescents and young adults with ovarian GCTs to identify genes that are important to pathogenesis and therefore potential targets for future treatments.

11.2.2.2 Sex Cord-Stromal Tumors

Sex cord-stromal tumors originate from the specialized gonadal stromal cells and their precursors. Granulosa cells and Sertoli cells arise from sex cord cells, while theca cells, Leydig cells, lipid cells, and fibroblasts arise from stromal cells and their pluripotent mesenchymal precursors. These tumors can occur as an isolated histologic type orin combination, and together they account for 7 % of all ovarian malignancies [22] and approximately 5 % of ovarian malignancies in women ages 15–24 years [5]. Granulosa cell tumors are the most common subtype and have both adult and juvenile subtypes. Juvenile granulosa cell tumors are more often found in the AYA population, but adult-type tumors can be found in this age range as well; diagnosis is made by histologic criteria and not patient age [23].

Gross inspection usually reveals a unilateral solid adnexal mass, often yellow and multilobulated in appearance or hemorrhagic with hemoperitoneum. Definitive diagnosis can be difficult on frozen section, and immunohistochemical staining may ultimately be useful, as inhibin, calretinin, and FOXL2 may be expressed. A reticulin stain may also be positive in patients with adult granulosa cell tumor and help differentiate it from fibrothecoma.

Sertoli-Leydig cell tumors recapitulate the phases of testicular development and may act in an aggressive fashion. It is therefore essential to distinguish it from the benign Sertoli cell tumor, which consists only of Sertoli cells. These tumors are categorized into three forms: well-differentiated, intermediate differentiation (based on immature Sertoli cells), and poorly differentiated forms (sarcomatoid or retiform). Over 95 % are unilateral.

A subgroup of the sex cord tumor grouping is the ovarian sex cord tumor with annular tubules. The biologic behavior of this lesion is thought to be intermediate between granulosa cell tumors and Sertoli cell tumors and is associated with Peutz-Jeghers syndrome [24, 25]. Patients should be carefully screened for adenoma malignum of the cervix, as 15 % of patients harbor an occult lesion.

Significant progress has been made in the molecular biology of stromal ovarian tumors. A missense point mutation in the FOXL2 gene (a 402C to G mutation) has been found in nearly all adult granulosa cell tumors and has been absent in other pure subtypes of stromal tumors [26]. This may be useful in diagnosis and may present an opportunity for targeted therapy in the future.

The presence of DICER1 mutations in stromal tumors, especially Sertoli-Leydig cell tumors, marks a major discovery important in diagnosis and detection of a previously unrecognized familial syndrome. Schultz et al. analyzed kindreds of 325 children with pleuropulmonary blastoma (PPB), a childhood syndrome that is usually fatal unless detected early. Among this cohort, two of the three children with both PPB and Sertoli-Leydig cell tumors had germline DICER1 mutations. In addition, six family members had stromal ovarian cancers, and four of these six patients had germline DICER1 mutations [27]. Subsequently, 14 of 26 patients (60 %) with Sertoli-Leydig cell tumors had somatic DICER1 mutations; four also had germline DICER1 mutations [28]. Schultz et al. have founded an Ovarian Stromal Tumor Registry in order to better characterize these tumors and identify babies at risk for PPB as well as Sertoli-Leydig cell tumors.

11.2.2.3 Epithelial Carcinomas

The primary subtypes of epithelial carcinoma in young women are the serous and mucinous types, but BRCA-associated serous cancers, low malignant potential tumors, and clear cell carcinomas are also found in the AYA population [29]. Adenocarcinoma is found very rarely before the age of 24 years [5]. Little information is available about the biologic issues unique to young women with epithelial ovarian cancer. However, approximately 10 % of ovarian cancers are caused by mutations in the tumor suppressor genes BRCA1 and BRCA2, and high-grade serous tumors with BRCA1 mutations tend to occur in women at younger ages than non-BRCA-mutated cancers. Females with a personal history of ovarian cancer, breast and ovarian cancer, and breast cancer at age 50 or younger with a close relative with ovarian cancer or a close relative with male breast cancer at any age; women of Ashkenazi Jewish ancestry in whom breast cancer was diagnosed at age 40 years or younger; or women with a close relative with a known BRCA mutation should be tested, and family members should be offered testing should the results of the index patient be positive. Not only is BRCA testing useful for confirmation of pathology, but AYA patients with a BRCA mutation require specific counseling regarding medical and surgical risk reduction [30].

Low-grade serous ovarian carcinomas are also found in women at a younger age than the typical high-grade serous ovarian counterpart. A two-tier grading system has been proposed to improve consistency in diagnosis. In this system, low-grade serous tumors have mild to moderate nuclear atypia and a mitotic index of up to 12 mitoses/10 high-power fields [31]. Analysis of clustering supports this approach, as high-grade serous ovarian cancers have a profile distinct from low-grade and borderline tumors, which resemble each other. Compared with high-grade serous ovarian cancer, low-grade serous ovarian cancers are more likely to express estrogen/progesterone receptors and e-cadherin and less likely to express p53, bcl2, WT1, HER-2/neu, c-KIT, Ki-67, or MMP-9 [32, 33].

Clear cell carcinomas may also occur in the AYA patient, and these tumors show a preponderance of ARID1A mutations.

11.2.2.4 Tumors of Low Malignant Potential

Tumors of low malignant potential (LMP) represent a category of neoplasms that are distinct from benign cystadenomas and cystadenocarcinomas. First described by Taylor in 1929, they have since been referred to as borderline tumors

or atypically proliferating tumors [34, 35]. These tumors arise from the surface epithelium of the ovary, and 80–95 % are of serous or mucinous histology. LMP tumors of the ovary comprise approximately 15 % of all epithelial ovarian tumors, and 71 % occur in premenopausal women at a median of 40 years [36–38]. The pathologic criteria for diagnosis of these tumors include the absence of stromal invasion in the ovary and any two of the following characteristics: epithelial "tufting," multilayering of the epithelium, mitotic activity, and nuclear atypia. Trisomy 12 has been reported in LMP tumors [39].

11.2.3 Presentation and Evaluation

Despite their low incidence, ovarian tumors represent a major diagnostic and treatment dilemma for treating physicians. While optimal care is provided through a multidisciplinary approach incorporating pediatric oncologists, pediatric surgeons, and gynecologic oncologists, this is often not the case. The rare nature of these diseases leads to lack of awareness by some treating physicians and may result in unnecessary second surgeries, otherwise unnecessary adjuvant therapy, and failure to preserve fertility and lack of age-appropriate care. Adolescents with ovarian tumors are grossly underrepresented on clinical trials, whether pediatric or adult cooperative group in origin, a finding which may adversely affect survival [40].

Appropriate treatment of ovarian tumors is determined by many factors, including patient age, karyotype, extent of disease, tumor histology, and comorbid conditions. Conservative surgery to maintain reproductive potential is an important consideration in all adolescents and young adults and is usually feasible. Appropriate surgical staging and assessment are necessary components in determining the extent of surgery required and the need for postoperative chemotherapy. An appropriate initial evaluation should be used to tailor therapy.

The most common presenting signs and symptoms of an ovarian tumor are abdominal pain, palpable abdominal mass, increasing abdominal girth, urinary frequency, constipation, and dysuria [41, 42]. Some tumors are asymptomatic and are discovered during routine examination. Abdominal pain is most often chronic, but torsion of an enlarged ovary can result in acute pain. Since normal stromal cells produce steroid hormones, physical manifestations of excess estrogen or androgen production (early menarche, hirsutism, virilism) suggest the possibility of a sex cord-stromal tumor. Gynandroblastomas, while rare, are composed of granulosa cells, tubules, and Leydig cells and can cause premature breast development, hyperestrogenism, or androgenism in adolescents [24, 25]. Isosexual precocity may also be seen in mixed malignant GCTs due to tumor production of β-HCG [43]. A complete history and physical examination should be performed, including abdominal palpation. Pelvic and rectal examination by a skilled practitioner should be considered and performed when appropriate; this may be delayed to an examination under anesthesia in the very young.

A panel of laboratory values should be obtained, including αFP, β-HCG, lactate dehydrogenase (LDH), CA-125, carcinoembryonic antigen (CEA), estradiol, testosterone, F9 embryoglycan, inhibin A and B, and anti-Mullerian hormone (AMH) [39, 44]. Elevated alpha fetoprotein (αFP) usually indicates a component of yolk sac tumor. An elevation of β-human choriogonadotropin (β-HCG) is always seen in choriocarcinoma but may also be present in embryonal carcinoma, polyembryoma, pure ovarian dysgerminoma, and mixed germ cell tumors [41, 44] (Table 11.3).

Imaging studies may include a pelvic ultrasound to delineate the characteristics of the pelvic

Table 11.3 Serum tumor markers in malignant tumors of the ovary [9, 10]

Tumor	hCg	aFP	ldH	Ca-125
Dysgerminoma	±	–	+	
Yolk sac tumor	–	+	±	
Immature teratoma	–	±	±	Rarely+
Embryonal carcinoma	+	+	±	
Choriocarcinoma	+	–	–	
Polyembryoma	±	±	±	
Mixed	+	+	+	
Epithelial				±

organs, specifically the ovaries. Specific characteristics may suggest the diagnosis, such as the presence of teeth in teratomas. A computed tomographic (CT) scan of the abdomen and pelvis may be helpful to determine the extent of disease preoperatively. If the ovarian mass is complex or solid, over 8 cm, and has persisted for more than 2 months, or if there is evidence of extraovarian disease, surgical exploration is indicated [45].

Gonadal dysgenesis, a developmental anomaly in which sex steroid production is diminished, is a risk factor for malignant ovarian GCTs. Patients may present with delayed puberty or primary amenorrhea. Malignant ovarian GCTs, especially dysgerminomas, can develop in up to 30 % of patients with Swyer syndrome (complete gonadal dysgenesis, with a 46 XY genotype and a female phenotype). Prophylactic removal of both gonads is indicated upon diagnosis of this syndrome [46]. Gonadoblastoma can develop in patients with Turner syndrome when mosaicism includes a Y chromosome [47]. These women should be screened with yearly transvaginal ultrasound and CA-125 beginning at age 25–30 years, and they should consider prophylactic oophorectomy after completion of childbearing or at the age of 35 years [48].

Based on this information, the evaluation for a young patient with an adnexal mass suspicious for malignancy should include routine preoperative blood work, chest radiograph, serum tumor markers guided by symptoms and signs, pelvic/transvaginal ultrasonography, and CT of the abdomen/pelvis. Indications for surgery in a child with an ovarian mass include persistent pain, suspicion of torsion, hydronephrosis, complex or solid mass on imaging, metastasis, ascites, positive tumor markers, unclear origin of mass, persistence or growth of cyst on serial imaging, large masses with complex features, and rapid virilization, estrogenization, or precocious puberty [49].

11.2.4 Surgical Treatment Guidelines

11.2.4.1 Surgical Management

When an adolescent or young adult patient presents with an adnexal mass, precise histology is often difficult to determine during intraoperative pathology consultation. Gross inspection does not yield a diagnosis, and recommendations for adjuvant therapy can only be based on final pathology with complete staging information. Therefore, it is imperative that the surgeon obtains the necessary information to determine the diagnosis and need for further therapy while preserving fertility in these young patients. The goals of surgery are to obtain the diagnosis, perform comprehensive surgical staging in clinically apparent early disease, and perform maximal cytoreductive surgery in patients with advanced disease. Often, this must be done in the setting of unclear intraoperative pathology, and the surgeon must then rely on preoperative imaging and tumor markers to gauge the extent of surgery [49]. The balance is obtaining enough appropriate samples to guide therapy, treat the disease surgically, and preserve reproductive function while avoiding the need for re-exploration. Immediate consultation with a gynecologic oncologist, if not done preoperatively, should occur intraoperatively at the time of diagnosis.

Fertility-Sparing Surgery

Young women who present with ovarian masses generally have many concerns regarding future reproductive potential. Preoperative discussions should occur to review options for maintaining ovarian and/or uterine function based on potential operative findings. In general, the unilateral nature of most of these tumors, preponderance of early-stage disease, and effective chemotherapy have allowed the successful use of conservative, fertility-sparing surgery in most adolescent and young adult patients with limited disease [45, 50]. An early report of 182 patients with early-stage ovarian germ cell tumors revealed no decrease in survival when fertility-sparing surgery was performed [51]. Since that time, fertility-sparing surgery has become the standard of care for AYA patients with limited disease, and it is now reported in the majority of patients [52–54]. While one report has focused on ovarian cystectomy [55], the standard of care refers to unilateral salpingo-oophorectomy with preservation of a normal-appearing contralateral adnexa and uterus [45]. Due to the low yield from random ovarian biopsy, and the potential

for disruption of reproductive potential due to adhesions or trauma, the routine biopsy of a normal-appearing contralateral ovary is not advised [56]. These recommendations hold true for patients with germ cell tumors, sex cord-stromal tumors, and epithelial carcinomas [25, 57]. Consideration should be given to removal of the residual ovary once childbearing is complete [29].

One caveat to fertility-sparing surgery is the diagnosis of dysgenetic gonads, which must prompt bilateral salpingo-oophorectomy. This finding is rarely associated with dysgerminoma, in which a dysgenetic gonad is present in a phenotypically normal female with abnormal karyotype. The contralateral dysgenetic or "streak" gonad also carries a high potential for a future malignant GCT. Therefore, in cases of intraoperative diagnosis of dysgerminoma, the pathologist should be asked to carefully evaluate any residual normal ovary and look for any elements of gonadoblastoma. As the pathologist is evaluating the specimen further, the surgeon should inspect the contralateral adnexa to determine whether a normal ovary or streak gonad is present. Normal ovarian tissue excludes the possibility of dysgenetic gonads, thereby allowing the surgeon to conserve the contralateral ovary and preserve reproductive potential. However, in the event of a "streak" gonad or diagnosis of gonadoblastoma, a bilateral salpingo-oophorectomy should be performed to remove any gonadal tissue, regardless of age [45, 58].

Even in the rare circumstance where both ovaries must be removed, the uterus should be left in place to allow for future assisted reproductive techniques using donor oocytes [56, 59, 60]. The only absolute indication for uterine removal in this group of patients is adenoma malignum of the cervix in patients with Peutz-Jeghers syndrome associated with ovarian sex-cord tumor with annular tubules [24, 25].

When an adnexal mass is found to be a mature cystic teratoma, areas of squamous differentiation and small nodules in the wall of the cyst should be evaluated for malignant elements or for immature neural tissue. These indicate malignancy and should prompt surgical staging. If no malignant elements are identified, the neoplasm is benign and an ovarian cystectomy is sufficient. The contralateral ovary should be inspected, as 12 % of cases are bilateral. If a cyst is found in the contralateral ovary, a cystectomy should be performed, preserving as much normal ovarian tissue as possible. The cyst should be sent for immediate histologic evaluation, and if malignant disease is revealed, bilateral oophorectomy is performed. In 5–10 % of malignant GCTs, there is an associated contralateral benign mature cystic teratoma, and in these situations, the remainder of the benign ovary can be preserved [61].

Patients with large ovarian cysts where the cortex has become quite thin still benefit from cystectomy with preservation of as much healthy cortex as possible, as this continues to function postoperatively [49].

Comprehensive Surgical Staging

The majority of AYA patients with a malignant adnexal mass present with clinically early-stage disease. The patient with no gross extraovarian disease should undergo comprehensive surgical staging in order to determine the stage, need for adjuvant therapy, and prognosis, as up to 30 % of patients can have occult disease. Staging consists of cytologic washings, infracolic omentectomy, and peritoneal biopsy specimens from each paracolic gutter, the vesicouterine fold, and the pouch of Douglas. The bowel should be inspected from the ileocecal valve to the ligament of Treitz, specifically evaluating for tumor implants and sites of obstruction. All peritoneal surfaces should be carefully inspected. Any suspicious areas should be sampled. Pelvic and para-aortic lymph node sampling is recommended for full staging, except in patients with sex cord-stromal and mucinous carcinomas [62, 63].

A different approach has been espoused in pediatric patients with ovarian germ cell tumors. A review of deviations from standard surgical guidelines failed to show any impact on survival. Therefore, a proposal for more limited surgical staging includes collection of ascites or cytologic washings, examination of peritoneal surfaces with biopsy or excision of any nodules but no random biopsies of normal-appearing peritoneum, examination and palpation of retroperitoneal lymph nodes and sampling only of any firm or enlarged

nodes, inspection and palpation of omentum with removal only of any adherent or abnormal areas, biopsy of any abnormal areas, and complete resection of the tumor-containing ovary with sparing of the fallopian tube if uninvolved [56]. This approach omits random biopsies of peritoneum, systemic lymphadenectomy, omentectomy, and salpingectomy and targets only tissue that is abnormal upon inspection. This has been suggested only for pediatric germ cell tumors, and prospective evaluation is in the planning stage.

Patients with malignancies who have not been staged at the time of their initial surgery present a dilemma – should reoperation proceed solely for the purpose of comprehensive surgical staging? For patients with apparent early invasive epithelial cancers (e.g., mucinous and clear cell carcinomas), comprehensive surgical staging is the standard approach, as the recommended treatment may drastically change with upstaging and outcomes in the setting of recurrent disease are dismal. In patients with apparent early-stage borderline tumors, germ cell tumors, and sex cord-stromal tumors, however, one approach is to obtain imaging studies and, if negative, omit a second procedure for surgical staging. This approach is supported in GCTs by the pediatric intergroup study, as noted above, and by a recent report from the Multicenter Italian Trials in Ovarian Cancer (MITO) group, in which 21/26 patients with clinically apparent early-stage pure ovarian dysgerminoma were unstaged at primary surgery. No additional surgery was performed and no adjuvant chemotherapy was given; three patients relapsed and all were cured [64]. Patients with evidence of limited extraovarian GCT who did not have complete staging do not usually warrant repeat surgery, as chemotherapy is indicated.

Route of Surgery

The standard route of surgery has been laparotomy through a vertical skin incision to ensure access for comprehensive staging or cytoreduction. Indeed, patients with evidence of metastatic disease, hemoperitoneum, or a large adnexal mass should have surgery performed via an open approach. Progress in minimally invasive surgery (MIS) has demonstrated that a laparoscopic or robot-assisted surgery is a viable approach for adnexal disease that appears to be limited to one ovary when a gynecologic oncologist skilled in MIS is available. The adnexa should always be removed in a specimen containment bag to prevent seeding of other structures or the scar. Once in the bag, cystic areas can be aspirated without intraperitoneal contamination in order to effect decompression and allow removal through an enlarged port site or minilaparotomy [49]. The tumor should never be morcellated intraperitoneally to effect laparoscopic removal, as this can upstage the patient. MIS should be the surgical approach of choice when a patient undergoes a second surgery for staging after an incomplete initial surgery [45].

Rupture of the Cyst

Every attempt should be made to avoid rupture, as this upstages an otherwise stage IA or IB carcinoma. The impact of intraoperative (iatrogenic) rupture on patient outcome appears to vary based on histology. Multiple studies suggest that while surface involvement or malignant ascites portends a worse prognosis than disease confined to the interior of one ovary, outcomes of patients with clear cell carcinoma who have iatrogenic rupture are no different than patients with true stage IA disease [65–68]. This also appears to be true for patients with other epithelial cancers, including endometrioid ovarian carcinoma, and pediatric ovarian neoplasms [69–71]. Tumor rupture does appear to increase the risk for recurrence in borderline ovarian tumors and granulosa cell tumors, so rupture should still be avoided [72, 73]. Fresneau et al. have demonstrated that in AYA patients with intraoperative rupture of granulosa cell tumor, adjuvant postoperative chemotherapy can effectively prevent recurrence [74].

Cytoreductive Surgery

If there is extraovarian disease, the surgeon must first determine if the disease can be resected to less than 1 cm of residual disease. This concept of a maximal cytoreductive surgical effort is imperative to a successful outcome. Every attempt should be made to remove all visible disease, as patients with no macroscopic disease at the completion of

the surgical procedure have the best prognosis. If the largest residual focus of disease after tumor reductive surgery is 1 cm or less, this is referred to as "optimal cytoreduction" and connotes a significant survival benefit. If the tumor is unresectable to this extent, leaving residual disease greater than 1 cm in any one location, this is considered "suboptimal," and the patient should have appropriate surgery to relieve symptoms and the procedure should then be terminated. That is, if an impending bowel obstruction exists, a bowel resection and reanastomosis should be performed; if the patient has a large amount of ascites with an omental cake, an omentectomy should be performed. However, there is no justification for performing extensive tumor reductive surgery if a focus of disease greater than 1 cm will remain at the completion of the surgery. Preservation of reproductive capacity in patients with advanced invasive epithelial ovarian cancer cannot be advised; in these patients, the uterus, cervix, tubes, and ovaries should be removed [8].

Treatment for patients with epithelial tumors who have had inadequate staging is a difficult issue. If the patient has documented large residual disease with a limited initial attempt at tumor reduction, repeat exploration with staging and tumor reductive surgery is indicated.

The extent of surgery in the setting of widespread disease in malignant ovarian germ cell tumors remains an area of discussion. Since these tumors are so chemosensitive, it has been suggested that less radical surgery may be warranted, but this remains theoretical at present and the standard remains maximal cytoreduction.

11.2.4.2 Staging

The International Federation of Gynecology and Obstetrics (FIGO) updated its staging system for ovarian tumors in 2014 (Table 11.4) [75]. Previous versions of this system provided the basis for several pediatric GCT staging systems [76, 77]. Modifications to the FIGO staging by the POG/CCG Intergroup led to a staging system that was similar to other staging systems used in childhood malignancies (Table 11.5). While the idea of stage determining prognosis and treatment recommendations is consistent across

Table 11.4 Modified (2014) International Federation of Gynecology and Obstetrics (FIGO) staging system [73]

Stage I: tumor confined to ovaries or fallopian tube(s)
Stage IA: tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
Stage IB: tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
Stage IC: tumor limited to one or both ovaries or fallopian tubes, with any of the following:
Stage IC1: surgical spill
Stage IC2: capsule ruptured before surgery or tumor on ovarian or tubal surface
Stage IC3: malignant cells in ascites or peritoneal washings
Stage II: tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
Stage IIA: extension and/or implants on the uterus and/or tubes and/or ovaries
Stage IIB: extension to other pelvic intraperitoneal tissues
Stage III: tumor involves one or both ovaries or tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
Stage IIIA1: positive retroperitoneal lymph nodes only (cytologically or histologically proven)
Stage IIIA1(i): metastasis up to 10 mm in greatest dimension
Stage IIIA1(ii): metastasis more than 10 mm in greatest dimension
Stage IIIA2: microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
Stage IIIB: macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
Stage IIIC: macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to the capsule of the liver and spleen without parenchymal involvement of either organ)
Stage IV: distant metastasis excluding peritoneal metastases
Stage IVA: pleural effusion with positive cytology
Stage IVB: parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Table 11.5 Pediatric intergroup trial (POG/CCG) – ovarian staging [74, 75]

I. Limited to the ovary, peritoneal washings negative for malignant cells; no clinical, radiological, or histologic evidence of disease beyond the ovaries (gliomatosis peritonei did not result in upstaging); tumor markers negative after appropriate half-life decline
II. Microscopic residual or positive lymph nodes (<2 cm); peritoneal washings negative for malignant cells (gliomatosis peritonei did not result in upstaging); tumor markers positive or negative
III. Gross residual or biopsy only, tumor-positive lymph nodes(s) >2 cm diameter; contiguous visceral involvement (omentum, intestine, bladder): peritoneal washings positive for malignant cells
IV. Distant metastases that may include the liver

staging systems, the FIGO system is based on surgical findings, and the POG/CCG Intergroup system is based on results of surgical resection. Groups are currently working together to develop a unified staging system applicable to all patients with ovarian malignancies.

11.2.5 Chemotherapy

11.2.5.1 Germ Cell Tumors

The current treatment regimen for all patients with resected early-stage GCTs of the ovary is adjuvant therapy with bleomycin, etoposide, and cisplatin (BEP) (Table 11.6) [78]. The only exceptions to this schema are patients with stage IA or IB, grade 1 immature teratoma, and stage IA pure dysgerminoma. These patients should not receive adjuvant chemotherapy, but should be closely observed following surgery [79]. In addition, there is also an increasing body of literature supporting no post-surgical treatment (observation only) in patients with any stage I GCT [80, 81]. Future clinical trials are expected to address and resolve this issue. When evaluating a patient, however, caution must be employed in labeling ovarian GCT as stage I. In a localized POG/CCG trial, surgical guidelines were followed in only 1 out of 56 patients. Since all patients subsequently received BEP, surgical attention to guidelines was not essential [11]. However, in trials where low-stage tumors are not treated with adjuvant chemotherapy, adherence to surgical guidelines will be critical.

Table 11.6 Bleomycin, etoposide, and cisplatin (BEP) regimen

Hydration and antiemetic regimen is administered, consisting of:
Granisetron 1 mg IV 30 min prior to cisplatin daily for 5 days or
Ondansetron 0.15 mg/kg IV 30 min prior and 4 h after cisplatin daily for 5 days plus
Dexamethasone 20 mg IV 30 min prior to cisplatin on days 1 and 2 plus
Aprepitant 125 mg PO on day 1 and 80 mg PO on days 2 and 3, prior to cisplatin infusion
Chemotherapy is then administered as follows:
BEP (adult)
Bleomycin 30 U/m^2 in 250 mL normal saline (NS) intravenously over 24 h on day 1; or 10 U/day on days 1–3;
or 10 U/day on days 1, 8, and 15;
or 30,000 IU weekly for 12 weeks, with the fourth course consisting of EP alone; maximum total bleomycin dose not to exceed 270 mg
Etoposide 100 mg/m^2 per day in 1 L 5 % dextrose in NS intravenously over 2 h on days 1, 2, 3, 4, 5
Cisplatin 20 mg/m^2 per day in 1 L NS with 50 g mannitol intravenously over 4 h on days 1, 2, 3, 4, 5
Regimen repeated every 3 weeks for 3–4 cycles
BEP (prepubertal children)
Bleomycin intravenous bolus 15 U/m^2 on day 1; max. dose 30 U
Etoposide intravenous infusion 100 mg/m^2 on days 1, 2, 3, 4, 5
Cisplatin[a] intravenous infusion 20 mg/m^2 on days 1, 2, 3, 4, 5

Regimen repeated every 3 weeks for three to four cycles
[a]For BEP, an accepted substitution for cisplatin among prepubertal children is carboplatin with a dose of AUC 7.9. This has less renal toxicity

While there is no consensus on the optimal number of treatment cycles, the authors suggest that patients with complete gross resection of disease should receive 3 cycles of BEP, and patients with incomplete resection of disease should receive 4 cycles of BEP. Historically, up to 6 cycles have been given, but concerns of lung toxicity and etoposide-induced leukemia limit this approach. Growth factors should be used when needed to assist recovery of leukocyte counts and to minimize associated treatment delays [10, 11]. These patients should be followed with CT and tumor markers; second-look surgery is not recommended [10].

Although patients with dysgerminoma have historically been noted to be sensitive to radiation therapy, chemotherapy with BEP is more effective, less toxic, and less likely to adversely affect reproductive potential and is therefore the first line of therapy. If LDH is elevated at diagnosis, levels can be followed to document serologic response and to detect subclinical recurrence. Radiation or chemotherapy may be used to treat biopsy-proven recurrent dysgerminoma.

Occasionally, patients with immature teratoma continue to have abnormal findings on imaging following chemotherapy. These patients usually have either benign mature teratoma or gliosis comprising the mass [82]. Likewise, patients with dysgerminoma who have a mass remaining at the conclusion of chemotherapy usually have only desmoplastic fibrosis [83]. CT-guided biopsy should be performed to confirm the absence of malignant disease, and the patient should be followed with serial imaging, reserving surgery for relief of symptoms.

No standard regimen exists for the unusual patient with a recurrent GCT. Regimens that have been useful include EMA-EP; vinblastine, ifosfamide, and cisplatin; TIP (paclitaxel, ifosfamide, and cisplatin); and ICE (ifosfamide, carboplatin, and etoposide; unpublished data, Thomas Olson). In selected patients one should consider consolidation with high-dose chemotherapy and stem cell rescue. This regimen in currently under investigation in the TIGER study, comparing TIP with high-dose chemotherapy using mobilizing paclitaxel plus ifosfamide followed by high-dose carboplatin and etoposide (TI-CE).

11.2.5.2 Sex Cord-Stromal Tumors

Adjuvant treatment for patients with surgically staged stage I disease is not indicated. Patients with stage IC disease may benefit from some adjuvant therapy such as paclitaxel and carboplatin or hormonal therapy with leuprolide acetate. Patients with more advanced disease are typically treated with combination chemotherapy, usually consisting of three to four courses of BEP [84]. A retrospective review of the utility of taxanes and platinum in this setting suggests activity, but confirmation of equivalent outcomes between these two regimens awaits results of the randomized trial that is currently underway [85, 86].

Adult granulosa cell tumors are indolent lesions and can recur many years, even decades, following initial diagnosis and treatment. When patients recur after a long progression-free interval, they are candidates for repeat tumor reductive surgery. With widespread disease or disease refractory to surgery, chemotherapy, hormonal therapy, and bevacizumab are options for treatment [87, 88]. Radiation is also occasionally employed in the treatment of localized or symptomatic disease.

Patients with Sertoli cell tumors do not require adjuvant chemotherapy, as these are benign tumors. Patients with Sertoli-Leydig cell tumors are treated based on specific criteria that are different than other histologic subtypes. Patients with disease greater than IB, with poorly differentiated tumors, or with heterologous elements present should be treated with BEP or paclitaxel and carboplatin [23, 89]. Patients can be followed with physical examinations and with serum αFP, inhibin, and testosterone levels. Of the 18 % of patients who recur, two-thirds do so within the first year after diagnosis. Additional platinum-based chemotherapy is the mainstay of treatment for recurrent disease.

Steroid cell tumors not otherwise specified are a distinct category of steroid cell tumor that can be malignant and aggressive; when diagnosed intraoperatively, these patients should be staged and aggressively cytoreduced, and adjuvant chemotherapy should be considered [8, 23]. Lipid cell tumors with pleomorphism, increased mitotic count, large size, or advanced stage should also receive additional postoperative platinum-based therapy [8, 23].

Patients should be followed at gradually increasing intervals with physical examinations and with markers. These include serum inhibin A and B, AMH, and CA-125 levels for granulosa cell tumors and inhibin, AFP, and testosterone levels for Sertoli-Leydig cell tumors.

11.2.5.3 Epithelial Tumors

Patients with stage IA or IB, grade 1 epithelial tumors can be treated with surgery alone. Patients with stage IA or IB, grade 2 epithelial tumors can either be treated with surgery alone or treated

with three to six cycles of chemotherapy with carboplatin and a taxane. Patients with stage IA or IB, grade 3 epithelial tumors and patients with stage IC or II of any grade should receive three to six cycles of chemotherapy with carboplatin and a taxane. By definition, clear cell carcinomas are considered grade 3, so patients should receive adjuvant chemotherapy according to the guidelines above at any stage [90].

11.2.5.4 Tumors of Low Malignant Potential

Multiple regimens of chemotherapy have been investigated for the treatment of advanced-stage tumors of low malignant potential (LMP). but no benefit in disease-free or overall survival (OS) has been demonstrated for any regimen at any stage. Therefore, chemotherapy is not administered to patients with LMP tumors of the ovary. A minority of patients with LMP tumors of the ovary will have invasive implants on staging biopsies. These patients have a worse prognosis and a higher recurrence rate than patients with noninvasive implants [91]. Since these invasive implants represent small foci of invasive carcinoma, treatment recommendations are similar to those for women with epithelial ovarian carcinoma.

11.2.6 Outcomes

11.2.6.1 Overall

Survival of women with cancer of the ovary has been inversely proportional to age. Compared with women over age 40, AYA women age 15–39 have a better 5-year relative survival (79.5% vs. 41.4%) [92]. However, improvement in the 5-year survival rate over the past quarter century has been less in 15- to 29-year-olds than in younger or

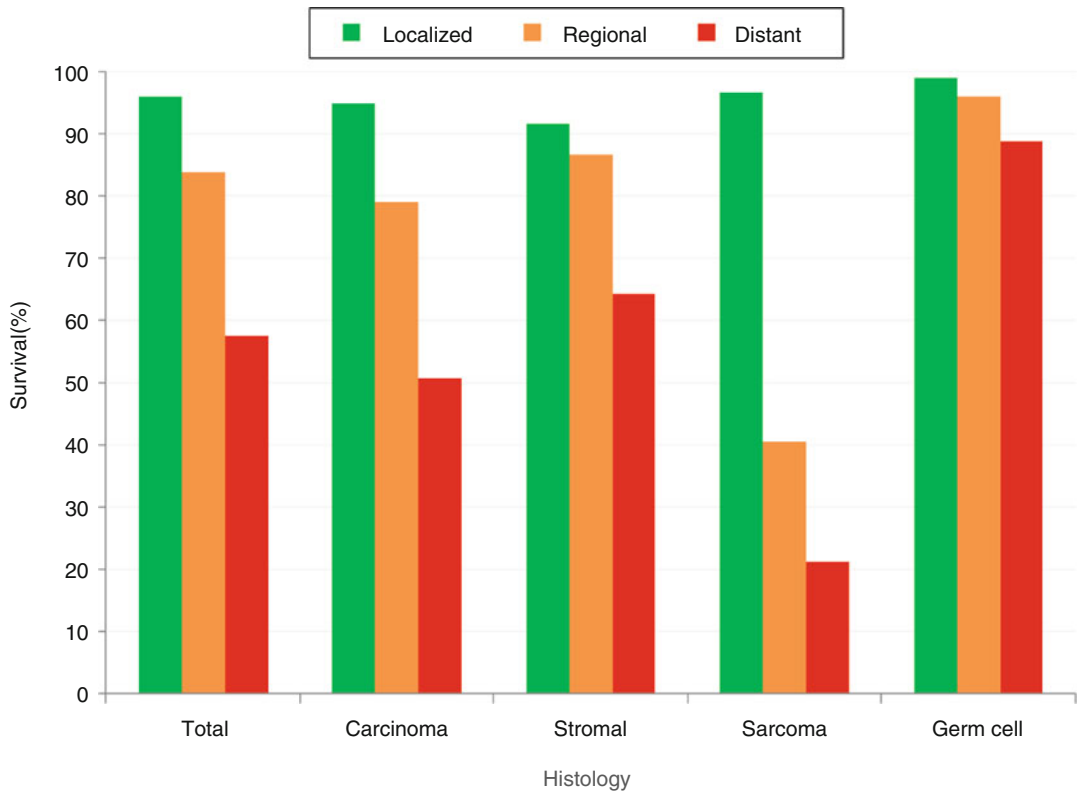

Fig. 11.6 5-year cancer-specific survival, AYA females (age 15–39), United States SEER 18 regions, 2000–2010, by histology and stage

older women, and a recent comparison of cancer survival trends in the United States shows no change in survival outcomes related to ovarian cancer in AYA females since 1992 [1, 92].

Figure 11.6 shows the 5-year cancer-specific survival for AYA females in the United States by histology and stage at diagnosis. Among AYAs, the 5-year ovarian cancer-specific survival rate was as low as 50% for those with distant metastasis at diagnosis. The 5-year ovarian cancer-specific survival was >95% for all AYAs with localized disease, except for stromal tumors, which reached 92%. Among AYAs with distant metastases at diagnosis, sarcomas presenting in the ovary had by far the worst 5-year cancer-specific survival (21%), and germ cell tumors had the best survival (89%).

Figure 11.7 depicts the 5-year cancer-specific survival of AYA women in the United States with ovarian cancer independent of race/ethnicity. In older women, however, blacks had the worst survival rates.

Figure 11.8 shows the 5-year cancer-specific survival trends for ovarian cancer in the United States by age and histology at diagnosis. While overall survival is much better than for older women, AYA women have had less improvement in the 5-year ovarian cancer-specific survival rate that either younger or older females.

Fertility after treatment for ovarian malignancies in AYA patients is a significant concern that should be addressed prior to surgery and/or chemotherapy. It appears that removal of one ovary leads to an elevated level of follicle-stimulating hormone at age 35–39, a decrease in anti-Mullerian hormone levels, an odds ratio for early menopause of 4.3, and a risk of infertility [49, 93]. Unfortunately, few facilities exist that have programs for oncofertility in young females. Ovarian tissue cryopreservation is a new approach to fertility preservation in prepubertal girls with cancer, though it is invasive. Girls who are at high risk of premature ovarian insufficiency may be candidates for this technique, in which ovarian tissue is

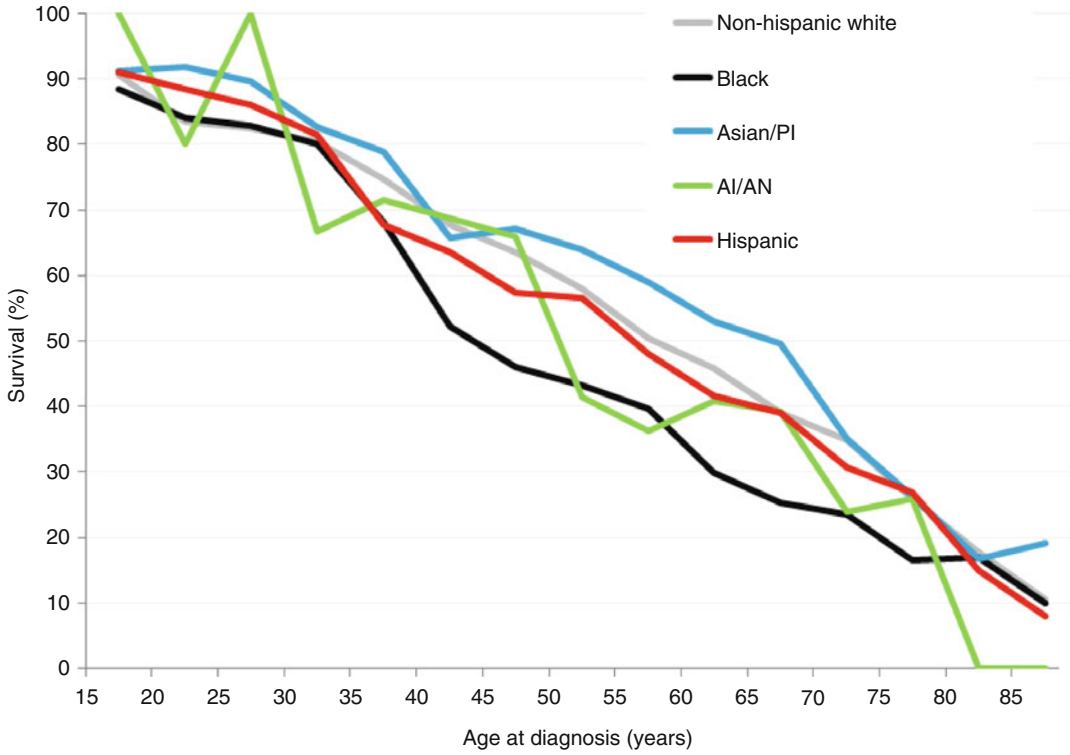

Fig. 11.7 5-year ovarian-cancer-specific survival, United States SEER 18 regions, 2000–2010, by age and race/ethnicity

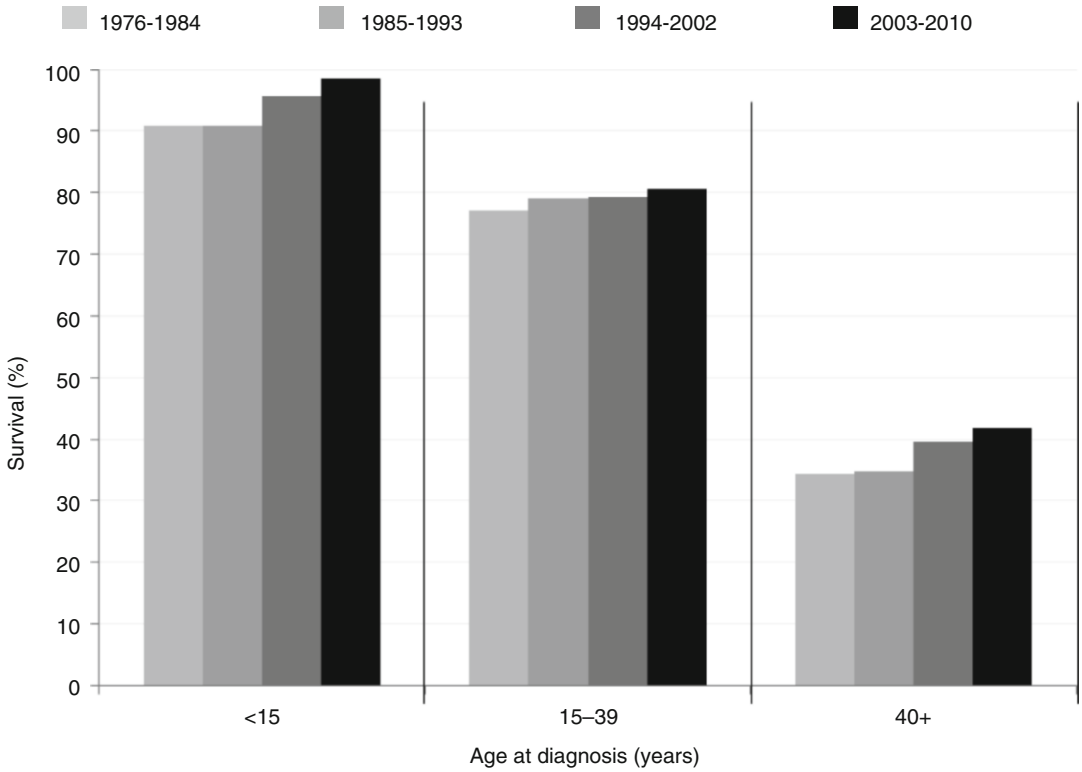

Fig. 11.8 5-year cancer-specific survival trends, ovarian cancer, United States SEER 18 regions, 1976–2010, by era and age

harvested, cryopreserved, and then reimplanted for the restoration of fertility or induction of puberty. Most females show restoration of ovarian function by 4 months after reimplantation, and over 60 live births have been reported (25 % of women followed after reimplantation) [94, 95].

The risk of secondary malignant neoplasms in AYA survivors following treatment for malignant ovarian germ cell tumors is significantly elevated [96]. Results of a Norwegian cohort study showed a second cancer in 23 of 139 women who had undergone cytotoxic therapy compared with 0 of 31 women who had surgery alone ($p = 0.08$) [97].

11.2.6.2 Germ Cell Tumors

Historically, patients with malignant ovarian GCTs treated with surgery alone had a poor survival rate, but with the advent of modern chemotherapy, most patients are cured. Prior to the consistent use of chemotherapy, the outcome for patients with ovarian nongerminomatous tumors was poor, with survival rates of 15–20 % [51]. Patients with germinomatous tumors could be cured with surgery alone [98, 99] or with surgery combined with chemotherapy [100]. In the POG/CCG Intergroup studies, patients were assigned treatment based on tumor histology (immature teratoma) and clinical (surgical) staging. Patients ($n = 44$) with ovarian immature teratomas were treated successfully with surgery and observation [79]. Despite the presence of yolk sac elements in resected specimens (13/44), only one patient relapsed and was salvaged with chemotherapy. In the POG/CCG study, all stage I/II ovarian GCTs were treated with four cycles of BEP, but only received 33 % of the adult bleomycin dose, due to concerns about pulmonary toxicity. Even at the reduced dose, there was a 6-year event-free survival (EFS) of 93 % and 6-year OS of 94 % in this group of patients [11]. Recent adult and pediatric studies suggest that patients with

stage I ovarian GCTs can be managed with surgery and observation [76]. In a report on 15 patients with ovarian stage I GCT (9 immature teratoma and 6 endodermal sinus tumors) treated with surveillance, only three relapsed (20 %), two of whom were salvaged successfully with chemotherapy. Salvage chemotherapy might be reserved for patients with progressive tumors or for those whose markers do not decline appropriately and normalize [101]. Several European studies have similarly shown that resected stage I tumors can be treated with observation alone, with a 20–50 % relapse rate; most, however, can subsequently be salvaged with chemotherapy [76, 77, 81].

Between 1990 and 1996, 299 eligible pediatric patients with stage III/IV gonadal and stage I–IV extragonadal GCTs were randomized on POG9049/CCG8882 to standard BEP or high-dose BEP (HDBEP), with high-dose cisplatin (40 mg/m^2/day × 5). HDBEP resulted in a significantly improved 6-year EFS (89.6 ± 3.6 % vs. BEP 80.5 ± 4.8 %; $p = 0.0284$). There was no difference in OS (HDPEB 91.7 ± 3.3 % vs. BEP 86.0 ± 4.1 %). Although the study was not designed to have sufficient power to test for differences within each smaller subset (testicular, ovarian, extragonadal), there was a trend toward improved EFS and OS for each subset. The trend was most pronounced for extragonadal GCT. However, severe ototoxicity (grade 3/4, resulting in the need for hearing aids) was a consequence of HDBEP (67 % vs. BEP 10.5 %). Few patients had stage IV ovarian GCT; the ten treated with HDBEP all survived. Two of six who were treated with BEP recurred, although one was salvaged. Both patients were under 10 years of age. These small numbers make conclusions difficult [10].

Outcomes may also depend on the age at diagnosis. Premenarchal girls and women older than 45 years who develop MOGCTs may have different tumor biology and a worse prognosis than postadolescent females in the reproductive years. Outcomes also appear to be superior when patients are treated in a large cancer center, likely due to the rare nature and infrequent presentation of these cancers [97].

11.2.6.3 Sex Cord-Stromal Tumors

In a study of 72 patients with sex cord-stromal tumors registered at the German Pediatric Tumor Registry, EFS was 88 % at 10 years. Refractory tumors in this group were characterized by high proliferative activity. Survival of patients with early-stage juvenile granulosa cell tumors is above 95 %. Advanced-stage disease is typically more aggressive and less responsive to therapy.

11.2.6.4 Epithelial Tumors

The prognosis for young women with epithelial ovarian cancer appears to be independent of age [29]. Surveillance after treatment may consist of a CT scan at the completion of therapy, followed by physical examinations and serum CA-125 levels every 3 months for the first year, every 4 months for the next year, every 6 months for the ensuing 3 years, and annually thereafter. CT surveillance is recommended only for patients with symptoms, physical findings, or elevated serum CA-125 levels. In 1 review of 19 patients diagnosed before the age of 21 years, 15 (79 %) had stage I disease and 4 (21 %) had stage III disease. There were two deaths in this series, both from small-cell anaplastic carcinoma, which is rare in this age group [103].

Patients with low-grade serous carcinomas appear to do better than patients with epithelial cancers of higher grade. A recent retrospective study of 350 patients demonstrated a median progression-free survival of 28.1 months and a median overall survival of 101.7 months; women under 35 years of age had worse outcomes than older women, and patients with persistent disease at the end of primary therapy had the worst outcomes [104].

11.2.6.5 Tumors of Low Malignant Potential

The indolent nature of LMP tumors is best demonstrated by the 95 % 5-year survival and 80 % 20-year survival for all stages. Although the recurrence rate is between 6 and 36 %, these tumors usually recur as LMP tumors and not invasive malignancies. Patients undergoing cystectomy have a higher recurrence rate than patients undergoing unilateral salpingo-oophorectomy, but recurrences are usually cured by repeat surgical

resection. Therefore, most suggest that cystectomy with close surveillance is an adequate treatment, with immediate surgery in the event of recurrent disease [49]. In one study of 12 patients <40 years of age with early-stage disease who were treated with fertility-sparing surgery, there was 100 % survival and up to 50 % subsequent conception [105].

11.3 Malignancies of the Uterine Corpus

11.3.1 Epidemiology

11.3.1.1 Incidence

Uterine malignancies are rare in adolescents and young adults. Endometrial cancer is the most common gynecologic malignancy in the United States, with a mean age at diagnosis of 61 years. In a SEER database review of registered patients between 2004 and 2009, invasive uterine (corpus) cancer was the seventh most common malignancy identified in AYAs age 15–39, and the incidence was 3.1 per 100,000 per year [3]. Approximately 5–30 % of women with endometrial cancer are younger than age 50 at diagnosis [106]. In British Columbia, 14 % of endometrial cancers arise in women under the age of 50 years, including 5 % under the age of 40 years [107].

Figure 11.9 depicts the incidence of uterine cancer in the United States by age over 15 years, invasiveness, and stage at diagnosis. The incidence of uterine cancer increases exponentially between ages 25 and 60 (inset). Invasive cancer of the uterus accounts for 98 % of the reported cases of uterine cancer in AYAs and 99 % over all ages. The distribution of stage at diagnosis favors AYA females in that they have relatively higher (~80 %) proportion of localized disease at diagnosis in comparison with older women (60–70 %).

Figure 11.10 shows the incidence of uterine cancer in the United States by race/ethnicity and

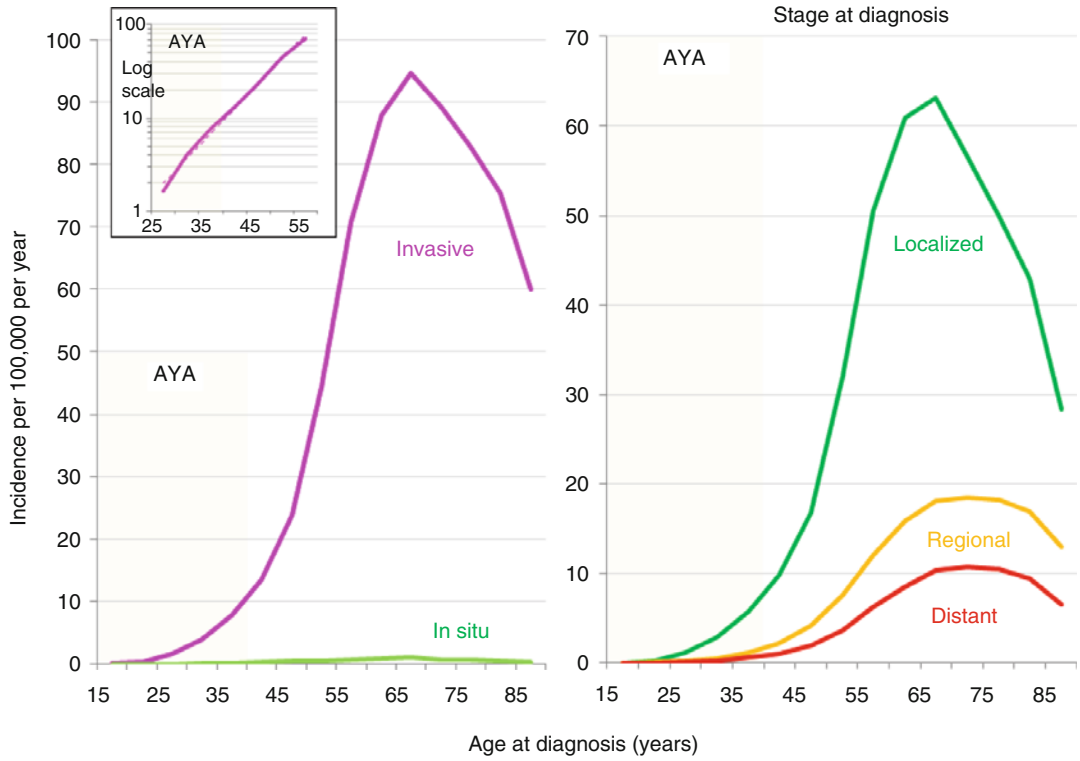

Fig. 11.9 Incidence of uterine cancer, United States SEER 18 regions, 2000–2012, by age over 15 years, invasiveness, and stage at diagnosis

age over 15 years. Whereas the incidence of uterine cancer among older females varies strongly with race/ethnicity, AYA women have comparable incidences across all the major races/ethnicities (inset). The mortality to incidence ratio is highest among blacks, with higher levels of poorly differentiated tumors across all stages, higher incidence, and higher mortality rates [108].

The vast majority of uterine (corpus) cancers are endometrioid carcinomas. Serous and clear cell histologies occur at a median age of 68 years [109]. Leiomyosarcoma, a rare histology overall, is rarely detected in this age group, as it usually occurs in women over 50 years of age [110]. Therefore, their existence in AYA patients is too rare to warrant further discussion here, and the chapter will focus on endometrioid histology.

11.3.1.2 Incidence Trend

Figure 11.11 shows the incidence of invasive cancer of uterine cancer in the United States by age. In both AYA and older adult women, the incidence declined during the 1970s and 1980s, but since then has increased steadily in AYA women (left panel) in contrast to a relatively steady rate in older women (right panel).

11.3.2 Pathology and Biology

The etiology of endometrial cancer in young women is multifactorial, including hormonal factors, insulin resistance, and mutations in mismatch repair genes. The majority of patients with endometrial adenocarcinoma diagnosed at a young age are obese and nulliparous. Soliman et al. reviewed 188 patients under 50 years of age with endometrial cancer; the mean body mass index (BMI) was 34 kg/m^2 (range, 18–68), and 58 % of patients had a BMI of at least 30. Among this cohort of women, 55 % were nulliparous and 39 % reported irregular menstrual cycles. Diabetes and hypertension each occurred in 23 % of patients [106]. The finding of obesity in these

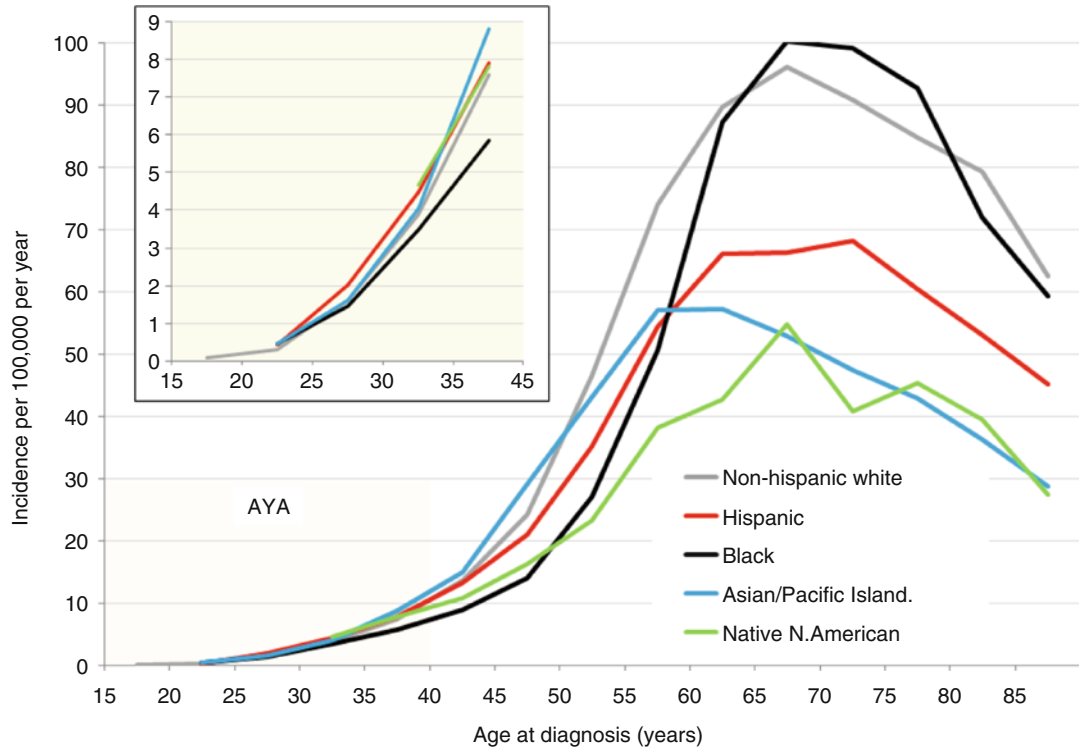

Fig. 11.10 Incidence of uterine cancer, United States SEER 18 regions, 2000–2012, by age over 15 years and race ethnicity

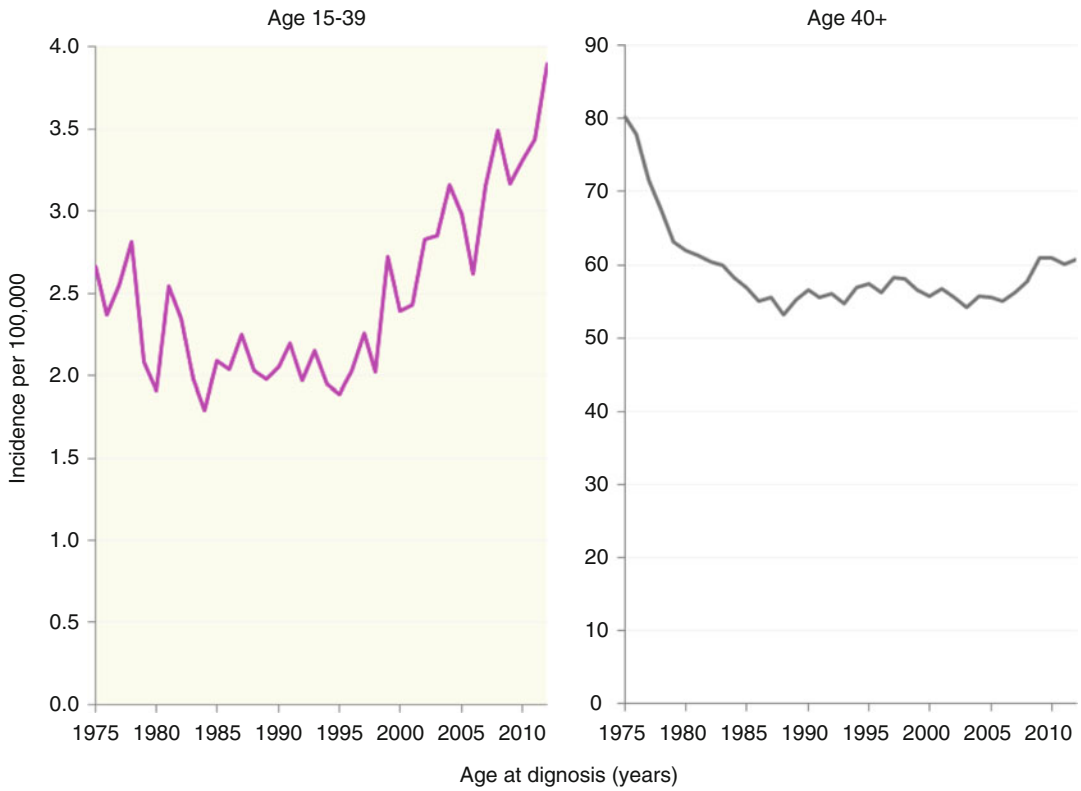

Fig. 11.11 Annual incidence of uterine cancer, United States SEER 9 regions, 1975–2012, by age

patients points to the role of anovulatory cycles, with endogenous estrogen stimulation inadequately opposed by progesterone, leading to endometrial hyperplasia, atypia, and eventually cancer. The pathway is somewhat more complex and involves insulin resistance, with upregulation of genes involved in the insulin signaling pathway (IGF1, PTEN, and IGFBP1) [111].

Among the M.D. Anderson cohort of 188 patients younger than 50 with endometrial cancer, normal-weight women were compared with overweight and obese women. Women of normal weight were less likely to have diabetes or irregular menstrual cycles than young overweight or obese women with endometrial cancer. Compared with the general population, they were more likely to be nulliparous, have a history of infertility, and have irregular menstrual cycles, suggesting the role of hormonal factors, polycystic ovarian syndrome (PCOS), and insulin resistance in normal-weight patients as well [112].

Lynch syndrome, or hereditary non-polyposis colon cancer (HNPCC), is etiologic in approximately 9 % of young patients with endometrial cancer and is an autosomal dominant condition caused by mutations in DNA mismatch repair genes, including MLH1, MSH2, MSH6, and/or PMS2 [107, 113]. In these patients, loss of PTEN is frequent, but additional mutations are seen less frequently than in patients without Lynch syndrome, leading to the suspicion that fewer additional mutations are required for cancer to arise when DNA mismatch repair is abnormal [114]. Among 188 patients under 50 years of age, 4 % of normal-weight women and 12 % of overweight women met criteria for HNPCC [112]. Additionally, HNPCC is responsible for a high incidence (19 %) of synchronous primary ovarian cancers among young women with endometrial cancer [106]. Synchronous primary ovarian cancers are found in 23 % of young women who meet the criteria for Lynch syndrome [107].

A third cohort of young patients with endometrial cancers is proposed whose tumors do not appear to be caused by hormonal factors or HNPCC. These tumors tend to present at a higher stage and show more aggressive behavior. Similar to patients with Lynch syndrome, these tumors have a 21 % incidence of synchronous ovarian cancer. Endometrial cancers in this third cohort may be caused by other mutations, including p53, PTEN, CTNNB1, PIK3CA, ARID1A, KRAS, and POLE, though some of these mutations may also be related to HNPCC [107].

11.3.3 Surgical Treatment Guidelines

In general, the rationale for surgery is to remove the primary tumor and obtain information necessary to guide further management or therapy. Upon confirmation of an endometrial carcinoma, the surgeon should determine if disease is limited to the uterus through preoperative examination, imaging, and exploration at surgery. If disease is limited to the uterus, a total hysterectomy with removal of tubes and ovaries is performed. This can be performed through laparotomy, vaginally, or through a minimally invasive surgical approach. Surgical staging includes pelvic and para-aortic lymphadenectomy in patients with risk factors based on tumor size, grade, histology, and depth of invasion and includes omental biopsy for serous, clear cell, or carcinosarcomas. Sentinel lymph node mapping is considered in selected patients but is not considered standard of care at present. Patients with cervical involvement may have radical hysterectomy and bilateral salpingo-oophorectomy or may be treated first with tumor-directed radiotherapy or chemotherapy followed by surgery. Widely metastatic disease may be treated with surgical debulking followed by adjuvant therapy, or by neoadjuvant chemotherapy and/or radiation therapy, sometimes followed by surgery [115].

The decision to remove or preserve the ovaries at the time of hysterectomy in young women is controversial. Since these tumors are associated with a high incidence of synchronous primary ovarian cancers, the NCCN guidelines suggest adnexal removal at the time of hysterectomy, and this is considered standard of care [106, 115]. Due to the desire to preserve hormonal function following definitive therapy, some investigators have considered leaving normal-appearing ovaries in place. A recent population-based analysis reviewed the surgical treatment and outcomes of 15,648 women younger than 50 years of age who had surgery for uterine cancer. Ovaries were removed in the vast majority of patients but were preserved in 7.7 % of women. Ovarian conservation was not independently associated with survival. While not the current standard of care, it may be safe to preserve the ovaries in premenopausal women who undergo surgery for endometrial cancer [116]. Other studies demonstrate no increase in cancer-related mortality in premenopausal women with early-stage endometrial cancer who have ovarian preservation [117].

Women under 50 years of age diagnosed with endometrial cancer should be tested for Lynch syndrome (HNPCC) [115]. Patients determined to have Lynch syndrome have a 40–60 % lifetime risk of endometrial cancer and a 10–12 % lifetime risk of ovarian cancer. The use of prophylactic total hysterectomy with bilateral salpingo-oophorectomy effectively prevents 100 % of these cancers, as demonstrated in a case-control study of 315 women with documented germline mutations associated with Lynch syndrome [118]. Therefore, prophylactic removal of the uterus, cervix, tubes, and ovaries is indicated at the completion of childbearing [115].

11.3.4 Nonsurgical and Adjuvant Treatment

Young women with grade 1 endometrial adenocarcinomas are usually hormone-receptor positive and often respond well to hormonal therapy. While the standard of care for treatment of endometrial cancer is definitive surgery as outlined above, patients with biopsy-proved grade 1, stage IA endometrioid carcinoma who wish to maintain their fertility may be candidates for fertility-sparing therapy. It should be noted that any patient with metastatic disease or high-risk histology

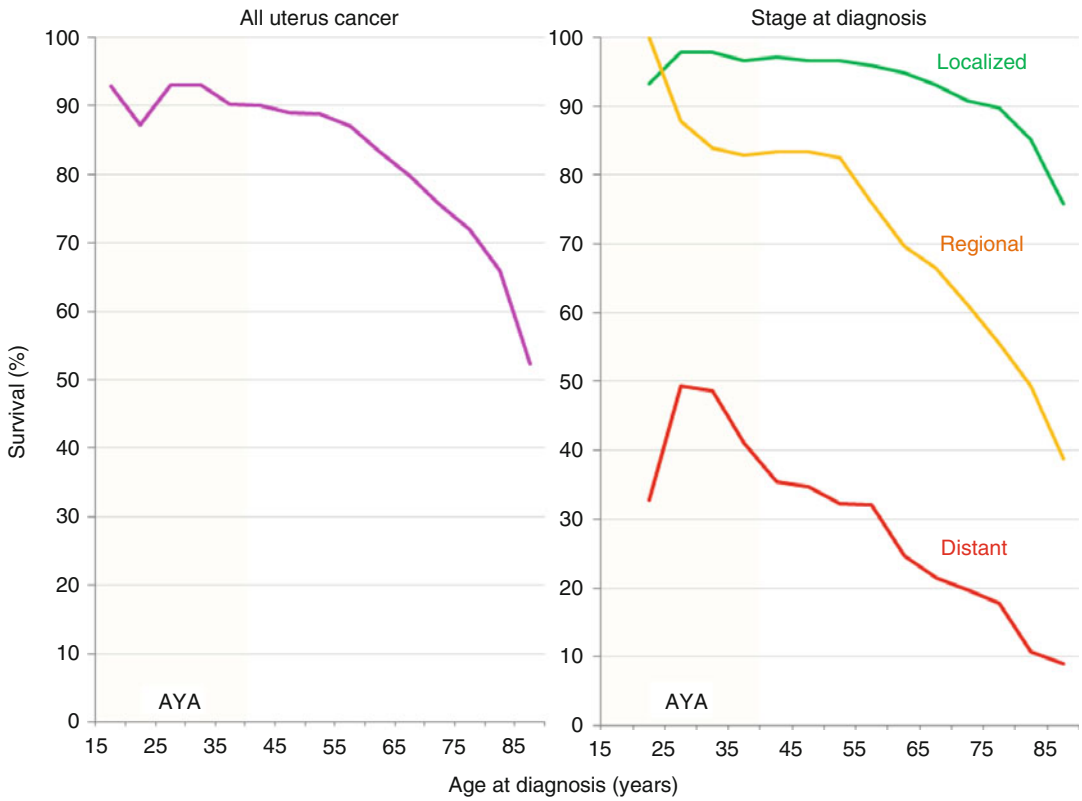

Fig. 11.12 Uterine cancer 5-year cancer-specific survival, United States SEER 18 regions, 2000–2012, by age and stage

(high-grade endometrioid, serous, clear cell, carcinosarcoma, or leiomyosarcoma) is not a candidate for fertility-sparing therapy [115].

Following genetic counseling and testing and fertility counseling, patients who meet these criteria may be treated with oral progesterone or with a progesterone-releasing intrauterine device (IUD). Approximately 70 % of women with grade 1 endometrial adenocarcinoma respond to hormonal therapy, but 35 % ultimately relapse and require definitive therapy with hysterectomy [119, 120]. However, this window of fertility may allow childbearing, and in some patients is curative, especially when combined with significant weight loss. Efficacy has also been reported with a levonorgestrel-releasing IUD, which may result in fewer side effects [121]. A prospective trial to determine specific efficacy and side effects is currently underway. If a patient treated with fertility-sparing therapy fails to respond within 6–9 months, progresses, or relapses, or when childbearing is complete, definitive total hysterectomy and bilateral salpingo-oophorectomy should be performed [115].

11.3.5 Outcomes

Figure 11.12 shows the 5-year cancer-specific survival for uterine cancer in the United States by age and stage. The 5-year rate is greater in AYA females than it is in older women, overall (left panel) and stage for stage (right panel). The 40–50 % rate in AYAs with distant disease at diagnosis represents one of the most favorable outcomes of solid tumors presenting with distant metastases at diagnosis. Overall, uterine corpus cancer is the eighth most curable cancer in this age group, in most cases with surgery alone. AYA patients fare better than women age 40 and older, except for those who present with distant disease and have only a 30–50 % 5-year survival. This is still better than patients age 40 and above who present with distant disease, who have a 23 % 5-year survival [92].

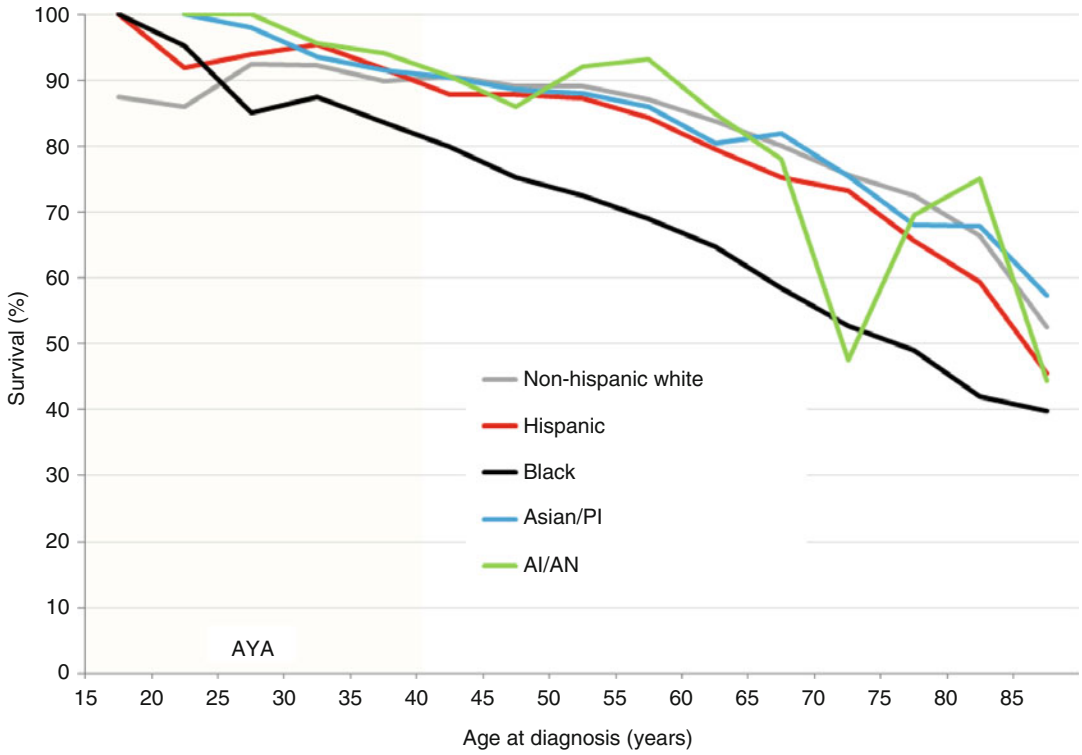

Fig. 11.13 Uterine cancer 5-year cancer-specific survival, United States SEER 18 regions, 2000–2012, by race/ethnicity and age over 15 years

Figure 11.13 depicts the 5-year cancer-specific survival for uterine cancer in the United by race/ethnicity and age over 15 years. Black females have the worst 5-year uterine cancer-specific survival at all ages in comparison to other races/ethnicities except the youngest of AYAs (age 15–25). Among non-Hispanic whites, the reverse appears to be true, with the youngest AYAs having a worse survival than older AYAs. The other major races/ethnicities have comparable survival rates at all ages.

Figure 11.14 shows the annual 5-year cancer-specific survival for uterine cancer in the United States among AYAs of age 15–39 and in older women. The 5-year survival rate of AYA females has been greater than 90 % since at least 1975 and better than in older women in whom it also has been stable, at 80–85 %, since 1975.

A significant opportunity for cancer prevention exists among AYA patients with Lynch syndrome (HNPCC), and routine screening should be incorporated into practice. Questions regarding family history can prompt genetic testing and indicate prophylactic surgery. When premalignant disease or early malignancy is detected, awareness of young age of onset, family history, body mass index, and attention to molecular tumor studies can improve the likelihood of detecting a Lynch associated germline mutation, providing the opportunity to intervene in index patients or their relatives [113].

11.4 Malignancies of the Uterine Cervix

11.4.1 Epidemiology

11.4.1.1 Incidence

Cervical cancer is the most common type of gynecologic malignancy in AYA patients [122]. Figure 11.15 shows the incidence of uterine cervical cancers in females in the United States by extent of disease at diagnosis and age over 15 years. The incidence of invasive cervical cancer increases from zero at age 10 to the peak of

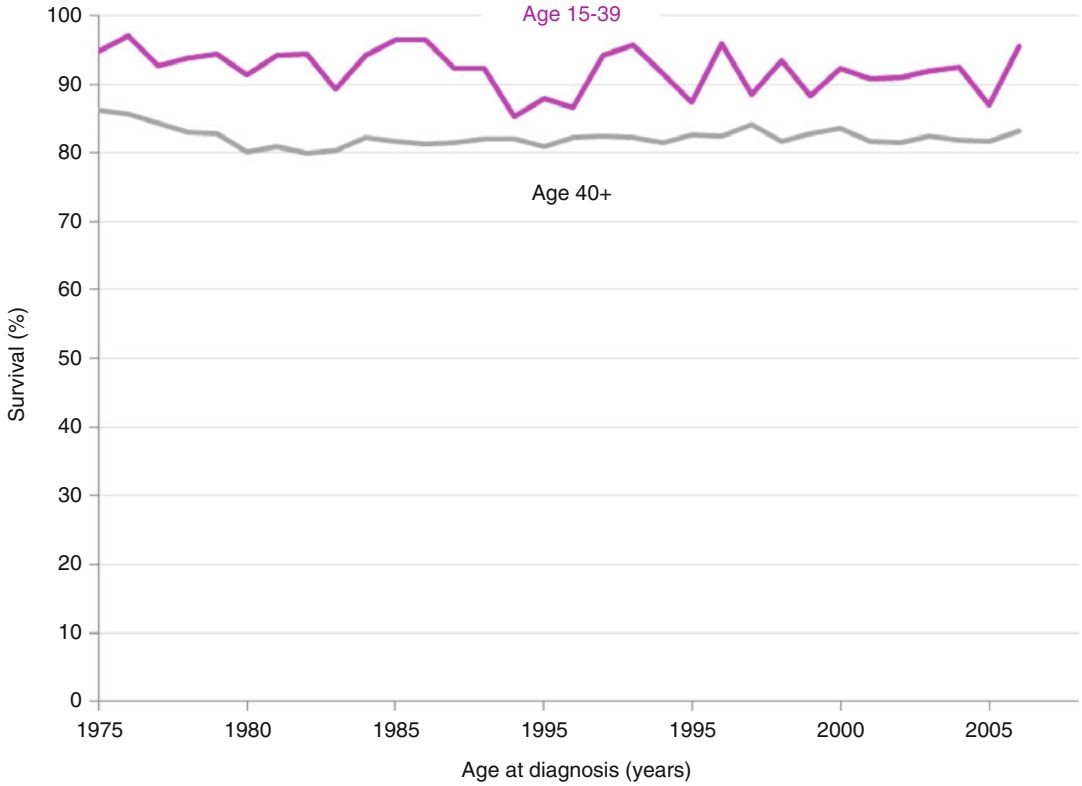

Fig. 11.14 Annual 5-year cancer-specific survival for uterine cancer, United States SEER9 regions, 1975–2012, by age 15–39 and 40+ years

all ages at age 35–40. AYA women (inset) are more likely to have localized disease at diagnosis of cervical cancer, whereas regional disease is the most common presentation in older women. AYA women 25 to 39 years of age have a higher incidence of localized disease than any other age group.

Figure 11.16 depicts the incidence of uterine cervical cancer in the United States by race/ethnicity and age over 15 years. The incidence of invasive cervical cancer in AYAs is similar in non-Hispanic whites, Hispanics, and blacks and distinctly less common in Asians/Pacific Islanders.

This implies that over 80 % of cervical cancers are preventable by HPV vaccination, and effective vaccines do exist. Of over 100 viral HPV genotypes, 13 are causative for cervical cancer. The quadrivalent vaccine targets the most common viral genotypes responsible for cervical warts (HPV 6 and 11) and cervical cancer (HPV 16 and 18), and the 9-valent vaccine approved in 2014 covers five additional genotypes responsible for cervical cancer (HPV 31, 33, 45, 52, 58). A vaccination program was first made available in the United States for girls aged 13–17 years in 2005. Current recommendations for vaccination are for all females aged 9–26 years and all males aged 9–26 years [123].

The prevalence of HPV has been estimated at 59 % in women 20–24 years old and 50 % in 25–29-year-old women [124]. As a result of vaccination, the prevalence of vaccine-type HPV decreased 56 % among females aged 14–19 years between 2006 and 2010 [125]. The most recent estimates demonstrate that within 6 years of vaccine introduction, there was a 64 % decrease in the viral genotypes covered by the vaccine among girls aged 14–19 years and a 34 % decrease among women aged 20–24 years [126]. Unfortunately, the lack of universal uptake has

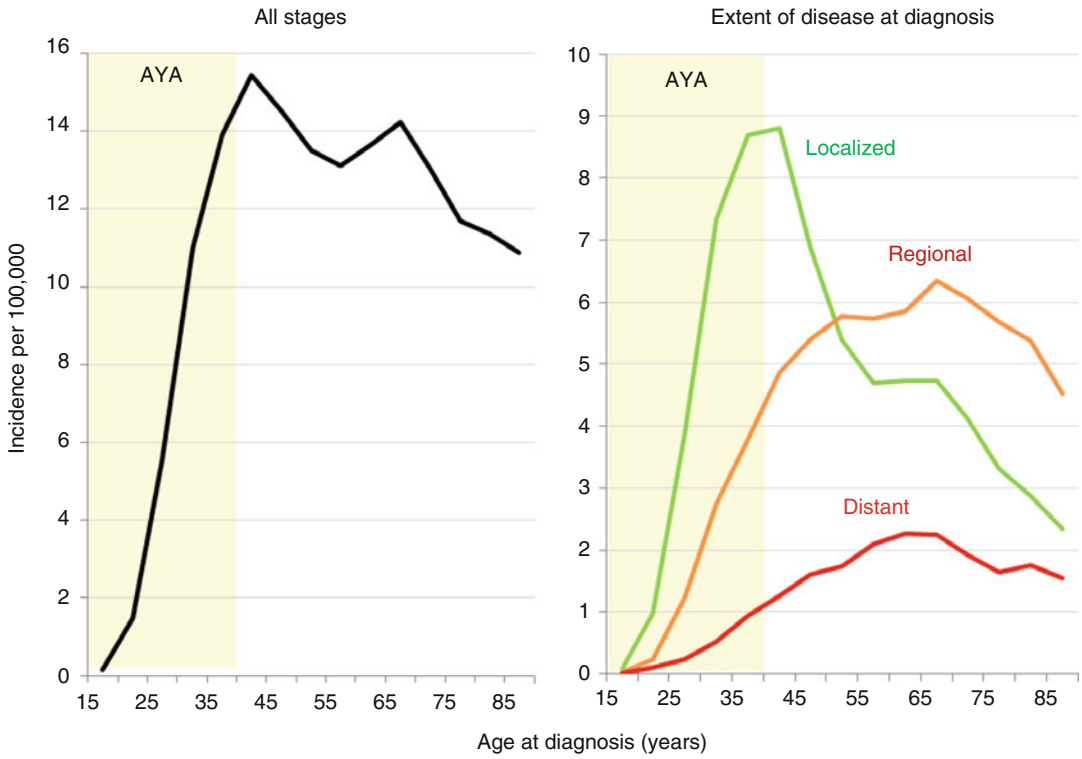

Fig. 11.15 Incidence of uterine cervical cancers in females, United States SEER18 regions, 2000–2011, by extent of disease at diagnosis and age over 15 years

prevented the near elimination of cervical cancer to date, but these data showing improved vaccine uptake are encouraging.

11.4.1.2 Incidence Trend

Figure 11.17 shows the annual incidence of invasive uterine cervical cancers in the United States by age and effect of HIV/AIDS era. AYA and older women have had a continuous decrease in incidence of invasive cervical cancer, except during the HIV/AIDS epidemic of the late 1980s and the 1990s. During the last decade, an apparent plateau in the decreasing incidence became apparent. These observations suggest that some cervical cancer in AYA women is caused or predisposed by HIV, similar to non-Hodgkin lymphoma. The decrease in incidence during the last decade may reflect effective prevention in populations vaccinated against human papillomavirus (HPV), the causative agent in over 80 % of cervical cancers [3, 123].

11.4.2 Pathology and Biology

Approximately 75 % of cervical cancers are squamous cell carcinomas, while 20–25 % are adenocarcinomas. The relative proportion of adenocarcinoma is increasing, likely due to identification and eradication of squamous cell preinvasive lesions. These histologic subtypes are distinct in their site of origin (ectocervical vs. endocervical glandular epithelium), histologic appearance, molecular signature, and clinical behavior. Many studies suggest that adenocarcinomas are more aggressive than squamous cell carcinomas of the cervix, yet treatment guidelines remain the same [127]. Squamous cell carcinomas include keratinizing and non-keratinizing subtypes, as well as papillary, basaloid, warty, and verrucous descriptors. Adenocarcinomas include mucinous, villoglandular, endometrioid, clear cell, serous, mesonephric, adenosquamous, and glassy cell

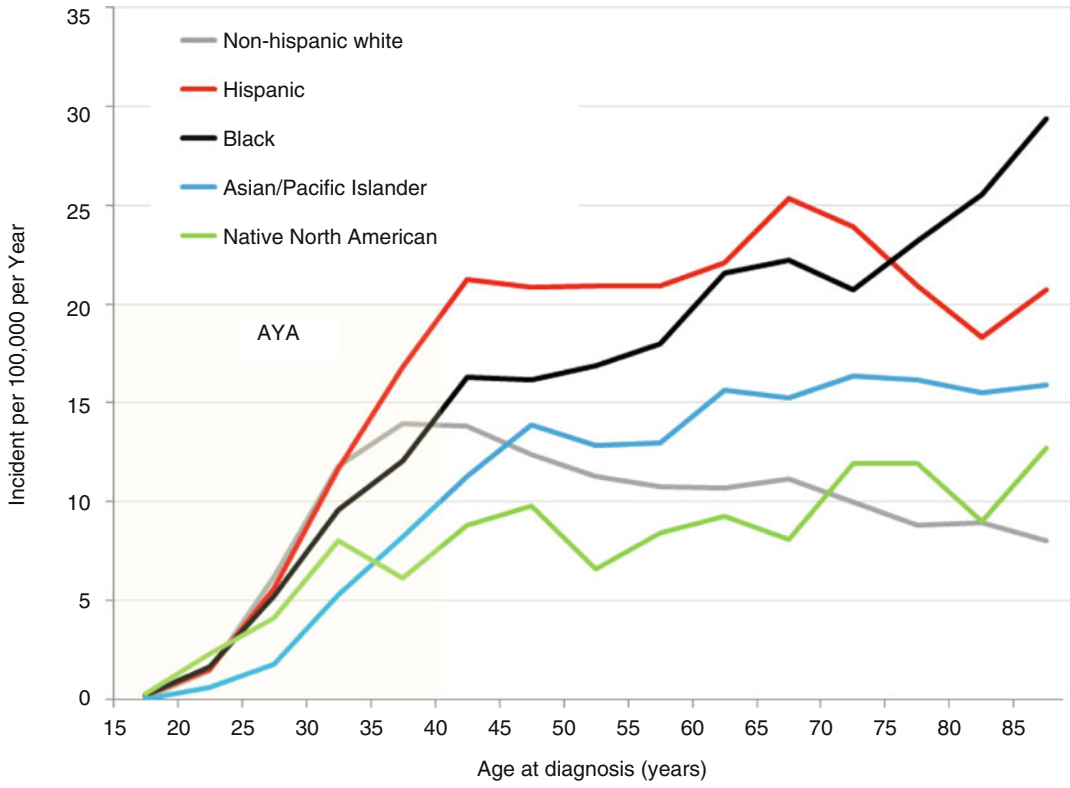

Fig. 11.16 Incidence of uterine cervical cancer, United States SEER 18 regions, 2000–2011, by race/ethnicity and age over 15 years

variants [128]. Other histologic subtypes of cervical cancer include small cell neuroendocrine tumors, melanoma, and other extremely rare variants.

As noted, most cervical cancers are caused by HPV infection. Over 80% of adenocarcinomas are caused by HPV 16 and 18, but only 70% of squamous cell carcinomas are caused by HPV 16 and 18. The remainder are caused by other high-risk subtypes, most of which are covered in the 9-valent vaccine [129]. Additionally, smoking is strongly associated with squamous cell carcinoma, but less so with adenocarcinoma [130]. Other differences in biology also exist between these subtypes, as adenocarcinomas are more likely to undergo hematogenous dissemination, have distant metastases, metastasize to the ovary, present as bulky endophytic masses, and have a higher risk of recurrence [127].

Pathologic diagnosis of adenocarcinoma of cervical origin often relies on immunohistochemical features, including the presence of carcinoembryonic antigen (CEA) and p16 expression, with an absence of hormone receptors and vimentin. Squamous cell carcinomas tend to be positive for pankeratin, p16, and p63 and are less often positive for CK7, CK14, CK5/6, and estrogen and progesterone receptors. They are usually negative for neuroendocrine markers and CEA [127].

11.4.3 Surgical Treatment Guidelines

In general, the rationale for treatment is based on stage, extent of disease, and histopathologic factors (Table 11.7). Surgical treatment is considered when the disease appears to be limited to the uterine cervix with a size around which negative margins can be obtained and with a low likelihood of lymphatic metastases which would require postoperative radiotherapy. Surgical

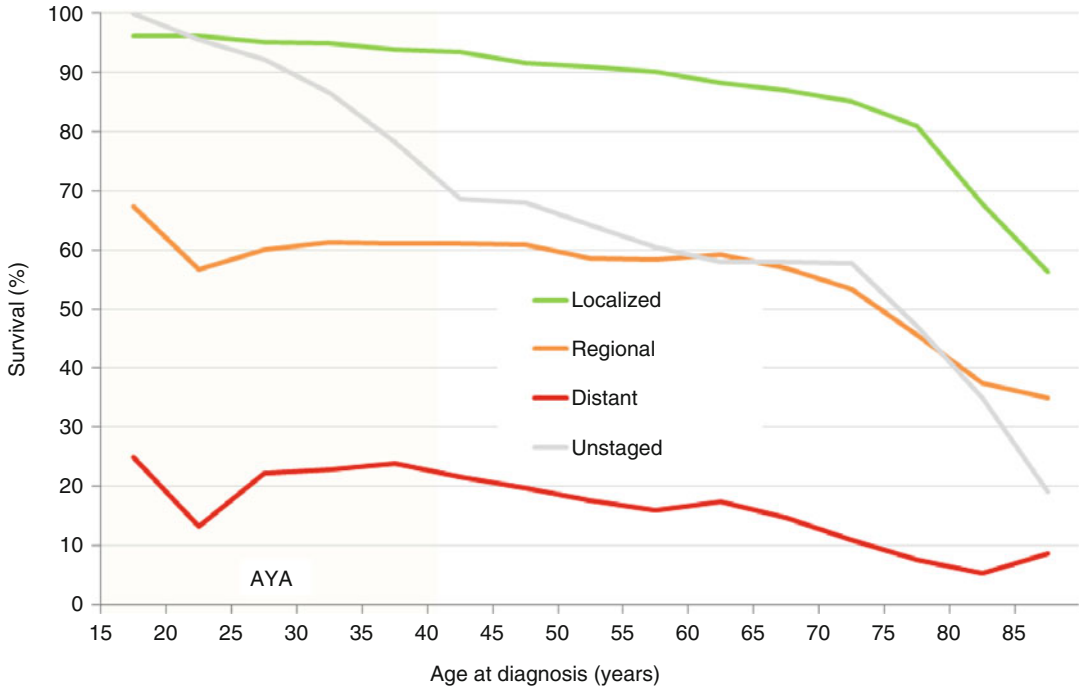

Fig. 11.17 Annual incidence of invasive uterine cervical cancers, United States SEER 9 regions 1975–2011, by age and effect of HIV/AIDS era. Regressions are 2º polynomials

Table 11.7 FIGO staging of cervical cancer

Stage I	Cervical carcinoma confined to the cervix
IA	Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm from the base of the epithelium and a horizontal spread of 7.0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification
IA1	Measured stromal invasion ≤3 mm in depth and ≤7 mm in horizontal spread
IA2	Measured stromal invasion > 3.0 mm and ≤5.0 mm with a horizontal spread ≤7.0 mm
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina
IIA	Tumor without parametrial invasion
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4.0 cm in greatest dimension
IIB	Tumor with parametrial invasion
Stage III	Tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctional kidney
IIIA	Tumor involves the lower third of the vagina, no extension to the pelvic wall
IIIB	Tumor extends to the pelvic wall and/or causes hydronephrosis or nonfunctional kidney
Stage IV	Tumor invades the mucosa of the bladder or rectum and/or extends beyond the true pelvis (bullous edema is not sufficient to classify a tumor as stage IV)
IVA	Tumor invades the mucosa of the bladder or rectum
IVB	Tumor extends beyond the true pelvis

Adapted from Pecorelli [136]

treatment should not be considered when there is evidence of disease beyond the cervix, unless confined only to a small portion of the vagina contiguous with the cervix (limited stage IIA disease).

Preoperative evaluation should include history, physical including pelvic examination, complete blood count, cervical biopsy with pathologic review, cone biopsy as indicated, liver function tests, renal function studies, and HIV testing. For patients with IB1 or higher tumors, chest x-ray, CT or PET-CT, and MRI as indicated can be considered. Smoking cessation and counseling should be provided when indicated. For patients with stage IB2 disease or greater, examination under anesthesia, cystoscopy, and proctoscopy may be considered to evaluate bowel and bladder involvement [131].

Patients with stage IA1 disease with no lymph vascular space invasion (LVSI) who desire fertility can consider a cone biopsy with negative margins; in the event of positive margins, a repeat cone biopsy or trachelectomy should be performed. If future fertility is not desired, these patients may undergo extrafascial hysterectomy. Patients with stage IA1 disease with LVSI and patients with stage IA2 disease who desire fertility can undergo a cone biopsy with negative margins with pelvic lymph node dissection; in the event of positive margins, a repeat cone biopsy or trachelectomy should be performed. Another option in these patients is a radical trachelectomy with pelvic lymphadenectomy. Sentinel lymph node mapping can be considered. If future fertility is not desired, the standard of care is modified radical hysterectomy with pelvic lymphadenectomy, with consideration for sentinel lymph node mapping, or pelvic radiotherapy plus brachytherapy. Patients with stage IB1 disease who desire future fertility are candidates for radical trachelectomy with pelvic lymphadenectomy, with consideration for sentinel lymph node mapping. Patients with stage IB1 who do not desire future fertility and all patients with stage IIA1 should undergo radical hysterectomy with pelvic lymphadenectomy, with consideration of sentinel lymph node mapping, or pelvic radiotherapy plus brachytherapy with consideration for concurrent cisplatin-containing chemotherapy. Surgery for patients with stage IB2 or IIA2 disease is controversial, but radical hysterectomy with pelvic lymphadenectomy; or pelvic radiotherapy with concurrent cisplatin-containing chemotherapy plus brachytherapy followed by adjuvant hysterectomy are options included in the NCCN guidelines [131].

Most would not consider patients with stage IB2 (>4 cm tumors apparently limited to the cervix) as candidates for extirpative surgery, but para-aortic nodal assessment may be considered prior to definitive chemoradiation in this population [131, 132].

Minimally invasive surgery has been widely adopted as an accepted surgical approach for these surgical procedures. A definitive prospective trial comparing minimally invasive approaches with laparotomy is underway.

11.4.4 Nonsurgical and Adjuvant Treatment

Patients who undergo surgical therapy as outlined above who have negative nodes and margins may be observed, unless they have a combination of high risk factors, including primary tumor size, stromal invasion, and/or LVSO that meet the so-called Sedlis criteria. If Sedlis criteria are met, pelvic radiotherapy with or without concurrent cisplatin-based chemotherapy is administered. Those patients with positive pelvic nodes and/or a positive surgical margin and/or positive parametrium should undergo pelvic radiotherapy with concurrent cisplatin-based chemotherapy, and vaginal brachytherapy should be considered. Patients who have positive para-aortic lymph nodes should undergo radiotherapy to the involved nodal bed with pelvic radiotherapy with concurrent cisplatin-based chemotherapy, and vaginal brachytherapy should be considered.

Patients with stage IB2 or higher are not candidates for surgery, except as outlined above. When disease is limited to the pelvis, these patients should undergo definitive treatment with pelvic radiotherapy and concurrent

cisplatin-based chemotherapy followed by brachytherapy. Bulky lymphadenopathy may be considered for surgical resection prior to definitive radiotherapy [131].

Patients with stage IVB or recurrent disease may consider chemotherapy. Options include paclitaxel or docetaxel with cis- or carboplatin and topotecan and paclitaxel. The addition of bevacizumab is a level 1 option and appears to confer an improvement in progression-free survival [127, 131, 133]. Additionally, patients with recurrent disease limited to the central pelvis may undergo pelvic exenteration as a potentially curative procedure [131].

Fertility preservation for patients undergoing chemotherapy and radiotherapy is similar to considerations outlined above for patients with ovarian cancer. Oncofertility consultation should be obtained when appropriate.

11.4.5 Outcomes

Figure 11.18 shows the 5-year cancer-specific survival for uterine cervical cancer in the United States during the last decade by stage and age over 15 years. For localized, regional, and distant disease of invasive cervical cancer, the 5-year cancer-specific survival rate was >90%, 60%, and 20%, respectively. For all three extents of disease at diagnosis, the rate was slightly better and corresponding stages in middle-aged women over 40 years of age.

Figure 11.19 depicts the 5-year cancer-specific survival for uterine cervical cancer in the United States during the last decade by race/ethnicity and age over 15 years. The 5-year cancer-specific survival of AYA women with invasive cervical cancer was worse in blacks than any other major race/ethnicity. In older women, Asians/Pacific

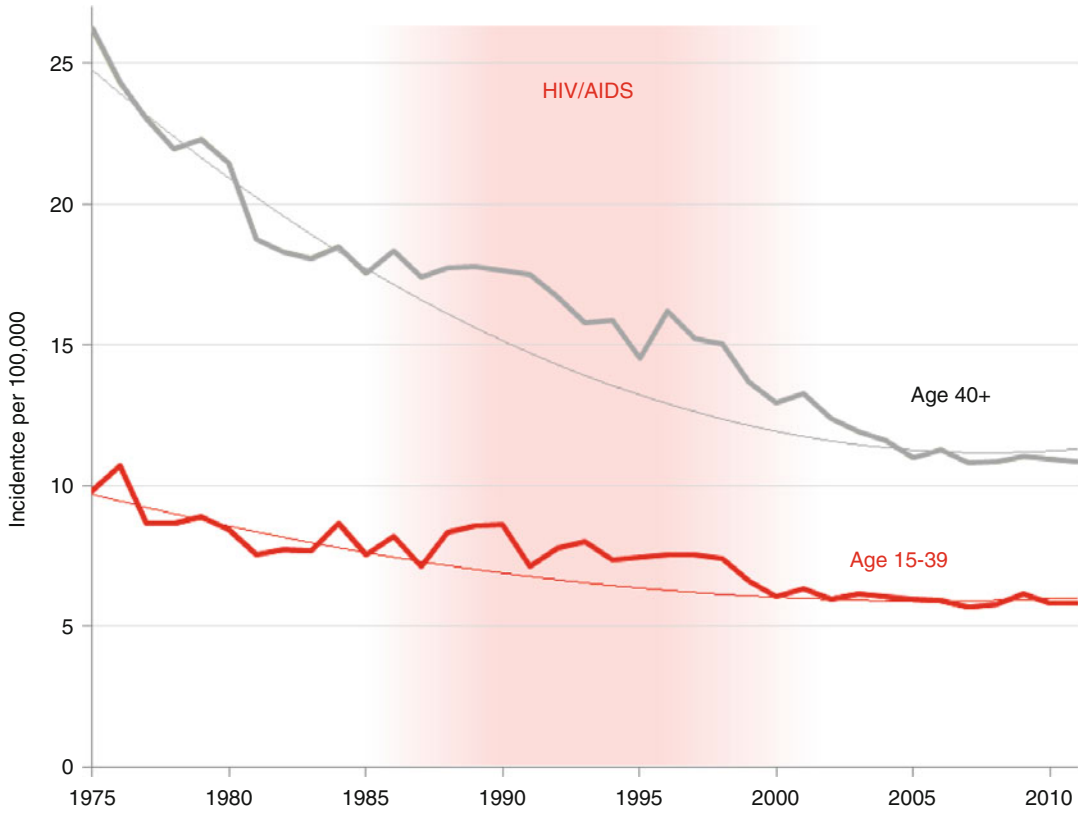

Fig. 11.18 Cervical cancer 5-year cancer-specific survival, United States SEER 18 regions, 2000–2011, by stage and age over 15 years

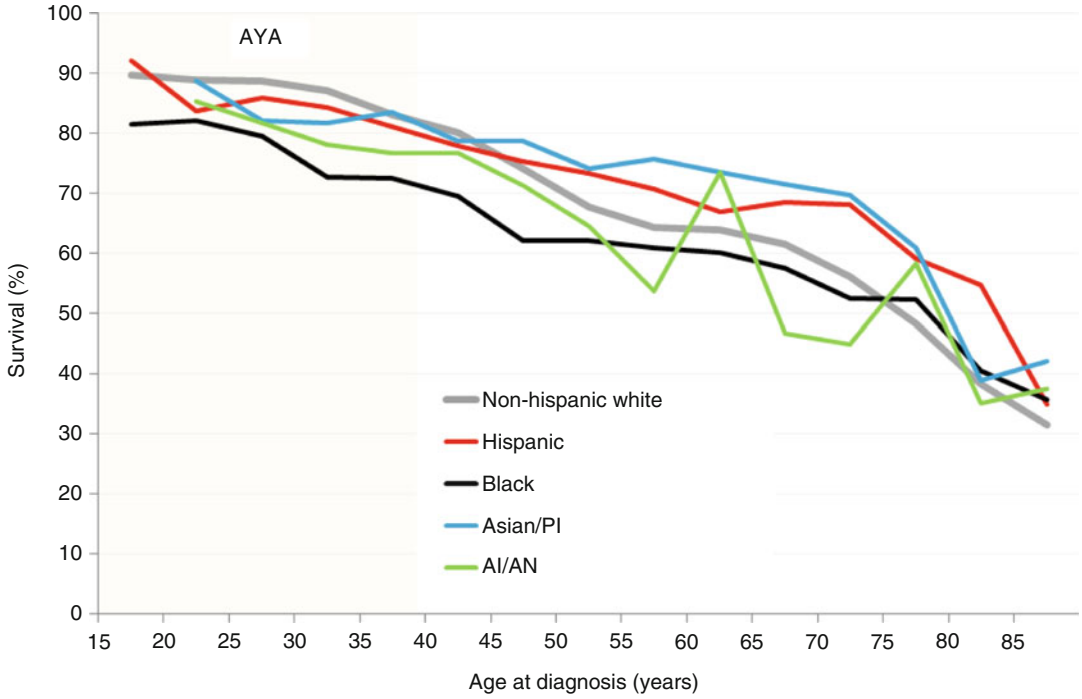

Fig. 11.19 5-year cervical cancer-specific survival, United States SEER 18 regions, 2000–2010, by race/ethnicity and age over 15 years

Islanders and Hispanics have had the best survival rates.

Prognosis related to cervical cancer relates to stage, histology, and parametrial involvement but does not depend on age as an independent risk factor [124], although one study suggested that teens and young adults with cervical cancer in the United Kingdom had worse 1-year survival but equivalent 5-year survival when compared with matched adults [134]. It appears that there has been no significant change in survival for AYA patients diagnosed with cervical cancer since 1992 [92].

Histology influences prognosis, as adenocarcinomas are less responsive to radiotherapy than squamous cell carcinomas and are more likely to have nodal involvement [135].

In terms of survival trends, Fig. 11.20 shows the 5-year cancer-specific survival for uterine cervical cancer in the United States by era during 1976–2011 and race/ethnicity. The improvement in the 5-year cervical cancer-specific survival rate among AYA women has been apparent in all races/ethnicities, including black AYA women, who have had a lower survival rate than AYA women of other races/ethnicities. Cervical cancer is one of the few cancers that have racial/ethnic equity in mortality rates among AYAs. Nonetheless, compared to 1976–1984, the 5-year survival rate has improved less in AYAs than in younger or older women.

Conclusions

Gynecologic cancers are relatively rare in children, adolescents, and young adults. As a result, relatively little information exists about incidence rates, treatment, and outcomes for specific tumor types in these age groups. This chapter is designed as a guide for the evaluation and treatment of gynecologic tumors in adolescents and young adults, with the goal of engendering interest in studies aimed specifically at this patient population.

An age-specific diagnostic and therapeutic dilemma exists because of the desire to maintain fertility in this young age group. Most neoplasms present at an early stage with generally good long-term survival, but appropriate surgical staging and assessment

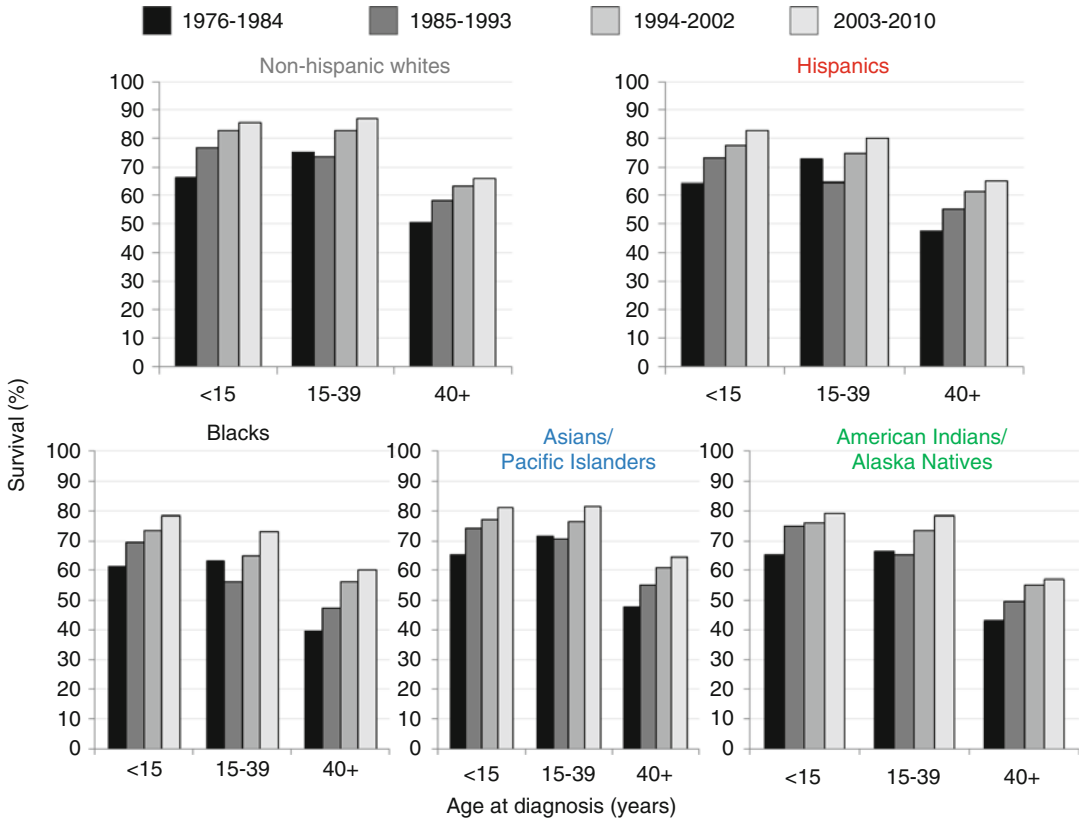

Fig. 11.20 5-year cancer-specific survival for uterine cervical cancer, United States SEER 9 regions, by era during 1976–2011 and race/ethnicity

are necessary components in determining the extent of surgery required and the need for postoperative therapy. With the advent of modern surgical and postsurgical techniques, response rates and survival have improved dramatically and are excellent for most tumor types.

Additional opportunities for cancer prevention exist with the ability to screen for, test, and perform prophylactic surgery for hereditary cancer syndromes involving the ovary and uterus, potentially preventing 10 % of each of these cancers. The advent of the vaccine for human papillomavirus affords an unprecedented opportunity to drastically reduce the incidence of cervical and other HPV-related cancers in the AYA population. It is through multidisciplinary care, public policy, and media attention that patients will see a substantial reduction in these cancers over time.

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Testicular Cancer

12

Brandon Hayes-Lattin and Archie Bleyer

Abstract

Although testicular cancer is highly curable, with 5-year testicular cancer-specific survival rates exceeding 95 %, AYA males have the lowest survival rate, correlated with a higher incidence of distant metastases at diagnosis. Hispanics are undergoing a dramatic increase in testicular cancer, the cause of which has not been ascertained. Testicular cancer among AYAs has unique biology, clinical features, and psychosocial impacts that distinguish its care from that of the general oncologic population.

12.1 Introduction

Of all the common cancers sustained by adolescents and young adults (AYAs), testicular germ cell tumors have the highest survival and cure rates (Fig. 2.14). Fortunately for AYAs, they are also among the most common of cancers in AYAs; in American AYA males, testicular cancer is more common than any other cancer by at least twofold (Fig. 2.4). The treatment to accomplish the high cure rate is multimodal, time- and expense-consuming, and associated with significant acute and long-term morbidities. The complications and sequelae are particularly problematic in AYAs.

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12.2 Incidence

The vast majority of testicular cancers among adolescents and young adult (AYA) patients are germ cell tumors, and germ cell tumor is the most common cancer among males in the 20–39-year-old age range, representing 20 % of invasive cancer diagnoses in the United States; 29 % in Western, Northern, and Southern Europe; and 9 % worldwide (Fig. 2.4). The highest age-standardized rates of testicular cancer are in Northern Europe and Australia/New Zealand [1]. In the United States, the incidence of testicular cancer in males had a distinct peak at 29 years of age (upper panel dashed vertical line) and a distinct onset during puberty at the age of 13 regardless of race/ethnicity (Fig. 12.1,

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upper and lower panel) [2]. In older patients, it declined steadily with age to nadir at about 75, after which it increases slightly due to noncarcinoma types of cancer such as non-Hodgkin lymphoma (upper panel). The dependence of the incidence of testicular cancer among AYAs on race/ethnicity is one of the strongest of all the common cancers in AYAs. In the United States, the peak incidence ranged sixfold, with blacks having the lowest incidence and non-Hispanic whites having the highest (Fig. 12.1, lower panel). The average number of men diagnosed with testicular cancer is about 8000 of all ages and 5500 AYAs (Fig. 12.1, inset).

The AYA age interval is the most dynamic of all ages in the composition of histologic types of testicular cancer and their dependence on age. In the United States, mixed germ cell tumors, rare in boys, strikingly increased with age to become the dominant type by age 15, which was replaced by middle age with seminoma as the predominant type (Fig. 12.2). Testicular choriocarcinoma was most common in AYAs and older boys (Fig. 12.2). Teratomas of the testis had a similar age distribution as choriocarcinoma except that it was far more common in male infants which may have included components of choriocarcinoma (Fig. 12.2).

The majority of men present with localized or regional disease, with a notable exception in children in whom local and distant metastases are rarely detected. In the United States, the age group with the highest incidence of distant metastases at diagnosis were 10- to 20-year-olds (Fig. 12.3).

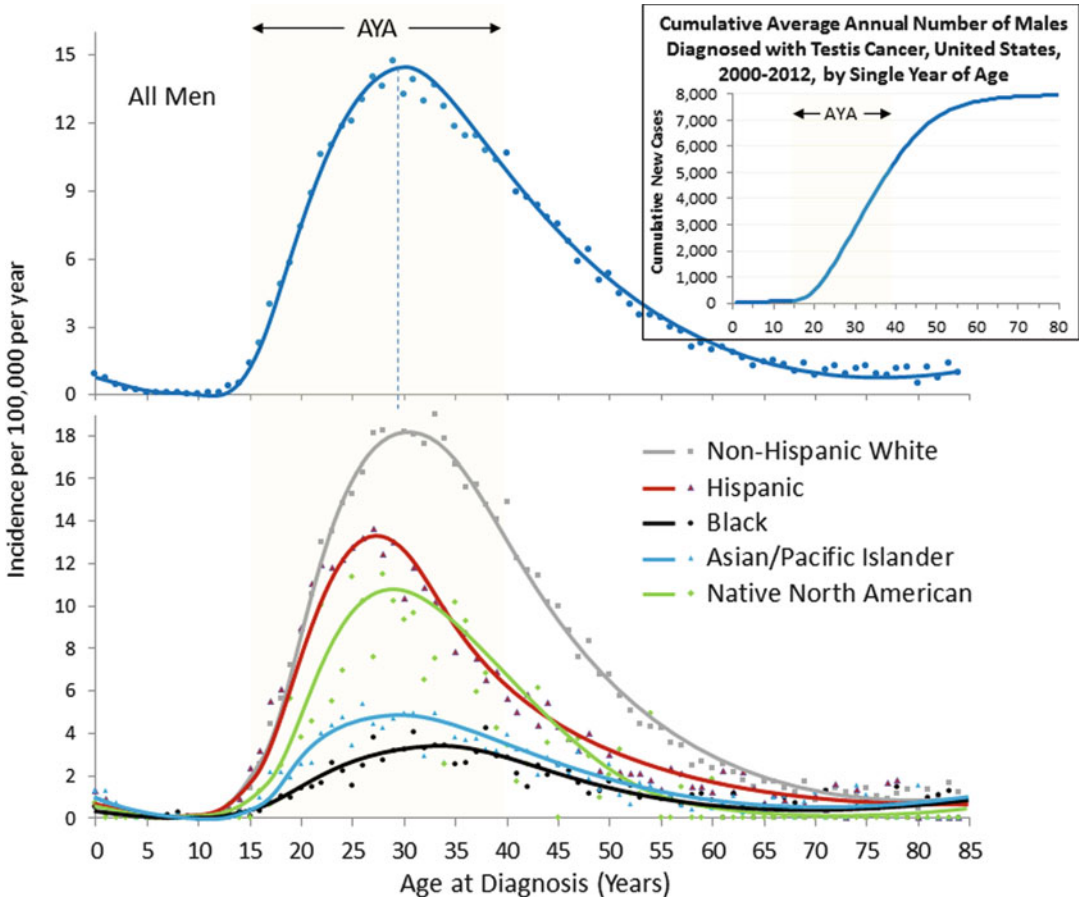

Fig. 12.1 Incidence and number of men diagnosed with testicular cancer, 2000–2012, SEER18, by single year of age and race/ethnicity (Data from United States National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program [2])

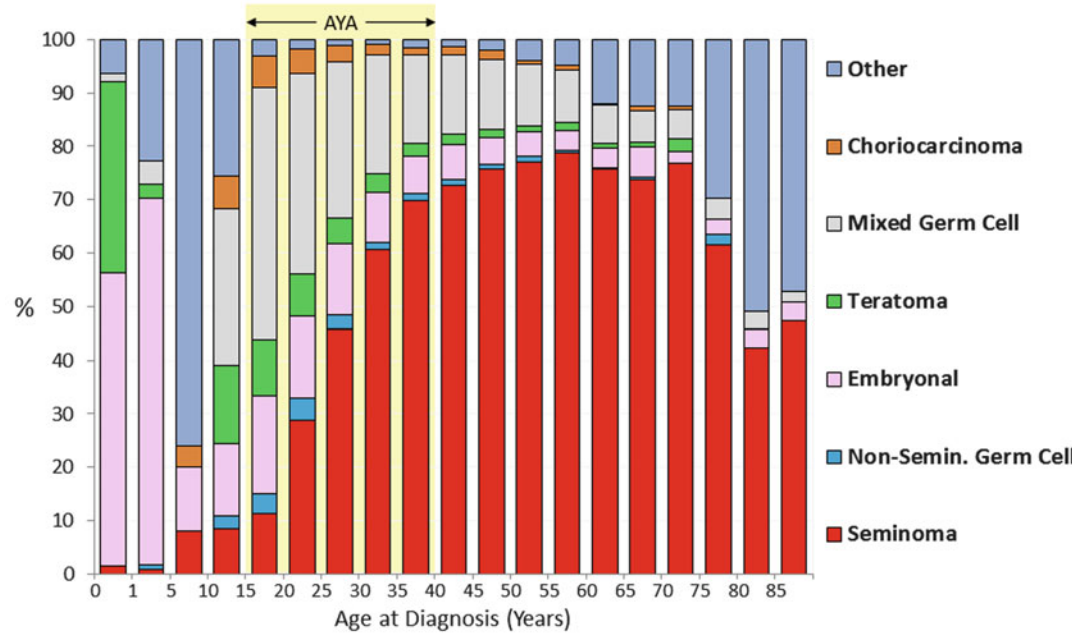

Fig. 12.2 Histology distribution of testicular cancer, 2000–2011, SEER18, by age (Data from United States National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program [2])

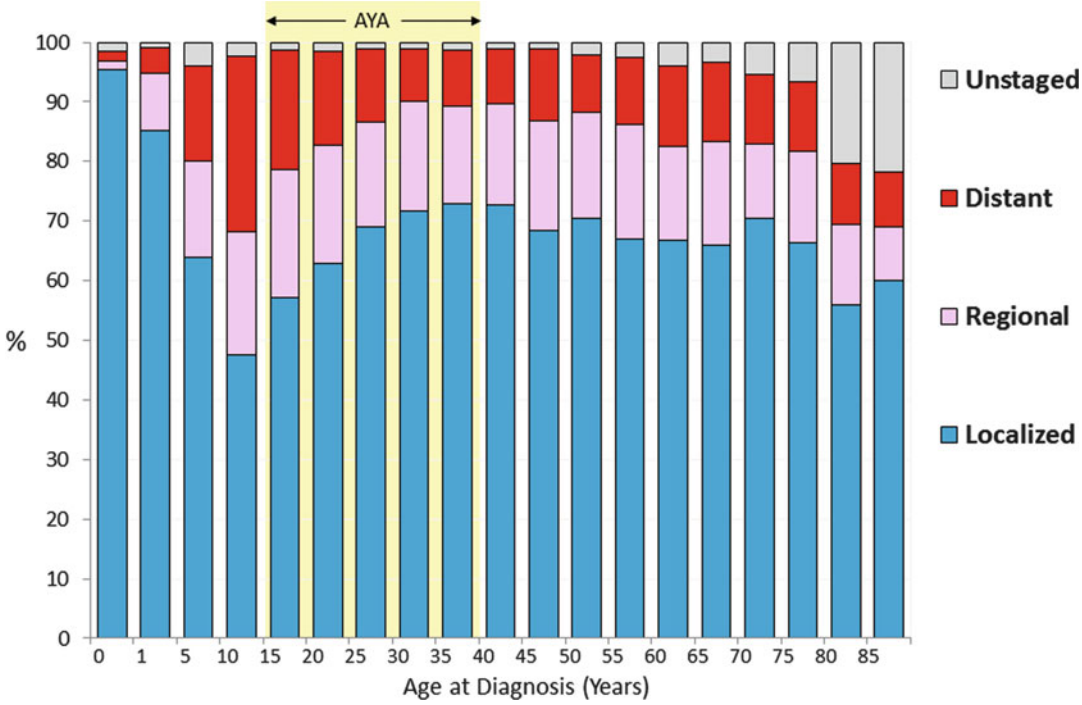

Fig. 12.3 Distribution of stage of testicular cancer, SEER 18, 2000–2011, by age (Data from United States National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program [2])

The incidence of testicular cancer has been relatively stable except for Hispanics. Since 1992 in the United States, Hispanic AYA males have had the greatest increase in incidence of testicular cancer, with no evidence for an increase in younger or older Hispanics (Fig. 12.4) [3]. Non-Hispanic whites had an increase in incidence in testicular cancer that subsided in the late 1990s.

12.2.1 Survival and Mortality

With modern therapy, testicular cancer represents a highly curable malignancy. In the 1970s and early 1980s, 15- to 19-year-olds had the worst 5-year testicular cancer-specific survival of all age groups. Since then, they have caught up, although 15- to 24-year-olds still lag behind younger and older patients (Fig. 12.5, upper panel) [4]. The latter is explained by the higher rate of metastatic disease in 15- to 19-year-olds than in all other age groups (Fig. 12.3). Deaths from testicular cancer have dramatically declined in all AYA age groups, although in 20- to 29-year-olds, the improvement ceased since the mid-1990s (Fig. 12.5, lower panel).

Among AYAs, choriocarcinoma and other non-seminomatous germ cell histologic types of testicular cancer had the worst prognosis when

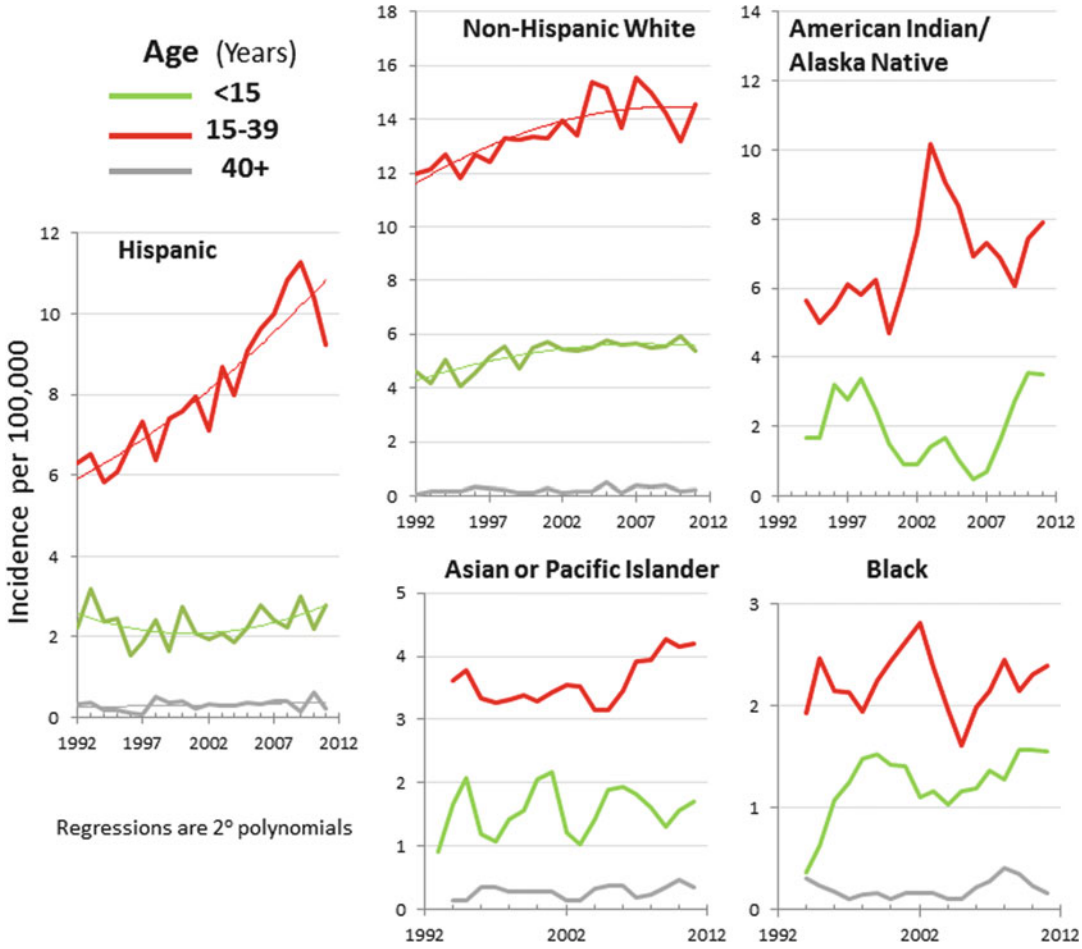

Fig. 12.4 Annual incidence of testicular cancer, 1992–2011, SEER13, by race/ethnicity, age, and year of diagnosis (Data from United States National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program [2])

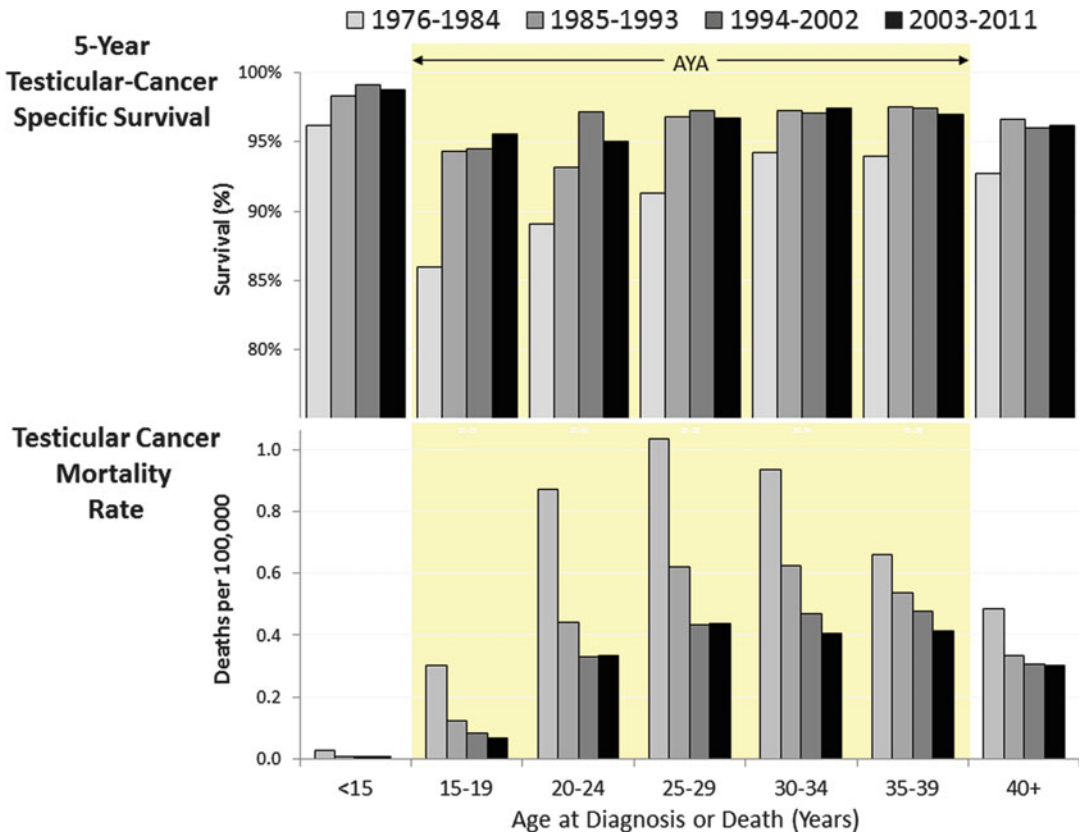

Fig. 12.5 Change in testicular cancer survival and mortality rates, age 15–39, 1976–2011, by era and age (Data from United States National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program [2, 4])

the distant disease was present at diagnosis, with one of each three males still dying of testicular cancer in 5 years (Fig. 12.6).

12.3 Biology

The vast majority of testicular tumors among AYAs are germ cell tumors, representing distinctive biology. Germ cell tumors are felt to arise from a precursor lesion of intratubular germ cell neoplasia within seminiferous tubules. Comparison of transcription factor expression with embryonic stem cells suggests the cell of origin is a pluripotent gonocyte [5]. The developmental migration of these cells along the gonadal ridge to the iliac fossa and finally to the scrotum explains the various patterns of mediastinal, retroperitoneal, and testicular presentation of germ cell tumors.

Testicular germ cell cancers are histologically and clinically divided into seminoma and non-seminoma. Seminoma is the most common histology after the age of 35. Among testicular cancer patients with a history of cryptorchidism, seminoma accounts for 60 % of tumors. Based on clinical outcome differences, only tumors with pure seminomatous features are categorized as seminoma, and tumors with mixed features (including those associated with any elevation in serum AFP) are treated as non-seminomas. A clinically distinct subtype of spermatocytic seminoma rarely metastasizes and is almost always cured with orchiectomy alone.

Non-seminoma includes all of the other histologic subtypes of germ cell tumor including yolk sac tumor, choriocarcinoma, embryonal cell carcinoma, and teratoma. While yolk sac elements are present in approximately half of

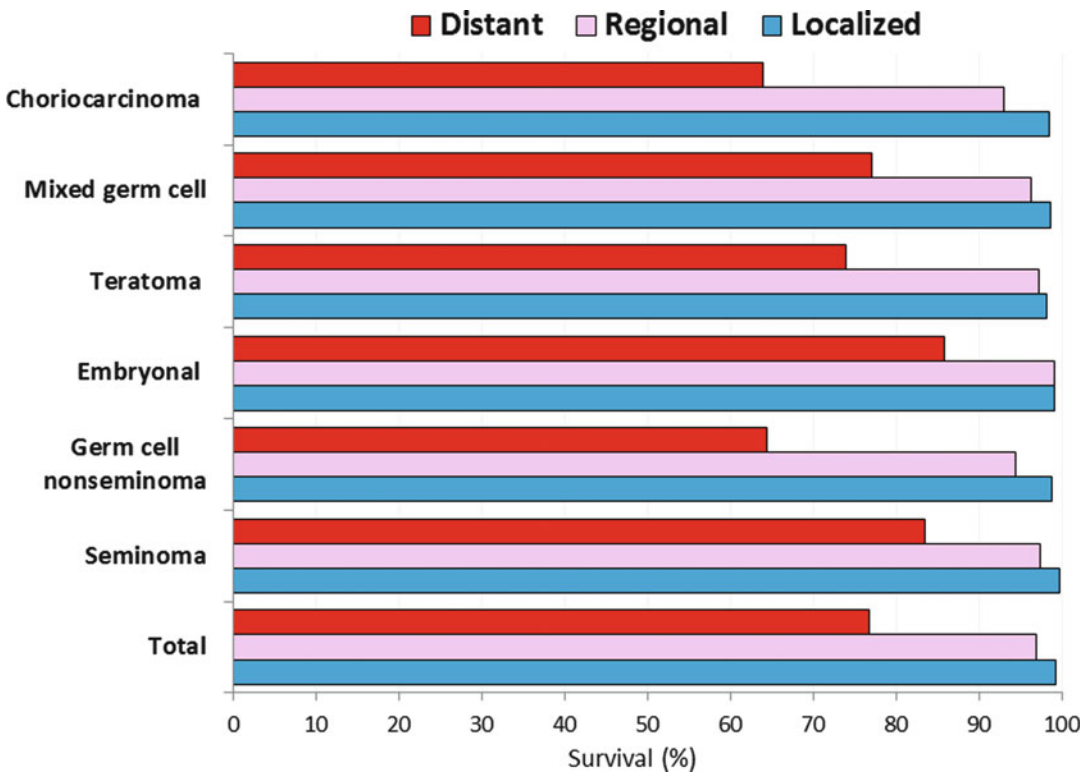

Fig. 12.6 5-year testicular cancer-specific survival, age 15–39, by histology and stage SEER 18, 2000–2010 (Data from United States National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program [4])

non-seminomatous germ cell tumors, the pure form of yolk sac tumor is rarely seen in postpubertal males. Progression from precursor lesions to invasive germ cell tumor among pubertal and postpubertal males is often associated with acquisition of excess genetic material from the short arm of chromosome 12, including isochromosome 12p [6]. This is in contrast to prepubertal males who develop pure yolk sac tumors that are commonly diploid or tetraploid [7]. Yolk sac elements are responsible for tumor production of alpha-fetoprotein (AFP). Choriocarcinoma is a less common element of germ cell tumors and rarely seen in its pure form but is associated with an aggressive course of pulmonary and extrapulmonary metastases, including the brain. The diagnosis requires a combination of cytotrophoblasts and syncytiotrophoblasts, the latter associated with production of human chorionic gonadotropin (HCG). Embryonal cell carcinoma elements are present in up to 90 % of germ cell tumors and are associated with high-level elevations in HCG. Finally, teratoma is a tumor that contains elements of endoderm, mesoderm, and ectoderm layers. The pure form of teratoma is also rare, most often seen in children under the age of 4 years.

The development of testicular germ cell tumor is likely related to a genetic predisposition and/or environmental event in fetal development based on associations with a history of cryptorchidism (including the contralateral testis), testicular atrophy, hypogonadism, infertility, testicular dysgenesis syndromes, inguinal hernias, and first-degree relatives with testicular cancer [8]. Other evidence linking genetic events includes associations with syndromes such as the dysplastic nevus syndrome or Klinefelter's syndrome, the latter linked to a higher incidence of germ cell tumors of mediastinal primary [9, 10].

12.4 Clinical Management

Testicular cancer should be the first consideration in evaluating a painless mass within the testis in a man, as this is the most common presentation. Prompt evaluation with ultrasound with help distinguish a testicular tumor from other abnormalities of the scrotum. Baseline serum tumor markers may assist in making a diagnosis of a testicular germ cell tumor and include AFP, HCG, and lactate dehydrogenase (LDH). Guidelines for the use of these tumor markers in adults with germ cell tumors have been published by the American Society of Clinical Oncology [11]. When a testicular mass is confirmed, the diagnostic procedure is a radical inguinal orchiectomy. Trans-scrotal biopsy should not be performed as seeding the scrotum with malignant cells may lead to a disruption in the pattern of regional lymphatic drainage or spread and compromise surveillance and surgical therapy. 25–35 % of young men with testicular cancer present with signs of metastatic disease, including abdominal or back pain, cough or hemoptysis, and headache. Fewer men are presenting with advanced metastatic disease over the past decade [12]. Due to predictable patterns of lymphatic spread, staging is completed with abdominal CT scan, chest x-ray or CT scan, and, in symptomatic patients, a brain MRI.

12.4.1 Prognostics

Significant differences in the approach to staging and prognostication exist between the pediatric and adult oncology fields, highlighting the need for increased cooperation across these subspecialties to harmonize the approach to caring for young adults with cancer. The pediatric staging system, outlined in the protocols of the Children's Oncology Group (COG), is listed in Table 12.1. In contrast, the adult staging system, outlined by the American Joint Committee on Cancer clinical staging, is listed in Table 12.2 [13]. The AJCC clinical staging utilizes the TNM system and limits the stages of testicular cancer to I–III, whereas the pediatric system utilizes four stages.

Table 12.1 Children's oncology group guidelines for staging of testicular germ cell tumors

Stage	Extent of disease
I	Limited to the testis (testes), completely resected by high inguinal orchiectomy; no clinical, radiographic, or histologic evidence of disease beyond the testes. Patients with normal or unknown tumor markers at diagnosis must have a negative ipsilateral retroperitoneal node sampling to confirm stage I disease if radiographic studies demonstrate lymph nodes >2 cm
II	Trans-scrotal biopsy; microscopic disease in the scrotum or high in spermatic cord (<5 cm from proximal end). Failure of tumor markers to normalize or decrease with an appropriate half-life
III	Retroperitoneal lymph node involvement, but no visceral or extra-abdominal involvement. Lymph nodes >4 cm by CT or >2 cm and <4 cm with biopsy proof
IV	Distant metastases, including the liver

In addition to different staging systems, other prognostic systems are used across the pediatric and adult world to guide treatment recommendations (Tables 12.3 and 12.4). The pediatric system focuses only on non-seminoma, as seminoma is rare in children. The adult International Germ Cell Cancer Collaborative Group (IGCCCG) system was derived from the combined analysis of over 5000 patients treated for disseminated (AJCC stage III) germ cell tumor, including patients with seminoma and non-seminoma [14]. An analysis of the application of the IGCCCG system to a cohort of pediatric germ cell tumor patients demonstrated only moderate concordance with the COG stratification system [15].

12.4.2 Treatments

Patients with stage I disease (no clinical evidence of involvement beyond the testis) are treated routinely with an orchiectomy followed by a choice of active surveillance, retroperitoneal lymph node dissection (RPLND), adjuvant radiation (for seminoma), or chemotherapy. However, large population-based studies have demonstrated that the majority of clinical stage I patients are cured by

Table 12.2 The American Joint Committee on Cancer clinical staging for testicular germ cell tumors

Tumor (pathologic)	T1: Limited to the testis/epididymis without lymphovascular invasion. May invade tunica albuginea but not tunica vaginalis
	T2: Limited to the testis/epididymis with lymphovascular invasion or extending to involve tunica vaginalis
	T3: Invades the spermatic cord with or without vascular/lymphatic invasion
	T4: Invades the scrotum with or without vascular/lymphatic invasion
Node	N1: Lymph node mass ≤2 cm in greatest dimension or multiple lymph nodes, not >2 cm in greatest dimension
	N2: Lymph node mass >2 cm but not >5 cm in greatest dimension, or multiple lymph nodes, any mass >2 cm but not >5 cm in greatest dimension
	N3: Lymph node mass >5 cm in greatest dimension
Metastasis	M1a: Non-regional lymph node or pulmonary metastasis
	M1b: Distant metastasis other than to non-regional lymph node and lungs
Stage	Extent of disease
I	Confined to the testis (any T, N0, M0)
II	Metastatic disease to the nodes of the periaortic or vena caval zone without pulmonary or visceral involvement (any T, any N, M0)
III	Metastasis above the diaphragm or involving other viscera (any T, any N, M1)

Edge et al. [13]

Table 12.3 Children's Oncology Group: risk stratification for newly diagnosed malignant germ cell tumors

Prognosis	Characteristics
Low/intermediate risk – 100 %/97 % 6-year survival	Testicular stage I/II
High risk – 90 % 6-year survival	Testicular stage III/IV Extragonadal stage III/IV

orchiectomy alone, without the need for other toxic therapies [16, 17]. Furthermore, those patients on surveillance who progress and require additional therapy have an outstanding cure rate. This has led to an increasing trend to manage stage I patients with active surveillance, regardless of prognostic features [18, 19]. Some providers instead apply a risk-adapted model in which stage I patients with high-risk features such as vascular invasion are offered adjuvant therapy with only one cycle of chemotherapy [20]. Proposals to decrease the frequency of surveillance testing, including the radiation exposure delivered by CT scans, have also been proposed [21].

For those patients with clinical stage II–III disease, including those with tumor markers that fail to normalize, cisplatin-based chemotherapy can lead to a very high rate of cure. It should be noted that again there may be differences in the approach of pediatric- and adult-trained oncologists. In the COG trial AGCT0132, patients with low-risk non-seminomatous disease were treated with surgery followed by observation. Patients with progression were treated as those with intermediate risk and given three cycles of compressed PEb [22]. This PEb regimen differs from the adult BEP regimen by reducing the dose of bleomycin from 15 U/m^2 weekly to 15 U/m^2 every 3 weeks and by compressing the doses of cisplatin (total dose 100 mg/m^2 per cycle) and etoposide (total dose 500 mg/m^2 per cycle) over 3 days instead of 5 days [23]. However, in a study of 3-day versus 5-day BEP in adults, increased nausea, ototoxicity, and neurotoxicity were observed without any improvement in outcomes, and hence a 3-day regimen has been largely abandoned [24]. Good-risk adult patients with stage II or III non-seminoma commonly receive three cycles of BEP, although those who cannot receive bleomycin due to allergic reaction or concerns for underlying pulmonary function may be offered four cycles of EP [25]. Adult patients with IGCCCG intermediate and poor prognosis non-seminoma receive four cycles of BEP. For all patients, carboplatin should not be substituted for cisplatin. In patients with non-seminoma and significant residual radiographic abnormalities after primary chemotherapy, RPLND is considered for both diagnostic and therapeutic purposes.

The treatment of seminoma differs from non-seminoma, due to the less aggressive biological

Table 12.4 International Germ Cell Consensus Classification: for metastatic germ cell testicular cancer

	Characteristics	
Prognosis	Non-seminoma	Seminoma
Good	Testis or retroperitoneal primary and no non-pulmonary visceral metastases and α-fetoprotein <1000 ng/mL, βHCG <5000 IU/L, and LDH <1.5 upper limit of normal –92 % 5-year survival	Any primary site and no non-pulmonary visceral metastases and normal α-fetoprotein, any βHCG, any LDH –86 % 5-year survival
Intermediate	Testis or retroperitoneal primary and no non-pulmonary visceral metastases and α-fetoprotein >1000 ng/mL and <10,000 ng/mL or βHCG >5000 IU/L and <50,000 IU/L, or LDH >1.5 normal and <10 normal –80 % 5-year survival	Any primary site and non-pulmonary visceral metastases and normal α-fetoprotein, any βHCG, any LDH –72 % 5-year survival
Poor	Mediastinal primary or non-pulmonary visceral metastases or α-fetoprotein >10,000 ng/mL or βHCG >50,000 IU/L or LDH >10 upper limit of normal –48 % 5-year survival	None

Mead [14]

behavior as well as the exquisite sensitivity of seminoma to radiation therapy and chemotherapy. Approximately 75 % of patients with seminoma present with clinical stage I disease. Surveillance studies have demonstrated that 80–85 % of patients with clinical stage I seminoma are cured with orchiectomy alone, although late relapses do occur. The addition of low-dose (20 Gy in 2 Gy fractions) adjuvant para-aortic radiation reduces relapse rates to only 4 %, with most patients responsive to additional radiation or chemotherapy after a relapse. Similar reductions in relapse rates have been shown with one cycle of adjuvant carboplatin [26]. For patients presenting with bulky stage II or stage III disease, cisplatin-based chemotherapy is associated with cure rates of more than 90 %. Unlike in non-seminoma, RPLND is rarely used for removal of residual masses after chemotherapy for seminoma, and PET scanning is of value in this setting.

Treatment of recurrent or refractory germ cell tumor is often referred to centers of expertise, but several important principles apply. First, the majority of patients may still be cured by second-line treatment that often includes high-dose chemotherapy and selective application of surgery [27]. Caution should be used when establishing a diagnosis of relapsed or refractory disease based on elevations in serum tumor markers. False-positive elevation of AFP is quite rare, with differential considerations including laboratory error, other tumor types such as hepatoma, or liver inflammation. False elevations of HCG may occur in patients who use marijuana, and there is some cross-reactivity in the radioimmunoassay with luteinizing hormone. In cases of persistently elevated HCG, patients should be asked about marijuana use, and testosterone should be administered to ensure that a hypogonadal state with resultant high levels of luteinizing hormone is not interfering with the HCG measurement. If the serum tumor markers remain elevated, restaging procedures and investigation of sanctuary sites, including the brain and contralateral testis, should be considered.

12.5 Psychosocial Impact and Late Effects

The high rates of survival, in some cases after multimodality therapies, in a young population with many years of life ahead bring challenges in addressing the survivorship needs of AYAs with testicular cancer. This is an area of growing research attention and clinical guidelines [28].

Late psychosocial effects among testicular cancer survivors may include fear of recurrence, survivor guilt, sleep disturbance, cognitive dysfunction, anxiety or depression, difficulty with formation of relationships, and sexual dysfunction [29–31].

Medical late effects related to either the underlying disease or the treatment can affect testicular cancer survivors. Cisplatin causes both renal glomerular and tubular dysfunction with decreases in glomerular filtration rate and wasting of magnesium, which fortunately is often subclinical [32]. Cisplatin is also associated with a dose-related high-frequency hearing loss among 20–40 % of patients (which may be permanent) and peripheral neuropathy [33, 34]. Bleomycin may be responsible for lung disease in a dose-related fashion, with approximately 5 % developing pulmonary fibrosis [35]. Risk factors for bleomycin lung toxicity also include increased age, concomitant chest radiation, decreased renal function, and high concentrations of inspired oxygen. Importantly, a radiographic presentation of bleomycin-induced lung disease may be subpleural-based nodules that may be mistaken for relapsed or refractory cancer.

Raynaud's phenomenon is the most common vascular toxicity, associated with bleomycin exposure [36]. However, acute arterial ischemic events including myocardial infarctions and cerebrovascular events have been reported after testicular cancer chemotherapy [37]. Long-term follow-up studies of testicular cancer survivors have documented components of the metabolic syndrome among testicular cancer survivors, including the risk factors of hypertension, glucose intolerance, and unfavorable lipid profiles [38].

Fertility after testicular cancer may also be impaired. Beyond the physical effects of orchiectomy and the rare complication of retrograde ejaculation after RPLND, it is reported that some men have testicular atrophy or baseline abnormalities in sperm counts and/or testosterone levels even prior to treatment of testicular cancer. Gonadal dysfunction is common in patients with a history of testicular cancer even when treated with orchiectomy only [39]. However, most patients return to their baseline fertility with one report of the probability of spermatogenesis after orchiectomy and cisplatin-based chemotherapy increasing from 48 % at 2 years to 80 % by 5 years [40].

The highest risk for second malignancy after testicular cancer is in fact a second primary testicular cancer in the contralateral testis. However, therapy-associated secondary cancer risks include carcinomas in sites of prior radiation or myelodysplasia and acute leukemia associated with etoposide and characterized by abnormalities in the MLL gene [41].

Conclusions

Testicular cancer is a prototypic young adult malignancy. Epidemiologic trends show that many facets of risk related to geography and race/ethnicity are still poorly understood. Survival rates with modern therapy are high, but delivery of care among AYAs is hampered by the need to develop standardized approaches to prognostication and therapy across the disciplines of pediatric and adult oncology. With high rates of survival, quality care must include attention to the long-term consequences of therapy.

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Colorectal and Anal Tumors

13

Kevin Zbuk, Oren Levine, James Trocoli, and Michael La Quaglia

13.1 Introduction

Cancers of the lower gastrointestinal (GI) tract are a major cause of morbidity and mortality and among the most common cancers affecting men and women alike. Adenocarcinoma of the colon and rectum and anal squamous cell carcinoma (SCC) are the predominant diseases in this category. Colorectal cancer (CRC) is the third most common malignancy in the US population with nearly 140,000 new cases diagnosed and over 50,000 deaths from CRC in 2014 [1]. The incidence of CRC in adolescents and young adults (AYAs) has been increasing in recent years. Anal SCC is less common, but its incidence is also increasing. Malignancy of the lower GI tract in the AYA population will be reviewed in this chapter.

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13.2 Incidence

As illustrated by Fig. 13.1, the incidence of CRC, as well as anal SCC, increases exponentially as a function of age from 15 to 40 years. Despite this trend, approximately 90 % of CRC cases occur after the age of 50 years, and the disease remains extremely rare in those ≤20 years of age, with an estimated annual incidence in the Unites States of around one case per one million persons [2]. Recent SEER data demonstrate that around 5 % of all CRC cases are diagnosed in patients younger than 45 years [3]. Rectal cancer appears to be more common among young adults, in whom 18 % are less than 50 years at the age of diagnosis [2]. CRC occurs at similar rates in AYAs of both genders.

Incidence of CRC varies by ethnic group. In those older than 25 years, rates of invasive CRC are highest among black and non-Hispanic white populations. At ages younger than 25, rates are comparable among different races. In general, CRC in young adults is more common among minorities and in those who are uninsured [4].

As illustrated in Fig. 13.2, the incidence of CRC in general has been decreasing since 1976, likely in part related to population-based screening; however, the incidence of CRC is increasing in AYAs [2]. The cause for increasing rates of CRC in this younger population is unclear. However, the trend has been consistently demonstrated in both hospital and population-based

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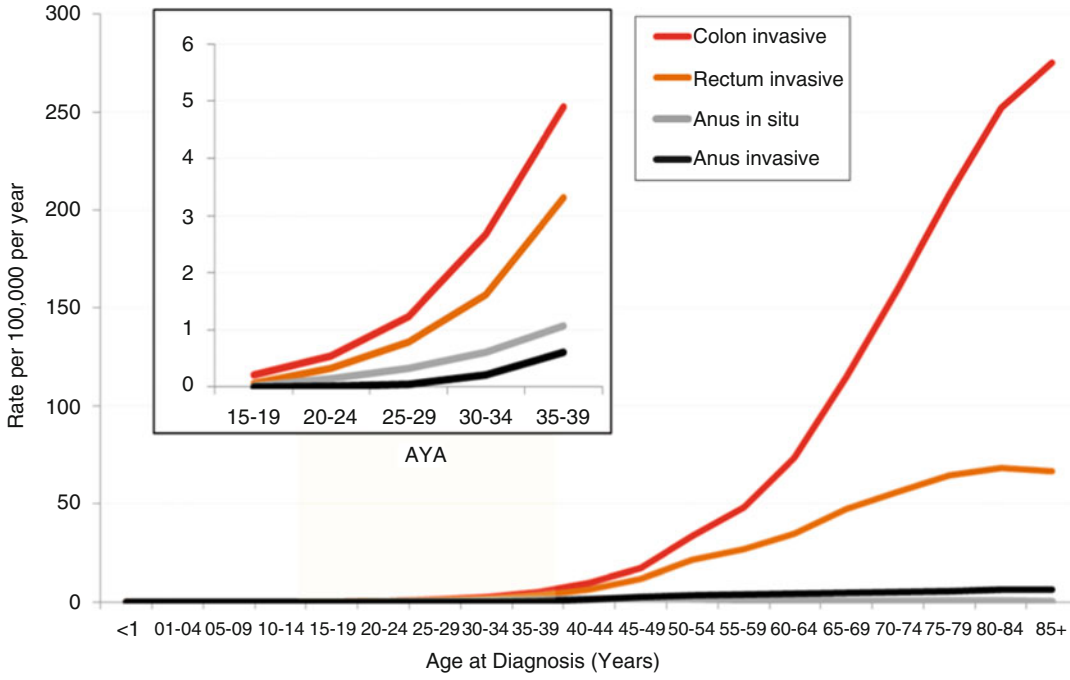

Fig. 13.1 Incidence of invasive and in situ malignancy of the colorectum (adenocarcinoma) and the anal canal (squamous cell carcinoma), United States, SEER 2000–2011. In AYAs (*inset*) incidence increases exponentially with age (Ries L, Bleyer A, personal communication 2015)

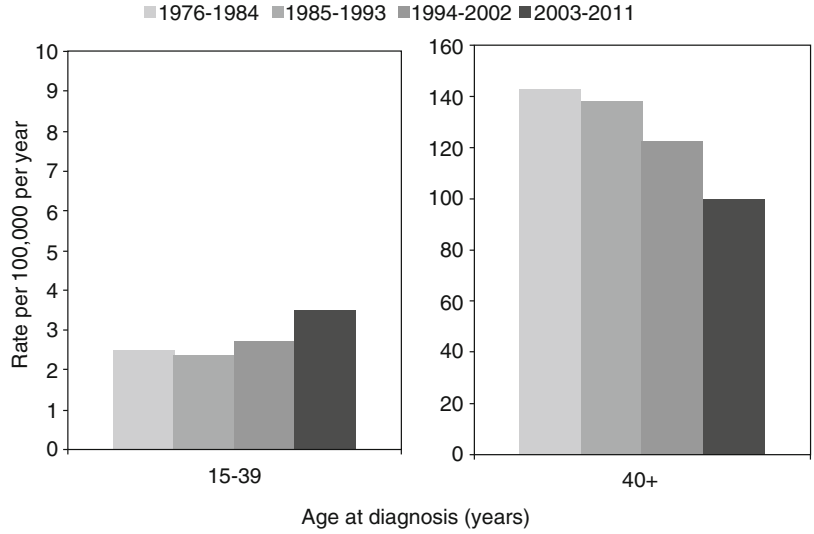

Fig. 13.2 Incidence trends for invasive adenocarcinoma of the colon by age and sex, United States, SEER 1976–2011. Rates of disease are decreasing in older adults, but increasing in AYAs (Ries L, Bleyer A, personal communication)

studies [5]. It is hypothesized that there may be an association with lifestyle factors, including obesity and lack of physical activity. Although similar lifestyle trends are affecting the older adult population, older patients are benefiting from risk reduction with colonoscopy and polypectomy, in addition to other forms of screening such as fecal occult blood testing [2]. Incidence of rectal cancer in AYAs appears to be increasing more rapidly than that of colon cancer [4].

13.3 Etiology

13.3.1 Inherited Syndromes

The majority of cancers of the colon or rectum, even in the AYA population, are sporadic in nature. In AYAs with CRC, only 22 % of patients have a family history of colorectal cancer, and 16 % have a clearly identifiable risk factor [6]. Nevertheless, several familial syndromes are well defined and confer an increased risk of CRC. Overall, 3–5 % of CRC cases are attributable to a defined hereditary syndrome [7].

13.3.1.1 Lynch Syndrome

Lynch syndrome (LS) is the most common form of hereditary CRC. It has also been termed hereditary nonpolyposis colon cancer, named as such to distinguish it from the polyposis associated with familial adenomatous polyposis (FAP). However, this name has recently lost favor, as it minimizes the importance of non-colorectal cancer risk associated with the syndrome. In addition, individuals with LS often do develop colonic adenomatous polyps, and these polyps progress though the adenoma to carcinoma sequence much more rapidly than sporadic adenomas of the colon. Lifetime risk of CRC in Lynch syndrome is 70 % with median onset in the fifth decade [8]. Importantly, 40 % of cases are diagnosed before age 40. Lynch syndrome-associated colon cancers are often right-sided lesions with mucinous histology and are high grade. Synchronous or metachronous bowel cancers are common. There is also an increased risk of extracolonic malignancies including cancers of the endometrium, ovary, stomach, small bowel, pancreas, biliary tree, ureter, and renal pelvis [9].

The clinical diagnosis has historically been made by applying the Amsterdam criteria that rely solely on personal and family history of LS-related cancers. In the adult population, sensitivity is reported to be 78 % [10]; however, in one series of 16 AYA patients with colon cancer, only 50 % fulfilled Amsterdam criteria, and 60 % of those not meeting Amsterdam criteria had a diagnosis of LS confirmed by molecular testing [11]. These results further support the general trend in recent years toward performing universal screening for LS on all incident colorectal cancer cases. Such screening involves relatively simple immunohistochemical analysis and/or microsatellite-instability testing (see below).

The mechanism underlying Lynch syndrome is defective DNA mismatch repair (MMR) genes. Germline mutations in the tumor suppressor genes *MLH1* and *MSH2* account for the majority of diagnoses; however, other genes including MSH6 and PMS2 have been implicated [12]. Furthermore, mutation of the *EPCAM* gene adjacent to *MSH2* can result in changes to the promoter region and subsequent gene silencing of *MSH2* [13]. DNA MMR defects result in accumulation of gene mutations, ultimately leading to tumorigenesis. The regions of DNA most susceptible to dysfunctional mismatch repair are areas known as micro- satellites, noncoding regions of repeating base pairs. These regions may increase or decrease in length, a finding known as microsatellite instability (MSI), that is, a hallmark of underlying deficiency of the MMR genes [9]. It is important to note, however, that the majority of tumors exhibiting MSI will not be due to Lynch syndrome. In fact, 10–15 % of sporadic colorectal tumors will also demonstrate MSI, but this is usually due to somatic *MLH1* hypermethylation, leading to decreased protein transcription rather than germline gene mutations [9]. Irrespective of the etiology, tumors with MSI are associated with distinct prognostic and predictive characteristics that are discussed later in the chapter.

Recently, patients with homozygous or compound heterozygous (bi-allelic) MMR gene mutations have been reported. Such cases, referred to as constitutive MMR gene mutations, are often associated with a strikingly young age of cancer diagnosis. Most affected individuals will have evidence of café-au-lait spots, and CNS and hematologic malignancies are common. Many families have evidence of consanguinity, and in most instances, parents of affected children have no evidence of LS-related malignancies themselves [11, 14]. The spectrum on GI manifestations is extremely variable; however, when present, CRC is often diagnosed in adolescence, with a mean age of onset of 16 years in one series [15]. A heightened awareness of this syndrome is necessary when an AYA presents

Table 13.1 Surveillance protocol for constitutive mismatch repair mutation carriers [14]

Cancer type	Screening test
Colon and rectum	Colonoscopy annually (beginning age 6)
Upper gastrointestinal	Esophagogastroduodenoscopy annually (beginning age 6)
Small bowel	Video capsule endoscopy annually
Brain	Ultrasound at birth, MRI biannually
Uterus	Ultrasound annually
Urinary tract	Ultrasound annually

with malignancy, given the absence of relevant family history in most cases. In addition, many individuals present with non-colonic malignancies as their first presentation, with CRC as a subsequent malignancy. A set of surveillance strategies has been developed recently for constitutive MMR mutation carriers (Table 13.1).

13.3.1.2 Familial Adenomatous Polyposis

Several genetic syndromes predispose to polyp formation, which is often a precursor to invasive CRC. Polyposis syndromes include family adenomatous polyposis (FAP) and MutYH-associated polyposis (MAP, an autosomal recessive disorder similar to FAP), characterized by adenomatous polyps. In contrast, Peutz-Jeghers syndrome, juvenile polyposis syndrome, and Cowden syndrome are often associated with hamartomatous and/or inflammatory polyps [7, 16, 17]. An exhaustive discussion of these syndromes is beyond the scope of this chapter, and, therefore, only FAP, the most common polyposis syndrome, will be discussed further.

FAP is an autosomal dominant condition occurring at a rate of 1/7,000 in the general population [18]. This syndrome classically manifests with hundreds to thousands of polyps throughout the colon. Around 95 % of affected patients will have polyps by age 35, but cases of polyposis with onset at ages as young as 5 years have been described [19]. Without surgical intervention, FAP carries at lifetime risk of invasive malignancy approaching 100 %, with median age of onset of 39 years. Invasive neoplasia affects 7 % by age 20 and 15 % by age 25. In addition to CRC, associated malignancies include duodenal adenocarcinoma and thyroid carcinoma [9].

FAP results from mutation of the adenomatous polyposis coli (APC) gene located on chromosome 5 that results in loss of function of this tumor suppressor gene [9, 20]. Mutations in different regions of the APC gene have been associated with variable phenotypes, and mutations of codon 1309 result in severe polyposis and a particularly young age of onset, with polyps sometimes developing in the first decade of life [21].

Patients with a family history of FAP should undergo colonoscopic screening for polyps starting at age 10–12 or 10 years earlier than the age at presentation of the youngest familial case [22]. Management ultimately involves prophylactic colectomy. Timing is individualized taking into consideration total adenoma burden, degree of dysplasia, mutational genotype, and emotional maturity of the patient. Three surgical approaches can be offered. Although most efficacious with respect to reducing cancer risk, total proctocolectomy with end ileostomy is least favored, due to requirement of a permanent ostomy. In most instances, subtotal colectomy and ileorectal anastomosis (IRA) or total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the treatment of choice. For IRA or IPAA, ongoing endoscopic surveillance is required due to cancer risk in the residual rectum or pouch [23].

13.3.2 Acquired Risk Factors

Beyond inherited syndromes, several predisposing factors for CRC in AYA have been described. Prior abdominal radiation, for example, in patients treated for childhood rhabdomyosarcoma, increases risk of CRC [24]. Screening with colonoscopy is recommended starting at age 35 or 10 years following radiation, whichever is later, for patients receiving ≥30 Gy of radiation

to the pelvis [25]. Inflammatory bowel disease increases the risk of malignancy. Those diagnosed in childhood or adolescence carry a higher risk of malignancy in young adulthood [26]. For patients with ulcerative colitis, the cancer risk is 10% for every decade of active disease beyond 10 years from diagnosis.

13.4 Biology

Compared to the very extensive study of CRC biology in older adults, there remains a paucity of data in AYA. However, there is a suggestion that the biology of CRC in this population demonstrates certain differences from that seen in older populations. Although some studies have suggested more right-sided tumors [27], others have in fact demonstrated a left-sided predominance [28]. Tumors often have a prominent mucinous component, are poorly differentiated, and display signet-ring cells. LaQuaglia et al. reported the presence of signet-ring cell histology in 45% of cases in a cohort of 29 patients 21 years of age or younger with CRC [29]. Karnak et al. reported a prevalence of mucinous adenocarcinoma of 80% in a series of 20 AYA patients with CRC [30]. In a review of pediatric CRC patients, mucinous features were present in 62% of cases. In a larger study of 167 patients younger than 21 years of age, LaQuaglia confirmed a predominance of high-grade tumors with frequent signet-ring histology [27]. In SEER data comparing patients under 40 years of age with older patients, mucinous tumors constituted 21% of the lesions in younger patients compared to 10–12% in older adults, while the percentage of tumors that were poorly differentiated was 27% compared with 15% for older patients [31]. Similar histologic finding was reported in a large retrospective cohort study [28]. These histologic features are often associated with poor prognosis in older populations. However, such features are also common in tumors exhibiting MSI and in such instances do not appear to portent a poorer prognosis in older populations.

MSI is more common in AYAs with CRC compared to older patients, irrespective of whether it is related to underlying Lynch syndrome. Datta et al. reported MSI in 6 out of 13 patients who were under 21 years of age [32]. LaQuaglia et al. found MSI in 17% of AYA patients [27]. However, unlike older populations, MSI does not appear to clearly correlate with distinct clinical, histological, or familial features compared to MSI-negative cancers in AYAs. Some studies in AYAs have suggested that, similar to MSI in older patients, MSI might be associated with better prognosis compared with microsatellite-stable tumors [27]. Microsatellite instability high (MSI-H) tumors also exhibit a significantly lower prevalence of k-RAS mutations that, when present, predict resistance to epidermal growth factor receptor (EGFR) inhibitors (see Management section 13.8.2.2).

Tumors without MSI in young adults appear to be associated with hypomethylation of proto-oncogenes, alluding to potential unique pathogenesis among this group of patients [33]. A study analyzing genomic complexity (gene copy number) and somatic mutation frequency in five genes critical to CRC development found that tumors from young adults tended to have more genomic complexity, P53 and PTEN mutations, and no PIK3CA mutations [34].

13.5 Presentation and Symptoms

The presenting symptoms of CRC in AYA, similar to older adults, are often nonspecific. With the exception of patients previously identified with a hereditary form of CRC predisposition, the diagnosis of CRC in asymptomatic AYA patients is uncommon. Vague, generalized abdominal pain is the most common symptom [29, 30, 35, 36]. Localizing abdominal pain is usually an indication of peritoneal involvement or perforation, indicating advanced disease locally. In this age group, localized pain is occasionally suggestive of appendicitis [37, 38]. Weight loss was noted in two thirds of young patients presenting with CRC

in a review from St. Jude Children's Research Hospital [24]. Other less frequent associated symptoms include nausea, vomiting, diarrhea, constipation, anorexia, rectal bleeding, pallor, abdominal distension, dysuria, and intestinal obstruction [29, 35, 36]. Symptoms generally relate to location of the primary tumor in the bowel. In young adults, the most common tumor location is the rectosigmoid followed by right-sided lesions. The former may cause changes in bowel habits and stool caliber, whereas the latter is more likely to present with symptoms associated with anemia. Very distal tumors may present with bleeding per rectum and tenesmus.

Studies suggest that there may be considerable delay in diagnosis of CRC in AYA, with time from symptom onset to diagnosis often exceeding 6 months [6, 29]. This is likely due to both patients and physicians having a low level of suspicion for a malignant diagnosis [2, 24]. Other contributors may include a sense of invincibility in AYAs and, in the United States, lack of medical insurance in this group [39, 40]. It has not been determined whether delay in diagnosis has a direct impact on outcome; however, it is apparent that CRC in AYAs is more likely to present at an advanced stage compared with older patients [30, 38]. In a retrospective review of pediatric CRC cases, 86% had advanced disease at presentation, with more than 50% of cases presenting with metastatic disease [27].

One study compared symptom burden among patients ages 18–39 to older adults (>40) diagnosed with CRC, most of whom where receiving chemotherapy and/or radiation. Young patients were more likely to report moderate to severe symptom scores for pain, fatigue, nausea, distress, dyspnea, drowsiness, and rash. This group reported that symptoms interfered with activity, mood, work, relations with others, and enjoyment of life to a greater degree than older patients [41].

13.6 Diagnosis and Staging

For diagnosis of CRC, colonoscopy is the investigation of choice, with the benefit of direct visualization of the mucosa and the ability to biopsy an abnormal lesion. It should be noted, however, that in the event of an obstructing malignant lesion, bowel preparation is unlikely to be tolerable, and in such instances patients may require definitive surgery without biopsy. Double-contrast barium enema offers low diagnostic yield and has largely been replaced by endoscopic investigation. Computed tomographic (CT) colonography is emerging as a useful test in screening for colorectal neoplasm; however it has a limited role in the workup of a symptomatic patient and therefore is rarely used in AYAs with suspected CRC [42].

For staging of CRC, CT scan of the chest, abdomen, and pelvis with lung and liver windows is the investigation of choice to identify distant metastasis. Both IV and oral contrast should be used for enhancement. Magnetic resonance imaging (MRI) of the pelvis is useful in staging of rectal tumors to assess for compromise of the mesorectal margin and/or regional lymph node enlargement [43, 44]. CT-PET may be useful in full staging of metastatic disease; however, currently this is not routinely recommended as a standard component of staging [45, 46]. Of note, positron emission tomography (PET) imaging is less sensitive at detecting metastasis in the setting of mucinous histology, a histologic feature more common in the AYA population compared to older patients. PET scan has been evaluated as a tool to identify the extent of metastatic disease prior to hepatectomy in the case of isolated liver metastasis. In a randomized trial, preoperative PET scan did not often change the surgical plan and hence is not recommended for routine use in this context [47].

Carcinoembryonic antigen (CEA) is a tumor marker commonly measured in older adults. When elevated, it may be a useful indicator of disease burden and response to treatment. This blood test has not been specifically studied in the AYA group.

Staging is performed following the American Joint Commission on Cancer tumor, node, and metastasis (TNM) guidelines [48]. This system is depicted in Table 13.2. Depth of tumor invasion, involvement of regional lymph nodes, and presence of metastases are combined to determine stage. Resulting subgroupings show significant differences in 5-year survival rates; hence stage is a powerful prognostic indicator.

Table 13.2 American Joint Commission on Cancer staging system for colorectal cancer [48]

Primary tumor (T)		Regional lymph nodes (N)	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastases
Tis	Carcinoma in situ	N1	Metastases in 1–3 nodes
T1	Invades submucosa	N1a	Metastasis in 1 node
T2	Invades muscularis propria	N1b	Metastases in 2–3 nodes
T3	Invades through muscularis propria into pericolorectal tissues	N1c	Tumor deposit(s) in subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
T4a	Tumor penetrates to the surface of the visceral peritoneum	N2	Metastasis in four or more nodes
T4b	Tumor directly invades or is adherent to other organs or structures	N2a	Metastasis in 4–6 nodes
		N2b	Metastasis in seven or more nodes
Distant metastases (M)			
MX	Presence of distant metastases cannot be assessed		
M0	No distant metastases		
M1	Distant metastases present		

13.7 Prognosis

Five-year survival rates for CRC have been improving over time for both AYAs and older adult populations (see Fig. 13.3). Improvements have been less pronounced for AYA females compared to males. The results of some studies suggest poorer survival in the young [6, 40, 49], while other studies show comparable or better survival relative to patients diagnosed as having later-onset disease [50–52]. Between 2000 and 2011, 5-year survival rates were higher in AYAs compared to older adults with CRC. As an illustration, 5-year survival in stage 4 disease was 18.1 % in AYAs versus 6.2 % in the older group [50]. A very large cohort study recently reported outcomes of younger adults with CRC compared to older patients. Utilizing the US cancer registry database, greater than 13,000 patients 18–49 years of age were compared with 37,000 aged 65–75 years. Similar to previous findings, the younger cohort often presented with advantaged stage disease (62 % stages 3 and 4). However, stage-specific survival was similar for those presenting with stage 2 disease in the two groups, while survival was marginally better for younger adults with stage 3 and 4 disease. Importantly, the younger age group was statistically more likely to be treated with systemic therapy at all stages of disease presentation. This included a significant proportion of patients with stage 1 and low-risk stage 2 disease, in which chemotherapy is not considered standard of care [53]. Similar results were found in a cohort of patients with rectal cancer, in whom rates of radiation treatment were much higher in younger versus older patients, and stage-specific disease-free survival was similar in the two cohorts [54].

The issue of prognosis of CRC in AYA compared to older populations is therefore complex. On one hand, AYAs present at later stages of diagnosis, and the biology might be more aggressive. Conversely, AYAs have less comorbidity and are treated more aggressively than their older counterparts. It is not surprising, therefore, that data on prognosis in AYAs with CRC has been inconsistent thus far. Prospective data from registries of AYAs treated with modern chemotherapy, in the era of aggressive treatment of metastatic disease, will be required to further clarify prognosis.

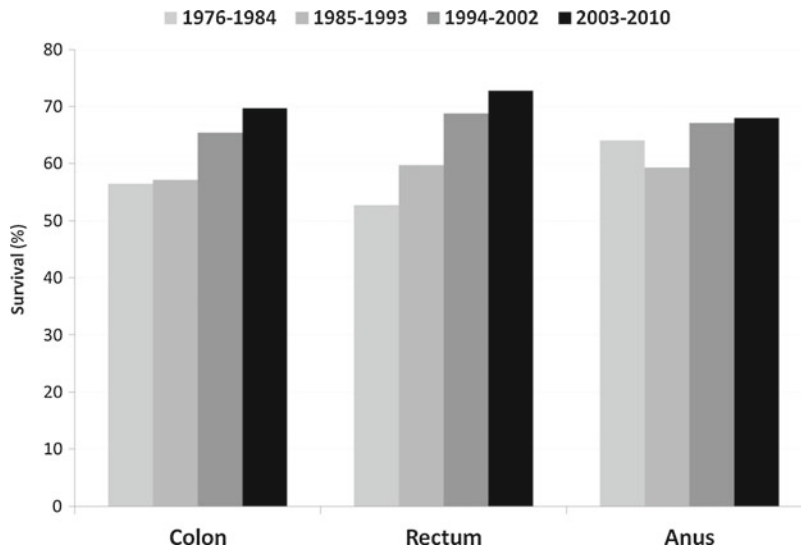

Fig. 13.3 5-year survival trends for invasive cancer of colon, rectum, and anus for patients aged 15–39, United States, SEER 1976–2010. Survival rates have improved over time (Ries L, Bleyer A, personal communication)

13.8 Management of Colorectal Cancer

Treatment guidelines for young patients are usually extrapolated from adult trials, as the rare nature of CRC in AYAs precludes dedicated trials with adequate statistical power. A multidisciplinary approach is essential, and early referral to centers that are expert in the care of young patients with cancer will ensure the best possible outcome.

13.8.1 Surgery

Extirpative surgery, including extensive regional lymphadenectomy, with curative intent is the mainstay of treatment. In fact, if patients cannot be rendered surgically free of disease, they are rarely cured. Resection should follow guidelines established in adults. In particular, primary and secondary draining lymph node echelons should be removed. The basic surgical principles include resection of the major vascular pedicle supplying the tumor along with its lymphatics and en bloc resection of any organs or structures attached to the tumor. A margin of at least 5 cm of normal bowel should be removed on either side of the tumor to minimize the risk of recurrence at the anastomosis [55]. For tumors of the cecum and ascending colon, a right hemicolectomy should be performed. Lesions of the descending and sigmoid colon are managed with left hemicolectomy. Rectal cancer should be resected following the principle of total mesorectal excision (TME) in order to limit risk of local recurrence [56].

Adequate lymph node resection is imperative because some patients with stage 3 tumors are cured by surgery alone. In addition, patients with inadequate lymph node sampling may be inaccurately under-staged. In the older adult population, the standard of care requires sampling of a minimum of 12 lymph nodes; however, in the AYA population, the ideal extent of nodal sampling is uncertain. In one pediatric study, sampling less than 17 nodes in stage 2 disease was associated with worse prognosis [24]. It is reassuring that younger patients are likely to have more nodes resected according to one study [51].

Since the pattern of spread of mucinous CRC may be intraperitoneal, a meticulous exploration of the peritoneal surface, including that overlying Gerota's fascia and the diaphragm, should be undertaken at laparotomy. If feasible, all peritoneal nodules should be removed. If CRC is found unexpectedly during abdominal surgery for another indication, the surgeon should convert

the procedure to a standard colon cancer resection with excision of draining lymphatics. This may necessitate closing the original wound (e.g., an appendectomy incision) and changing approach. Cases of localized recurrence may benefit from re-excision.

Hyperthermic perfusion of the peritoneal cavity after colon resection and peritonectomy has been applied, but even in the adult population, evidence is limited. One randomized trial and several cohort studies support survival benefit with peritoneal stripping and hyperthermic intraperitoneal chemotherapy for the carefully selected patient with isolated disease recurrence in the peritoneum [57–59]. Thus, referral to a center experienced in cytoreductive surgical management may be appropriate for some patients. There are not enough data to recommend this approach in all patients.

Unfortunately, the initial surgery is not performed as a cancer operation in many AYA patients. In those instances, reexploration of the abdomen with the goals of achieving a full oncologic resection should be performed at a center experienced with this type of surgery.

13.8.2 Systemic Therapy

13.8.2.1 Adjuvant Therapy for Early-Stage Disease

Systemic chemotherapy is often given following resection of CRC, with the goal of eradicating micrometastatic disease and preventing cancer recurrence. Prognostic features of the primary tumor are used to determine the role for adjuvant chemotherapy and, most importantly, stage.

Completely resected early CRC with adequate lymph node sampling that does not invade through the muscularis propria (T1S-2, N0, M0; stages 1–2) has an 80–90 % overall survival rate with no additional therapy. Clinical surveillance is recommended. For stage 2 or greater, minimal follow-up recommendations according to the American Society of Clinical Oncology (ASCO) endorsement of Cancer Care Ontario guidelines include history, physical exam, and measurement of CEA levels every 3–6 months for 5 years. Colonoscopy should be done within 1 year of surgery and then every 5 years or at a frequency determined by findings on the previous test. CT scan of the chest and abdomen should be carried out annually for 3 years [60]. Recurrent CRC is often limited to the liver and, if detected early, may be managed with curative resection in some circumstances. Hence, there is a role for close surveillance even in the asymptomatic patient.

Adjuvant chemotherapy should be considered for stage 3 colon cancer (T1-4, N1-2, M0) or stage 2 (T3-4, N0) with high-risk features. High-risk stage 2 CRC, defined by obstruction or perforation at presentation, high-grade histology, tumor penetration of visceral peritoneum, inadequate lymph node sampling, or presence of lymphovascular and/or perineural invasion, carries a higher risk of disease recurrence. In the adjuvant setting, 6 months of fluorouracil- and oxaliplatin-based chemotherapy (FOLFOX) has become the standard of care, having shown improvement in overall survival compared to 5-FU and leucovorin (LV). Although most evidence comes from the older adult population, the landmark Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial enrolled patients as young as 19 years of age [61]. A pooled analysis of nine adjuvant chemotherapy trials suggested that patients less than 50 years old experienced less diarrhea and neutropenia and more nausea associated with chemotherapy, compared to older patients [62]. Although progression-free survival was slightly worse in the younger population, overall survival was no different. A larger pooled analysis of 24 randomized trials showed similar toxicity and efficacy outcomes [63].

In addition to stage, detection of MSI carries prognostic and predictive information. Deficiency in DNA mismatch repair confers a better prognosis compared to microsatellite-stable disease regardless of stage [64]. Furthermore, MSI-H predicts a lack of benefit from fluorouracil chemotherapy in the adjuvant setting; however, response to oxaliplatin based on MSI status is undefined [65, 66].

When adjuvant chemotherapy is offered, time from surgery to start of chemotherapy is impor-

tant. Optimal survival outcomes occur when systemic therapy is initiated within 4 weeks of surgery (which is generally the required time to recover from a colon resection), but with every additional 4 weeks of time elapsed there is detriment to survival [67].

13.8.2.2 Metastatic Disease

In the context of extensive distant metastatic disease, systemic therapy is provided for palliative intent. Recent approval of novel chemotherapeutic agents and targeted therapies has incrementally improved median overall survival with distant disease. With multiple lines of therapy, median survival exceeds 2.5 years, and a small subset of patients will achieve durable disease control exceeding 5 years. First-line therapy may include combination chemotherapy containing fluorouracil and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). The alternative regimen can be used in the event of disease progression [68]. A meta-analysis shows that age less than 50 years is not predictive of survival outcomes with the use of palliative chemotherapy [69]. Bevacizumab, an antiangiogenic monoclonal antibody, improves response rate and survival when added to first-line chemotherapy [70]. There is modest benefit when antiangiogenic agents are offered in combination with second-line chemotherapy with evidence supporting continuation of bevacizumab [71] or the use of aflibercept, a recombinant fusion molecule [71, 72]. For k-RAS wild-type disease, targeted therapy against the EGFR may be effective after the use of standard cytotoxic chemotherapy or in combinations in first- and second-line treatment [73, 74]. Regorafenib, a small-molecule-targeted antiangiogenic agent, has been approved for use in advanced disease after progression on all standard therapies [75]. Patients with minimal hepatic or pulmonary metastases should be evaluated for resection.

13.8.3 Radiation

The role of radiation therapy in AYAs with CRC depends on the location of the primary disease. In general, radiation reduces the risk of local recurrence of primary rectal cancers, and occasionally it is useful in managing locally advanced, inoperable disease. Preoperative MRI can be used to assess the depth of penetration and nodal status of a primary rectal cancer [76]. If there is concern for threatened mesorectal margin and/or pathologic lymph node enlargement, neoadjuvant chemoradiation should be offered. Evidence supports long-course concurrent therapy to improve local control [77]. Radiation is more effective when given concurrently with continuous-infusion 5-fluorouracil (5-FU). Capecitabine, the oral prodrug of 5-FU, is also effective when given concurrently with radiation. It has a similarly tolerable toxicity profile and avoids the requirement for central venous access [78].

13.9 Special Considerations in the AYA Population

13.9.1 Fertility

Family planning is an important consideration in the younger patient. Chemotherapy can have effects on reproductive health; however, 5-FU is not likely to impair fertility. Oxaliplatin shows a moderate detriment to fertility in animal studies, and one case series suggests that 40 % of patients had difficulty with conception after treatment [79, 80]. Unfortunately, this issue is not consistently addressed in counseling patients prior to therapy with one study showing discussions of fertility documented in only 20 % of cases [80].

Surgery and postoperative adhesions likely contribute to fertility changes in women, with pelvic surgery carrying the highest risk [81]. Radiation therapy routinely given for rectal cancer is highly likely to cause premature ovarian failure due to high-dose exposure to the ovaries which are radiosensitive [82]. Fertility preservation options may be considered including ovarian transposition or cryopreservation of embryos, oocytes, or ovarian tissue.

This must be balanced against possible worsened outcomes with delayed initiation of therapy. For male patients, sperm banking can be facilitated with little delay. The effect of newer chemotherapeutic agents on spermatogenesis is unspecified although 5-FU likely only has temporary effects [83].

13.9.2 Pregnancy

Although diagnosis of CRC during pregnancy is uncommon, there may be delay in the diagnosis due to changing abdominopelvic symptoms associated with pregnancy. Multidisciplinary participation of specialists in oncology and maternal-fetal medicine is necessary. Chemotherapeutic agents are potentially teratogenic (FDA class D) with greatest risk in the first trimester [84]. If reasonable to delay treatment, induction of labor can occur safely around 31 weeks of gestation. Otherwise termination of pregnancy may be considered. Case reports are available with the use of FOLFOX after 20 weeks of gestation without adverse effect on the fetus [85, 86]. Radiation is contraindicated in pregnancy. Following delivery, breastfeeding is contraindicated, while a mother is receiving chemotherapy.

13.9.3 Oxaliplatin-Induced Neuropathy

A common side effect of oxaliplatin is peripheral neuropathy, typically manifesting as a cold-induced dysesthesia or paresthesia in a glove and stocking pattern. In severe cases, significant disability can result that may be long lasting. Most patients experience mild symptoms while on treatment that resolve over months following discontinuation of oxaliplatin. In the MOSAIC trial, 29.5 % had persistent symptoms of neuropathy 1 year after completing a 6-month course of adjuvant therapy, but only 1.1 % had grade 3 symptoms. At 4-year follow-up, rates of grades 1, 2, and 3 peripheral neuropathy were 11.9 %, 2.8 %, and 0.7 %, respectively [61].

13.10 Anal Cancer

13.10.1 Epidemiology of Anal Cancer

The term anal cancer is often used synonymously with squamous cell carcinoma of the anal canal (SCCA). The incidence of SCCA in the general population has risen substantially since 1976. Rates have risen across all age groups. One notable trend has occurred in male AYAs, in whom the disease is more prevalent than in females. Anal cancer incidence increased substantially from 1976 to 1994, but rates have subsequently decreased (see Fig. 13.1). This trend may be the result of HIV infection, the emergence of AIDS-related malignancies, and the recent decline in AIDS-related complications due to highly active antiretroviral treatments. There is no clear hereditary component to the development of anal cancer; rather the disease is clearly associated with acquired risk factors (see below). Anal cancer is more frequent among blacks in patients younger than 40, in contrast to older patients in whom the disease is most common in non-Hispanic whites.

Anal cancer is strongly associated with oncogenic types of human papillomavirus (HPV). Most importantly, HPV strains 16 and 18 are linked to carcinogenesis in 65–89 % of cases of SCCA [87]. Human immunodeficiency virus (HIV) is also implicated in the development of SCCA. The prevalence of anal HPV is 90 % in HIV-infected individuals, and HIV increases the risk of persistent HPV infection. Consequently, persistent HPV infection contributes to dysplasia and the development of invasive disease. Epidemiologic data have shown temporal trends linking the HIV epidemic in the United States to increased incidence of anal cancer and a concurrent rise in the rates of HPV infection. Longer duration of HIV infection and progression to AIDS are associated with an increased risk of SCCA. The AIDS epidemic in North America started in the 1980s, and the incidence of SCCA markedly increased after 1997, highlighting the impact of prolonged duration of infection [87]. Sexual practices including multiple partners, anal intercourse, and males having sex with males have been associated with higher rates of anal cancer. Other risk factors include smoking, Crohn's disease, and chronic immunosuppression associated with organ transplantation [88].

Vaccines effective at reducing the prevalence of several types of HPV infections are clinically available, and universal vaccination is recommended for both boys and girls (ages 11–12 years)

by the Center for Disease Control [89]. However, publically funded programs for male vaccination have not yet been widely implemented in many countries [90]. A study of adolescent males engaging in sex with males suggested a very high incidence of acquired anal HPV infection in this group, alluding to the potential benefit of vaccination in this group of patients [91]. However, there are concerns that this group is often identified at an age at which many individuals have already been exposed to HPV infection [92, 93]. It is likely that further studies demonstrating cost-effectiveness for male vaccination will be required before universal male vaccination is adopted.

13.10.2 Management of Anal Cancer

Localized disease is treated with curative intent. In most instances definitive treatment involves combined chemotherapy and radiation. This approach optimizes oncologic control and decreases the risk of permanent colostomy compared with surgical resection. Mitomycin C and 5-fluorouracil are the standard chemotherapeutic agents that are combined with radiation. There is no role for adjuvant chemotherapy, and surgery is usually reserved for "salvage" of recurrent local or regional disease. Surgical resection alone may be an option for very early disease, but excision of more advanced disease is likely to result in loss of sphincter function, necessitating a permanent colostomy. Advanced disease may be treated with systemic chemotherapy or radiation in the palliative setting [88].

Conclusions

Although malignancies of the lower GI tract are rare in the AYA population, the incidence of CRC is increasing in younger patients despite falling rates in older adults. Cancer of the anal canal is occurring more frequently across all age groups. In the case of CRC, delay in diagnosis contributes to more advanced disease at presentation. Some cases may be associated with a well-defined risk factor or heritable syndrome, but many cases are sporadic. Symptoms are often vague and the medical community must be vigilant in excluding malignant diagnoses. Despite a trend toward more advanced disease at presentation, prognosis by stage is comparable to the older adult population, and younger patients may be fit enough to pursue aggressive treatments. In the management of disease in this age group, oncologists must be sensitive to the unique needs of younger patients, such as social and professional development and reproductive health. A deeper understanding of the molecular etiology of lower GI malignancy in AYAs remains a crucial focus of investigation, with the hope of improved personalization of systemic therapy in this group of patients.

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Central Nervous System Tumors

14

David Walker, Anne Bendel, Charles Stiller, Daniel Indelicato, Stuart Smith, Matthew Murray, and Archie Bleyer

14.1 Introduction

The diagnosis of a brain tumor in someone traversing adolescence to early adulthood poses a variety of clinical challenges and inevitable reactions in the patient and their family. Tumors involving the brain, if malignant, combine the shock of life-limiting consequences of cancer and the risk and consequences of acquiring brain injury due to the tumor's growth or the consequences of treatment. Fifty percent, however, are benign, and so a more measured approach, frequently with surgery alone and with minimal consequences, can be appropriate. There are a number of predisposing conditions that are associated with brain tumors, which need special management including consideration of new biologically targeted treatments and the influence of natural history of brain growth and development upon the nature of the condition. These alternatives with different consequences can either fundamentally alter the young person's life expectations, family and social relationships, and career ambitions or be a clinical interlude associated with neurosurgery and imaging surveillance, presenting as part of life-long genetic condition.

The anatomical location of the tumor and the risks of associated injury to the brain are central to assessing the impact of the tumor, its treatment, and its consequences. The consequences are compounded by the changes that are occurring in the brain itself as part of maturation, coupled with sexual development driven by puberty. The brain undergoes massive biological change from infancy through to early adulthood leading to the adult brain functioning summarized in Fig. 14.1. Brain development during adolescence supports

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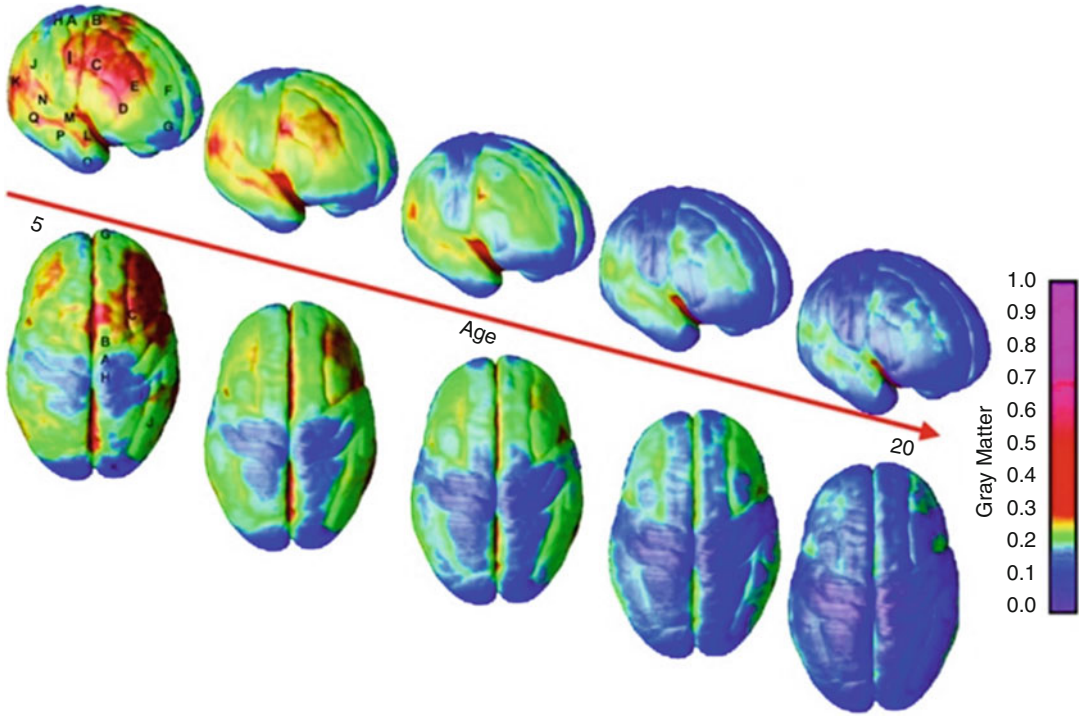


Fig. 14.1 Right lateral and top views of the dynamic sequence of gray matter maturation over the cortical surface. The *side bar* shows a color representation in units of gray matter volume [1]

these essential processes of myelinization, trophic stimulation, cortical reconnection, cortical cellular loss, neural pruning, and arborization that are central to the refinement of motor and cognitive functioning. Furthermore, these changes are also associated with progressive loss of neural plasticity, a central feature of the immature brain's capacity to recover from neural injury.

The impact of these factors on brain tumor development is currently poorly understood. The evidence from age-incidence data and epidemiological studies concerned with oncogenesis need to be integrated with science of the AYA brain development for their full interpretation. Brain tumors are the second most common group of cancers in childhood yet fall in the ranking during adolescence, suggesting that the brain's state of development that promoted tumor formation in childhood is reducing at this stage in life (Fig. 14.2) [2].

Brain tumors are highly complex involving over 100 different histological types with a rapidly growing evidence base of informative biological differences, which are becoming increasingly discriminant in the identification of tumor types and selection of treatments for trial to improve outcome. For these reasons, brain tumors are the most complex to manage, investigate, and deliver transformative clinical practice in this age group [3].

This chapter describes the models of care applicable to AYA practice in neuro-oncology, age incidence of different tumor types, and recent molecular observations that offer biological explanations that may help select targeted therapies [4]. Epidemiological research into environmental causes describes the growing range of predisposing conditions and the associated tumor types. Outlined are applications of neurosurgical techniques, radiotherapy, and chemotherapy to tumor therapies and their limitations. Also described is evidence for a new consensus on clinical practice emerging from trials over the past two decades, concerning intracranial germ cell tumors. This malignant tumor is primarily associated with the AYA age range. The long-term consequences for brain tumor survivors in

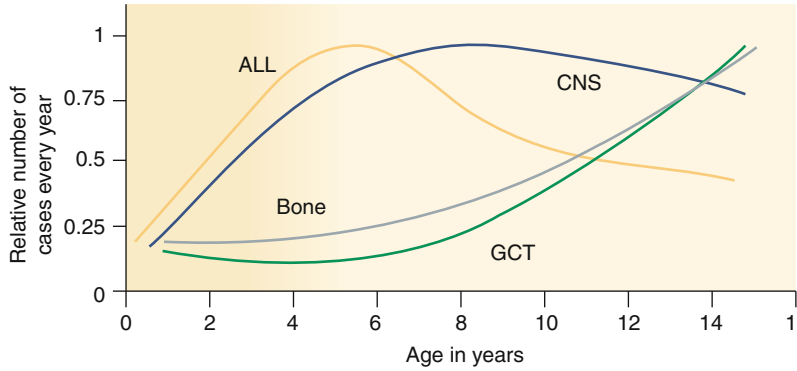


Fig. 14.2 Tumor incidence by age. Age incidence of cancers arising in developing tissues, as registered by the International Childhood Cancer Registries (represented on the y-axis as the actual number of cases, relative to the maximum set a 1, registered internationally per year) (Data are derived from the *International Incidence of Childhood Cancer*, Volume II [3]). *ALL* acute lymphoblastic leukemia (*y*-axis maximum incidence approximately 600) per year, *CNS* central nervous system tumors excluding germ cell tumors (*y*-axis maximum incidence approximately 1,400) per year, *GCT-CNS* germ cell tumors of the CNS (*y*-axis maximum incidence approximately 100 per year). Note that the incidence profile of GCT is more completely shown in Fig. 14.16

adult life are highlighted. The chapter concludes with a summary of research priorities that have recently been developed by a public, professional consensus process in the UK.

14.2 Incidence, Pathology, and Etiology of CNS Tumors in AYAs

According to the United States National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER), the incidence of CNS tumors in the 15- to 39-year-old age group is ranked fifth compared to other tumor types (Table 14.1) and accounts for 6 % of all neoplasms [5]. AYAs with CNS tumors have a better overall life expectancy than children and older adults, in part because 50 % are benign tumors, many with low risk of malignant transformation in adolescence and adulthood. Age and disease-specific comparisons are rare however, and the poor track record for recruiting AYAs to cancer trials [6] suggests that this favorable comparison of survival requires careful application on a case by case basis. Developing new treatments in the AYA age group requires trials developed with eligibility criteria that embrace the full age range applicable to the disease process. The legal barrier of 18 is in general not biologically relevant to any tumor type yet is a frequent barrier to developing better scientific evidence to justify progress by excluding those, for research governance reasons, for whom the trial is not applicable.

Table 14.1 Five most frequent cancers in AYAs 15–39 years of age, United States SEER18, 2000–2012

Neoplasm (ICD-O-3, AYA recode)	Number of cases[c]	Incidence per 100,000[d]	
		All	Invasive
Carcinoma of the breast	36,664	10.24	10.24
Thyroid carcinoma	32,364	8.63	8.63
Melanoma	27,330	7.31	7.31
Germ cell tumors[a]	22,724	5.9	5.88
CNS tumors[b]	18,536	4.92	2.87

[a]Including trophoblastic neoplasms
[b]Including other intracranial and intraspinal neoplasms
[c]Newly diagnosed, first cancer in patient
[d]Age adjusted to year 2000 US standard population

14.2.1 Incidence of CNS Tumors in AYAs

Incidence data for CNS tumors in AYAs are difficult to compare across population studies due to differences in the age group definitions and the

way that registries have applied them. Furthermore historically many registries had inconsistent criteria for brain tumor registration frequently excluding benign or premalignant tumor types. In the AYA age range, international comparison identifies a range of incidence per 100,000 populations, determined by inconsistencies of this type. In the United States, population-based incidence data by histological subgroup is available from two large US databases, namely, the SEER Program and the Central Brain Tumor Registry of the United States (CBTRUS) the latter of which published a report on primary brain and other CNS tumors in AYAs in the United States [7]. Historically SEER data included primarily malignant CNS tumors and grouped CNS tumors into five somewhat broad categories (astrocytoma, other gliomas, medulloblastoma/primitive neuroectodermal tumors (PNETs), ependymoma, and miscellaneous CNS tumors), with CNS lymphoma and germ cell tumors registered lymphomas as (all sites) and germ cell tumors with gonadal tumors, disregarding their primary brain site. In 2004, SEER began to include benign CNS tumors in its database and use a more detailed histological classification of both benign and malignant tumor using 5-year age groups.

14.2.2 Invasive Versus Benign and Sex Age-Incidence Patterns

SEER data for 2008–2012 shows that benign CNS tumors had an incidence that steadily increased with age, whereas malignant CNS tumors were least common in young AYAs with an incidence nadir at age 20 (Fig. 14.3). Among AYAs, the proportion of all CNS tumors that were "nonmalignant" increased steadily with age accounting for 54 % of the brain tumors at age 15 and 74 % by age 40 (Fig. 14.3). In females, the increase was more dramatic than in males, increasing to 84 % by age 39 (Fig. 14.4, right panel). The high proportion of "nonmalignant" CNS tumors in older AYAs creates a greater neuropathologic challenge to evaluate the virulence of CNS tumors in this age group and manage the patients accordingly [7].

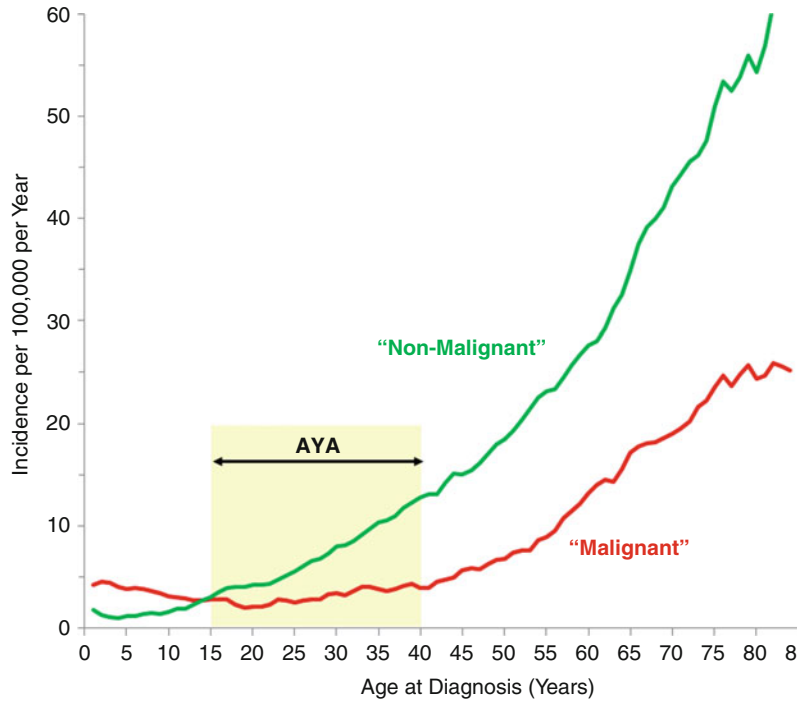


Fig. 14.3 Incidence of malignant and nonmalignant CNS tumors, United States SEER18, 2008–2012, by single year of age at diagnosis [5]. Regressions are 2-year moving averages

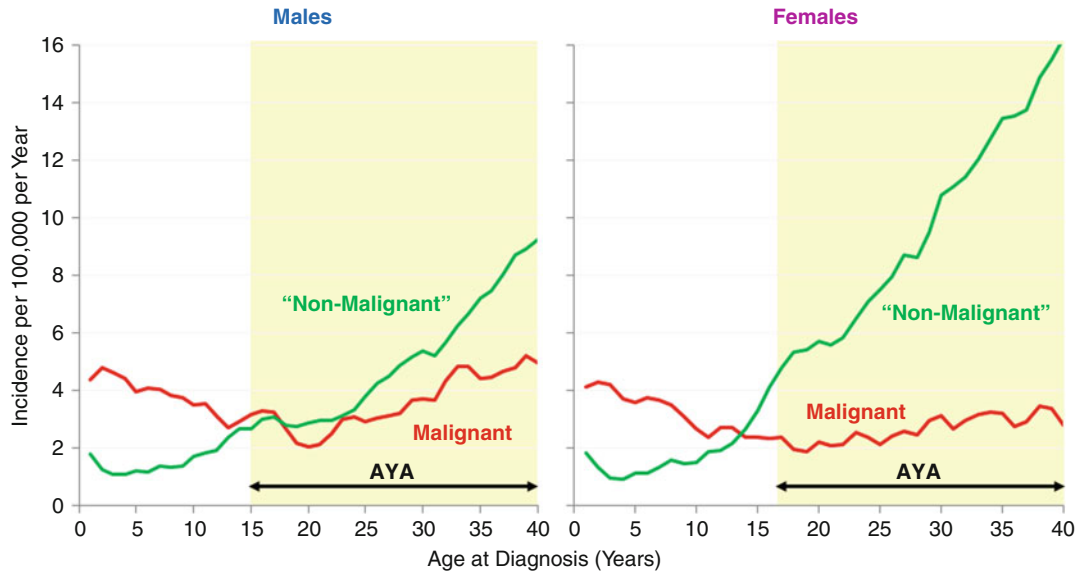


Fig. 14.4 Incidence of malignant and nonmalignant CNS tumors, United States SEER18, 2008–2012, by single year of age at diagnosis up to the age of 39 and sex [5]. Regressions are 2-year moving averages

14.2.3 Histology and Anatomical Region Age-Incidence Patterns

In AYAs, neuroepithelial and sellar region tumors predominate, followed by tumors of the cranial nerves (Fig. 14.5). Tumors of the meninges were the most age-dependent histological type, increasing nearly exponentially as a function of age starting at age 15 years. Astrocytoma accounted for 64 % of malignant CNS neoplasms in the 15–29-year age group, whereas "other gliomas" accounted for 19 %, primitive neuroectodermal tumor (PNET) 8 %, ependymoma 6 %, and miscellaneous CNS tumors 3 %.

These registries studying overlapping populations from a single large nation permit the impact of adolescent age groups on the types of tumors arising during the final stages of brain growth and development into early adult life. The nature of the changing incidence patterns highlights the vulnerability of different tissue types to generate benign, premalignant (grade 2), and malignant (grades 3 and 4) tumors. The comparison with childhood CNS tumor distribution where grade 1 astrocytomas predominate premalignant tumors (grade 2) and the different spectra of malignant tumors featuring medulloblastoma, ependymoma, diffuse intrinsic pontine glioma, and rare entities such as atypical teratoid rhabdoid tumors (ATRT), high-grade glioma, and supratentorial PNET/embryonal tumor with abundant neuropil and true rosettes (ETANTR) entities are rare, most of which are extremely rare after puberty. An additional contrast with AYA incidence is the older age primary brain tumors which are dominated by glioblastoma and meningioma. Finally, metastatic brain tumors are exceptionally rare in childhood, but as the epithelial cancer incidence rises in adolescence and early adulthood, the risk of secondary brain tumor rises in parallel and becomes a significant part of adult neuro-oncology practice, particularly in older age groups. With increasing life expectancy of AYAs with early-onset carcinomas, prevention or management of secondary brain metastases will become an increasing focus for neuro-oncology practice in this age group.

Four patterns of tumor incidence can be recognized from these databases: peak incidence in the 15–19-year age group (sellar region tumors and germ cell tumors and cysts), decreasing incidence with age (PNET and pilocytic astrocytoma), rising incidence with age (grades 2–4

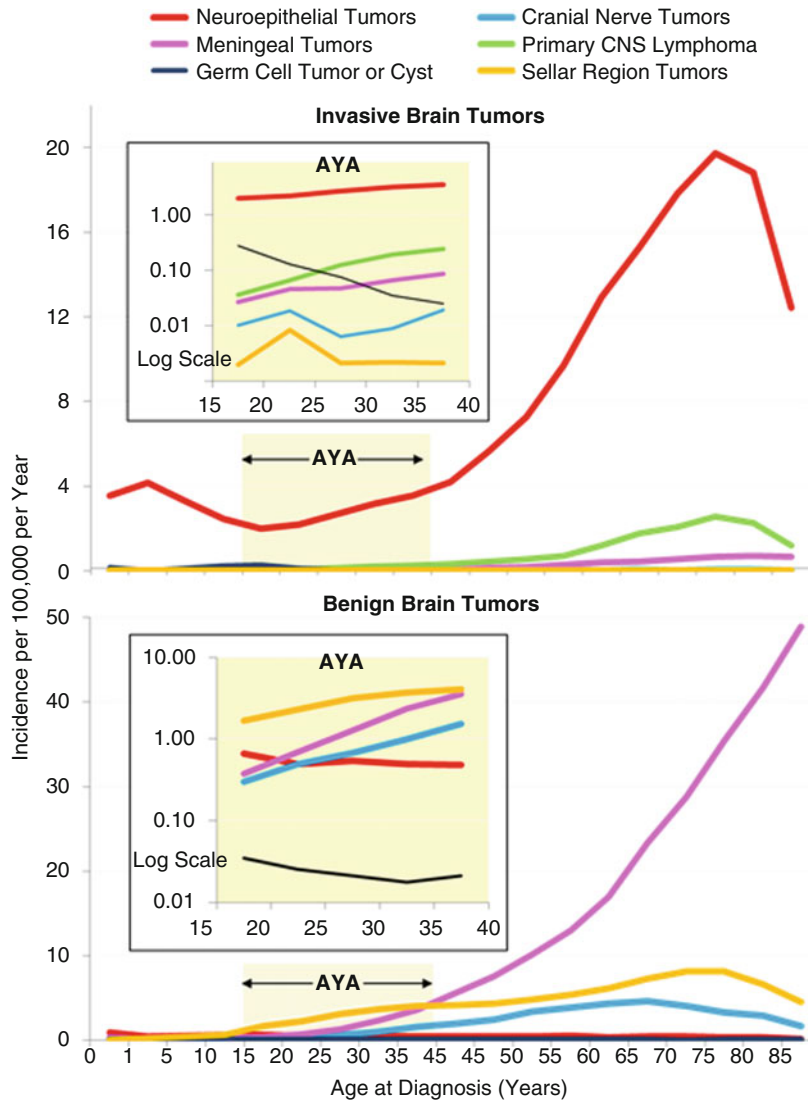


Fig. 14.5 Incidence of invasive (*upper panel*) and benign (*lower panel*) CNS tumors, 2004–2011, United States SEER18, by histological type, anatomical region, and age [5]. The insets depict the AYA age range and have log scales for the y-axis

astrocytoma and meningioma), and varying incidence with age (ependymoma and craniopharyngioma). These population observations are interpreted further scientifically, by recent work identifying specific molecular drivers identified in newly recognized subclasses of medulloblastoma. Looking in more detail at these groups and further characterizing the molecular subgroups permit more subtle relationships between age, tumor subtypes, and anatomical origins to be identified, building upon the developmental hypothesis proposed linked to age-incidence curves in Fig. 14.6; it can be envisaged that this new information will become central to diagnostic assessment and strongly influence trials of novel therapies in the future [9] (Fig. 14.7).

The peak incidence of GCTs, with a male preponderance that is also seen in extracranial GCTs, is considered to be a consequence of pubertal development and the tumor growth promoting consequences of the associated surge in sex hormones. For this reason, intracranial GCTs are a "model" CNS tumor for an AYA neuro-oncology service, despite its relative rarity. The history of translational research is described in detail later in the chapter.

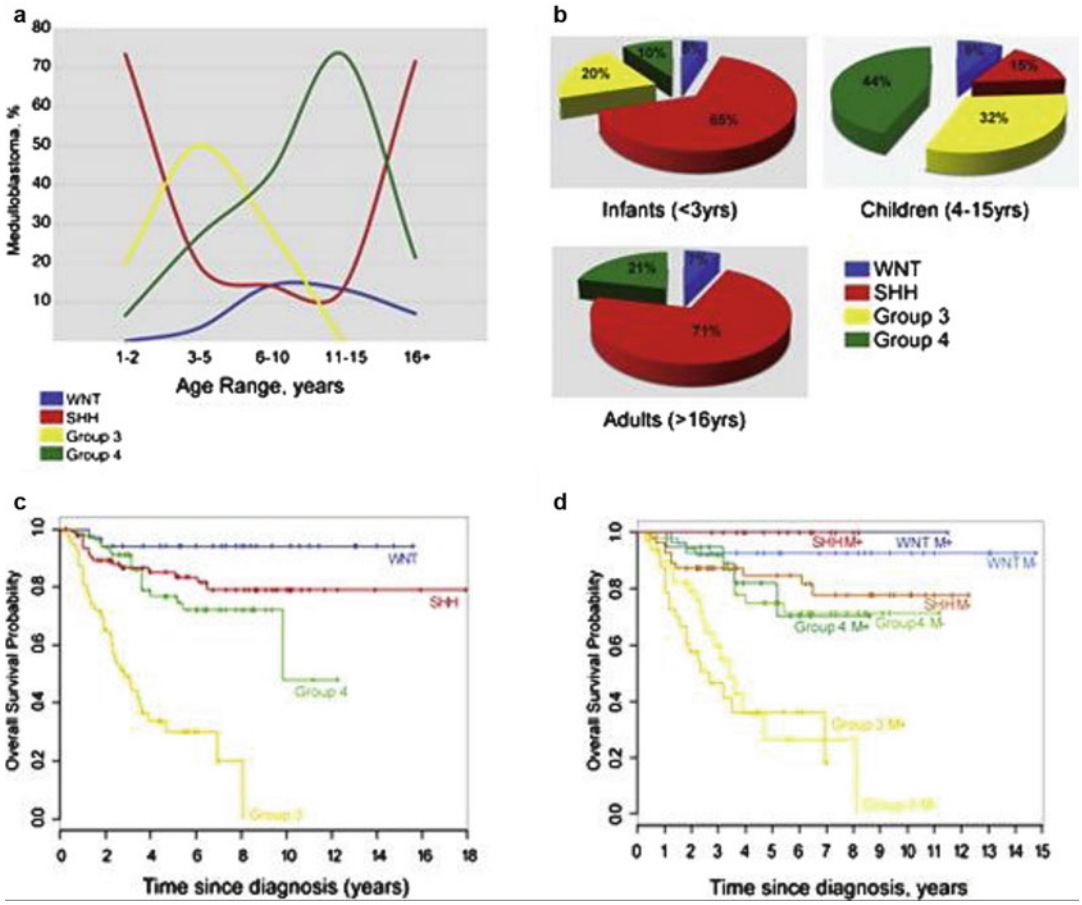


Fig. 14.6 The age distribution and outcome in medulloblastoma. (**a**) Age at diagnosis by medulloblastoma subgroup. (**b**) Frequency of subtypes in <3-year-olds, 3- to 16-year-olds, and adults (age >16 years). (**c**) Kaplan–Meier analysis of overall survival (*OS*) of combined tissue microarray cohorts from both DKFZ/Heidelburg and Johns Hopkins University ($N=287$) separated by subgroup. (**d**) Kaplan–Meier analysis of metastasis status of sites in panel (**c**) (Adapted/reprinted with permission of the American Society of Clinical Oncology. All rights reserved [8])

14.2.4 Race/Ethnicity Incidence Patterns

Figure 14.8 shows the racial/ethnic incidence in the United States of invasive tumors (left panel) and benign tumors (right panel) in AYAs as a function of age. At all ages, non-Hispanic whites had the highest incidence of malignant brain tumors. In AYAs, non-Hispanic whites had 1.8×, 1.9×, 2.1× and 1.6× greater incidence of malignant brain tumors than in blacks, Asians/Pacific Islanders, native North Americans, and Hispanics, respectively.

14.2.5 Incidence Trends

The incidence of invasive (malignant) brain tumors in AYAs has increased since 1976, as it did in younger or older persons and at approximately the same rate (Fig. 14.9). Incidence trends for benign tumors are difficult to assess since they have only recently been included in cancer registry statistics. Explanations for this include enhanced registration and awareness and wider application and access to brain scanning techniques with enhanced sensitivity over this time period.

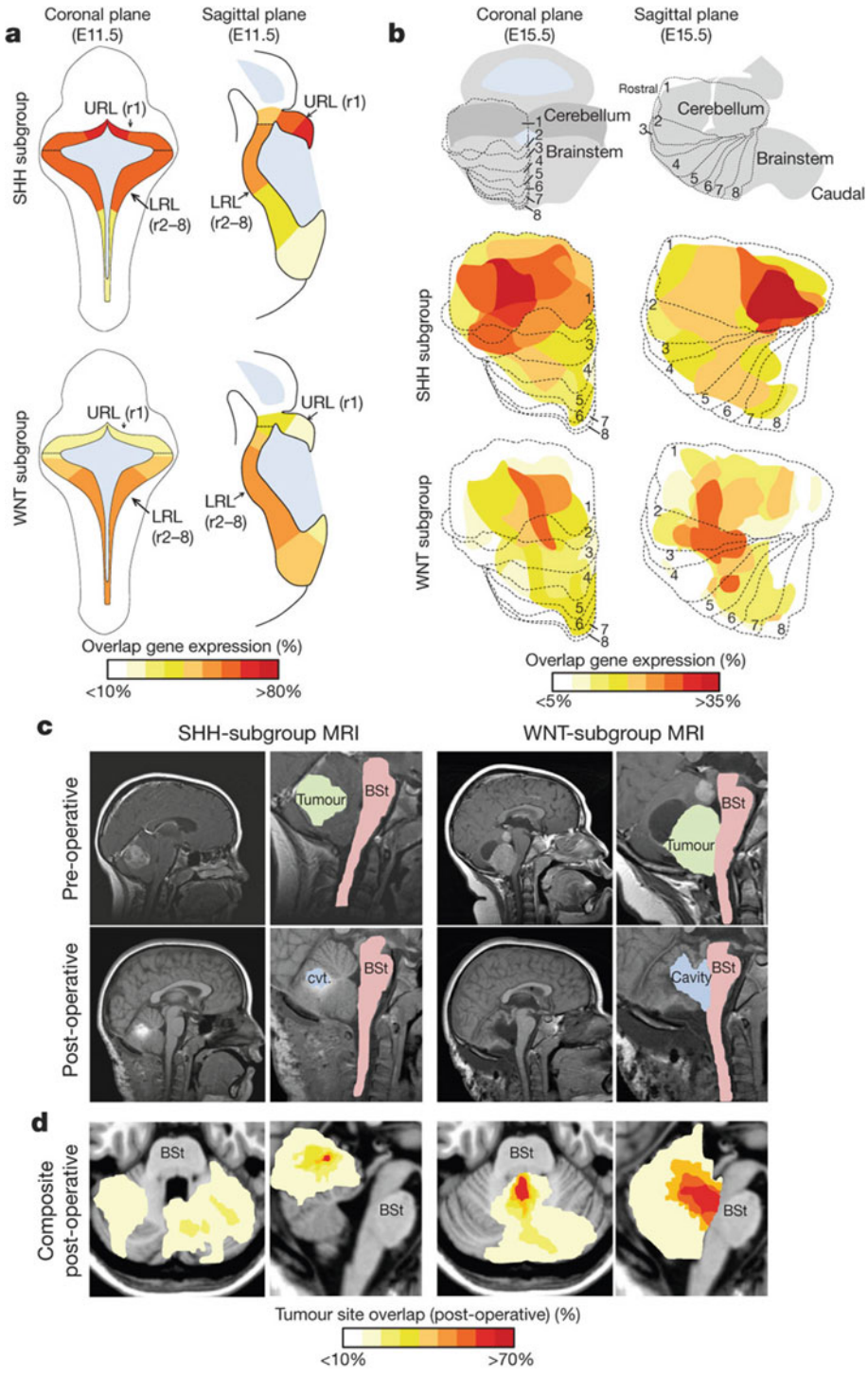


Fig. 14.7 WNT and Sonic Hedgehog (SHH) subtypes of medulloblastoma are anatomically distinct. (**a**) Expression distribution in (**a**) E11.5 and (**b**) E15.5 mouse hindbrain of orthologs that distinguish human WNT- and SHH-subtype medulloblastoma. Cartoons in (**b**) denote the position of rhombomeres relative to the cerebellum and brain stem. (**c**) *Top* = pre- and *bottom* = postoperative MRI scans of exemplary SHH- and WNT-subtype medulloblastomas. Right panels show closeup views of the left. Brain stem (*BSt*), postoperative tumor cavity (*cvt.*). (**d**) Frequency and site of postoperative surgical cavities of SHH ($n=6$)- and WNT ($n=6$)-subtype medulloblastomas. Axial (*left*) and sagittal (*right*) views are shown [9]

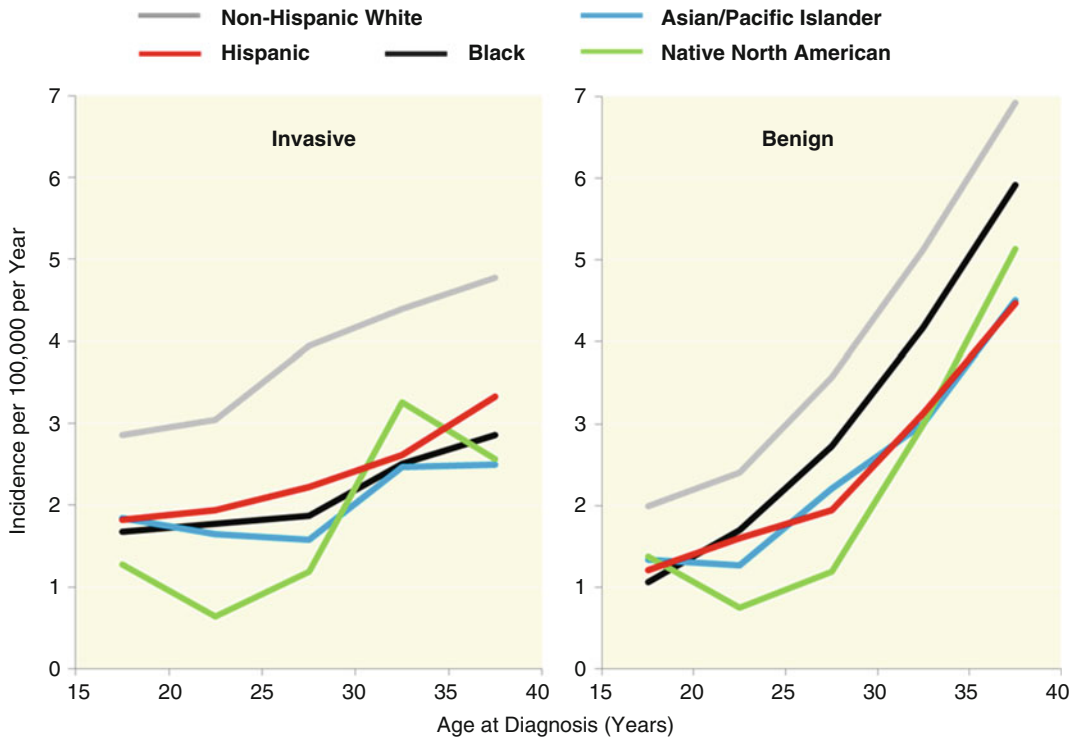
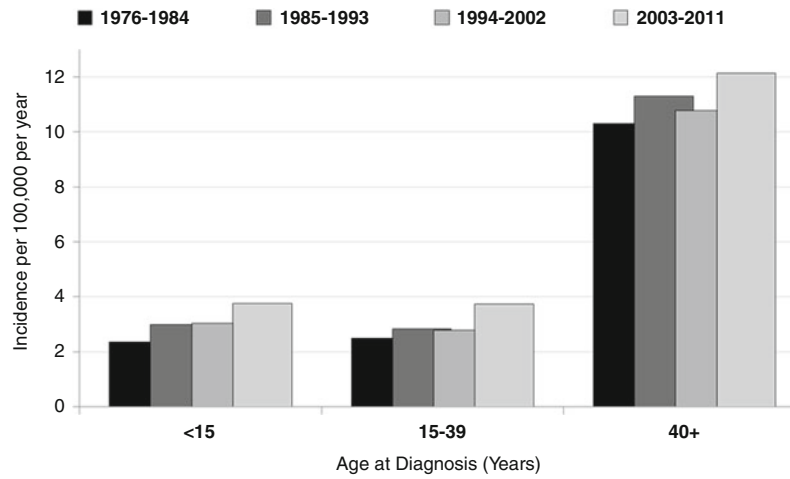


Fig. 14.8 Racial/ethnic incidence of invasive and benign CNS tumors, United States SEER, by age [5]

Fig. 14.9 Change in incidence of invasive CNS tumors by 9-calendar-year intervals, 1976-2011, United States SEER9, by age [5]



14.2.6 Environmental and Exogenous Risk Factor

With the processes of brain growth and development as a backdrop, genetic and environmental factors are the most commonly considered potential causes of brain tumors and have been the focus of much research, as the causes of most brain tumors cannot be attributed to rare predisposition syndromes or high doses of ionizing radiation, and so remain elusive. There have been no analytical epidemiological studies of CNS tumors specifically among adolescents and young adults. The diversity of tumor subtypes and the fact that most brain tumors occur in older adults mean that even the best substantiated risk factors do not necessarily apply to tumors occurring in the AYA age range (Table 14.2).

Table 14.2 Established and suspected environmental and exogenous risk factors for brain tumors

Elevated risk			
Risk factor	Tumor types	Details	Comment
Ionizing radiation – therapeutic	Glioma, embryonal tumors, and meningioma	Case-control studies of childhood cancer survivors: increasing risk of glioma/PNET and of meningioma with dose of radiation for previous childhood cancer [10, 11]	Glioma/PNET tend to have shorter latency than meningioma
Ionizing radiation – childhood CT scans	Brain/CNS cancers	UK retrospective cohort study: Excess Relative Risk (*ERR*) per mGy = 0.023 (95 % CI 0.010, 0.049) [12] Australian record-linkage study: after brain scan, *ERR* = 2.44 (95 % CI 2.12, 2.81); after non-brain scan, *ERR* = 1.51 (95 % CI 1.19, 1.91) [13] German cohort study: SIR = 1.35 (95 % CI 0.54, 2.78) [14] French cohort study: ERR per mGy was 0.022 (95 % CI -0.016, 0.061) when excluding tumors diagnosed <2 years after scan and not adjusting for predisposing factors, but zero when excluding tumors diagnosed <3 years after scan and adjusting for predisposing factors [15] Institutional cohort study of 104 children who underwent shunt placement: no tumors detected after ≥10 years follow-up [12]	UK and Australian studies probably made inadequate allowance for scans being indicated by symptoms of undiagnosed tumor [16]. German cohort study result based on only seven cases. French study shows importance of adjusting for predisposing factors
Ionizing radiation – natural background	Childhood brain/CNS tumors	Swiss national cohort: HR per millisievert increases in cumulative dose = 1.04 (95 % CI 1.00, 1.08) [17]. Results of other studies of childhood tumors are nonsignificant but consistent with risk predicted by high-dose and high-dose-rate studies [18–21]	Statistical power of even the largest studies is low [20]
	Adult brain tumors	Danish cohort study of older adults: adjusted IRR per 1,000 Bq/m^3-year increase in cumulated residential radon = 1.37 (95 % CI 1.03, 1.82) [22]	Subjects were aged 50–64 at enrolment and followed up for 12–16 years
Dietary N-nitroso compounds	Childhood brain tumors	Meta-analysis of six studies: RR = 1.68 (95 % CI 1.30, 2.17) for maternal cured meat intake during pregnancy [23]. A later international study of 1,218 cases in seven countries found similar increases in risk for astrocytoma and ependymoma but no association for medulloblastoma [23]	Dietary information apparently not validated
	Adult glioma	Meta-analysis of nine studies: RR = 1.48 (95 % CI 1.20, 1.83) for cured meat intake [24]. A later international study of 1,185 cases in six countries found modest increase in risk with increase in consumption of non-cured meat, but no association with cured meat [25]	Most studies failed to adjust for total energy intake

Pesticides	Childhood brain tumors	Meta-analysis of five studies of indoor pesticide exposure: nonsignificant RR = 1.11 (95 % CI 0.87, 1.42) [26] Meta-analyses of 16 case-control studies and five cohort studies of parental occupational exposure: RR = 1.30 (95 % CI 1.11, 1.53) and RR = 1.53 (95 % CI 1.20, 1.95), respectively [27]. In case-control studies, RR = 1.39 (95 % CI 1.10, 1.75) for maternal exposure (six studies), RR = 1.19 (95 % CI 1.03, 1.38) for paternal exposure (13 studies), RR = 1.44 (95 % CI 1.05, 1.98) for astrocytoma (five studies), and nonsignificant RR = 1.18 (95 % CI 0.81, 1.71) for embryonal tumors (four studies)	No breakdown by tumor type Upper age limit for diagnosis was 20 years in several studies and 25 years in one study. Impact of other occupational factors was unknown
Other parental occupational exposures	Childhood brain tumors	Pooled analysis of three case-control studies. For paternal exposure around time of conception, nonsignificant OR = 1.22 (95 % CI 0.98, 1.52) for polycyclic aromatic hydrocarbons, OR = 1.12 (95 % CI 0.95, 1.32) for asbestos, and OR = 1.18 (95 % CI 0.96, 1.46) for metals [28]	Lower OR for exposure around time of diagnosis. No association with exposure to diesel exhaust or crystalline silica. No association for any maternal exposure
Methotrexate	Meningioma	UK case-control study of childhood cancer survivors: unadjusted RR = 6.4 (95 % CI 1.7, 23.5) for intrathecal dose ≥70 mg/m^2 and RR = 35.6 (95 % CI 4.8, 599) adjusted for radiation exposure [11]	Lower RR for lower doses. No other published study of this risk factor
Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS)	Lymphoma	Primary NHL of the brain is an AIDS-defining illness in about 0.5 % of people with AIDS [29]. Risk among HIV-seropositive people decreased substantially with the introduction of highly active antiretroviral therapy; adjusted incidence among nearly 48,000 HIV-positive people from North America, Europe, and Australia fell significantly from 1.7 per 1,000 person-years during 1992–1996 to 0.7 per 1,000 during 1997–1999 [30]	

(continued)

Table 14.2 (continued)

Elevated risk			
Risk factor	Tumor types	Details	Comment
Birth weight and fetal growth rate	Childhood CNS tumors	The UK and US case-control studies: OR per 0.5 kg increase in birth weight for all tumors in ICCC-3 group III was 1.07 (95 % CI 1.04, 1.10) in the UK and 1.05 (95 % CI 1.01, 1.08) in the Unites States [31]	Similar results for astrocytoma and embryonal tumors. Similar but nonsignificant OR for ependymoma/choroid plexus tumors Inconsistent results between the UK and United States for germ cell tumors No evidence of effect for other astrocytoma, medulloblastoma, or ependymoma
		Swedish national cohort study: IRR per 1 SD increase in fetal growth rate was 1.04 (95 % CI 1.01, 1.08) overall and 1.05 (95 % CI 1.00, 1.12) for pilocytic astrocytoma [32]	
Adult stature	Adult glioma	Meta-analysis of 15 studies: RR = 1.70 (95 % CI 1.11, 2.61) for ≥190 cm vs. 170–174 cm in males, nonsignificant RR = 1.06 (95 % CI 0.70, 1.62) for ≥175 cm vs. 160–164 cm in females [33]	Association slightly stronger when restricted to glioblastoma. No obvious reason why effect should vary by sex
High BMI	Adult glioma	Meta-analysis of nine studies: RR = 1.17 (95 % CI 1.03, 1.32) for obesity or overweight in females, but nonsignificant RR = 0.96 (95 % CI 0.76, 1.23) in males [34]. Meta-analysis of seven studies: no significant effect of obesity or overweight, but males and females not analyzed separately [35]	
	Meningioma	Meta-analysis of 11 studies: RR = 1.78 (95 % CI 1.22, 2.61) for obesity in males and RR = 1.48 (95 % CI 1.28, 1.71) in females [34]. Meta-analysis of nine studies: RR = 1.54 (95 % CI 1.32, 1.79) for obesity and RR = 1.21 (95 % CI 1.01, 1.43) for overweight [35]	
Reduced risk			
Prenatal vitamin and folic acid supplements	Childhood brain tumors	Numerous studies have found protective relationship [36]	Some inconsistency between studies regarding effects of specific supplements and by tumor type

History of allergic/ atopic conditions	Adult glioma	Meta-analysis of eight studies: allergy, OR = 0.61 (95 % CI 0.55, 0.67); asthma, OR = 0.68 (95 % CI 0.58, 0.80); eczema, OR = 0.69 (95 % CI 0.58, 0.82) [37] Meta-analysis of 11 studies: allergy, OR = 0.60 (95 % CI 0.52, 0.69); asthma, OR = 0.70 (95 % CI 0.62, 0.79); eczema, OR = 0.69 (95 % CI 0.62, 0.78); hay fever, OR = 0.78 (95 % CI 0.70, 0.87) [38] Pooled analysis of 3 studies for any atopic condition by ethnicity: OR = 0.47 (95 % CI 0.41, 0.55) in whites; OR = 0.32 (95 % CI 0.14, 0.75) in Asians; nonsignificant OR = 0.96 (95 % CI 0.50, 1.84) in blacks, and OR = 0.81 (95 % CI 0.42, 1.57) in Hispanics [39]	Similar results when restricted to glioblastoma
	Oligodendroglioma (including anaplastic oligodendroglioma)	Pooled analysis of seven studies: asthma and/or allergies, OR = 0.7 (95 % CI 0.6, 1.0); asthma, OR = 0.4 (95 % CI 0.2, 0.7) [40]	Effect for asthma and/or allergies limited to anaplastic oligodendroglioma. Nonsignificant reduced OR for eczema in both tumor subtypes
	Meningioma	Meta-analysis of seven studies: eczema, OR = 0.75 (95 % CI 0.65, 0.87); nonsignificant for asthma, OR = 0.88 (95 % CI 0.75, 1.04); and hay fever, OR = 0.90 (95 % CI 0.79, 1.03) [41] Case-control study in four regions of the United States: allergy, OR = 0.6 (95 % CI 0.5, 0.7); asthma, OR = 0.7 (95 % CI 0.5, 0.9) [42] INTERPHONE study from five countries: allergy, OR = 0.77 (95 % CI 0.63, 0.93); nonsignificant for asthma, OR = 0.78 (95 % CI 0.59, 1.03) [43]	
High level of physical activity	Adult glioma	Meta-analysis of five studies: RR = 0.86 (95 % CI 0.76, 0.97) vs. low physical activity [35]	
	Meningioma	Meta-analysis of four studies: RR = 0.73 (95 % CI 0.61, 0.88) vs. low physical activity [35]	
History of diabetes	Adult glioma	Pooled analysis of seven studies: OR = 0.58 (95 % CI 0.40, 0.84) [44] Meta-analysis of the above plus 10 other studies: OR = 0.79 (95 % CI 0.67, 0.93) [45]	Association similar for males and females and after restricting to glioblastoma Association appeared to be confined to males and to people of Caucasian race
Female reproductive hormones	Adult glioma	Meta-analysis of 11 studies: age at menarche, RR = 1.40 (95 % CI 1.05, 1.87) for oldest vs. youngest; the use of oral contraceptives, RR = 0.71 (95 % CI 0.60, 0.83) [46] Pooled analysis of three studies: age at menarche, OR = 2.00 (95 % CI 1.47, 2.71) for >15 vs. <12; the use of oral contraceptives, OR = 0.61 (95 % CI 0.50, 0.74) and P_{trend} <0.0001 for duration of use [47]	Results for premenopausal and postmenopausal women combined; no analysis of either factor by menopausal status. No analysis of duration of oral contraceptive use Results for premenopausal and postmenopausal women are combined. Data for premenopausal women are not presented separately, but premenopausal status is not associated with glioma risk

(continued)

Table 14.2 (continued)

Elevated risk			
Risk factor	Tumor types	Details	Comment
Little or no evidence of elevated or reduced risk or conflicting evidence			
Nonionizing radiation	Childhood brain tumors	Meta-analysis of 13 studies of residential magnetic field exposure: nonsignificant summary OR = 1.68 (95 % CI 0.83, 3.43) for measured or calculated exposures above 0.3 or 0.4 μT; OR for lower exposures were lower and nonsignificant [48] Pooled analysis of ten studies of exposure to extremely low-frequency magnetic fields: no significant results and no evidence of dose–response [49] CEFALO study of mobile phone use by children and adolescents in four countries: nonsignificant OR = 1.36 (95 % CI 0.92, 2.02) for regular vs. never regular use, OR = 1.26 (95 % CI 0.70, 2.28) for use over ≥5 years vs. never regular use [50]	Moderate risk increase in the highest exposure category could not be excluded, but no evidence of increased risk for lower exposures The absence of exposure–response argues against causal association
	Adult brain tumors	Meta-analysis of 47 studies of occupational exposure to electromagnetic fields (EMF): RR = 1.14 (95 % CI 1.07, 1.22) [51]	Studies showed considerable heterogeneity, many studies involved small numbers of cases, and there was little evidence of dose–response
	Adult glioma	Meta-analysis of 22 studies of occupational EMF exposure: RR = 1.18 (95 % CI 1.10, 1.26) [51] INTEROCC study of occupational ELF exposure in seven countries: no association with cumulative exposure, average exposure, and maximum exposed job or duration of exposure and no evidence of dose–response; OR = 1.67 (95 % CI 1.36, 2.07) for ≥90th percentile vs. <25th percentile cumulative ELF 1–4 years pre-diagnosis with $P_{\text{linear trend}}$ <0.0001 [52] Meta-analysis of 17 studies of mobile phone use: nonsignificant OR = 0.99 (95 % CI 0.84, 1.17) forever vs. never regular use, OR = 1.26 (95 % CI 0.86, 1.84) for long-term vs. never regular use [53]	As above. Results of more recent studies of glioma have been mixed [54]. Weaker association for 5–9 years pre-diagnosis, and inverse association ($P_{\text{linear trend}} = 0.04$) for ≥10 years pre-diagnosis Significant heterogeneity between studies ($P = 0.001$)
	Meningioma	INTEROCC study of occupational ELF exposure in seven countries: no association with cumulative exposure, average exposure, or maximum exposed job; OR = 1.30 (95 % CI 1.03, 1.64) for ≥25 years vs. <5 years exposure; $P_{\text{linear trend}} = 0.02$ for cumulative ELF 1–4 years pre-diagnosis [52] Meta-analysis of 15 studies of mobile phone use: nonsignificant OR = 0.91 (95 % CI 0.78, 1.05) forever vs. never regular use, OR = 1.02 (95 % CI 0.74, 1.40) for long-term vs. never regular use [53]	

Smoking	Childhood brain tumors	Meta-analysis of 17 studies: nonsignificant RR = 0.93 (95 % CI 0.85, 1.00) for maternal smoking before pregnancy, RR = 1.09 (95 % CI 1.00, 1.20) for paternal smoking before pregnancy, RR = 0.96 (95 % CI 0.86, 1.07) for maternal smoking during pregnancy, and RR = 1.09 (95 % CI 0.97, 1.22) for paternal smoking during pregnancy [55]	Similar results for astrocytoma, ependymoma, and embryonal tumors
	Adult glioma	Meta-analysis of 17 studies: nonsignificant RR = 1.06 (95 % CI 0.97, 1.15) forever vs. never smoking [56]	Little evidence of any dose–response
	Meningioma	Meta-analysis of 9 studies: nonsignificant RR = 0.95 (95 % CI 0.87, 1.05) forever vs. never smoking [57]	RR = 1.49 (95 % CI 1.06, 2.09) among men and RR = 0.86 (95 % CI 0.65, 1.13) among women, but no obvious reason why risk should vary by sex
Alcohol	Adult brain tumors	Meta-analysis of 12 studies: nonsignificant RR = 0.97 (95 % CI 0.82, 1.15) for drinkers vs. nondrinkers [58]	Broadly similar results for glioma and meningioma
Coffee	Adult glioma	Meta-analysis of six studies: nonsignificant RR = 1.01 (95 % CI 0.83, 1.22) for highest vs. lowest consumption [59]	
Tea	Adult glioma	Meta-analyses: RR = 0.86 (95 % CI 0.78, 0.94) for regular vs. never/occasional consumption based on three studies, nonsignificant RR = 0.88 (95 % CI 0.69, 1.12) for highest vs. lowest consumption [59]	
Exposure to common infections	Childhood brain tumors	Several studies suggest protective effect of early exposure, but elevated risk with exposure later in childhood [36]	Level of risk often varied with tumor type and age at diagnosis
	Oligodendroglioma (including anaplastic oligodendroglioma)	Pooled analysis of seven studies: chickenpox, OR = 0.6 (95 % CI 0.4, 0.8) [40]	Result for both tumor subtypes combined; effect similar for each subtype
	Meningioma	Case-control study in four regions of the United States: chickenpox, OR = 0.6 (95 % CI 0.5, 0.8) [42]	
Anti-inflammatory drugs	Adult brain tumors	Meta-analysis of ten studies: RR = 1.01 (95 % CI 0.89, 1.15) for overall use of nonsteroidal anti-inflammatory drugs (NSAIDs) [60]	Results were similar for aspirin and nonaspirin NSAIDs and for glioma and meningioma
	Adult glioma	Recent studies of antihistamine use have inconsistent results [54]	
SV40	Ependymoma, choroid plexus tumors	Danish national incidence study: no evidence of increased incidence associated with contaminated poliovirus vaccine [61]	Unlike in previous studies, period of contamination was known and extent of use was well documented

14.2.7 Meta-analysis of Epidemiological Studies

This section draws on recent meta-analyses, pooled analyses, and reviews of specific risk factors and selected individual studies, together with the most recent comprehensive reviews of environmental and exogenous risk factors for childhood brain tumors [36], adult gliomas [54], and meningioma [62]. The results for factors regarding which there is most evidence are discussed briefly.

Acquired Immune Deficiency Syndrome (AIDS) Primary non-Hodgkin lymphoma (NHL) of the brain has occurred consistently as an acquired immune deficiency syndrome (AIDS)-defining illness in around 0.5 % of AIDS patients [29] and brain NHL being associated with HIV infection in 55 % at ages 15–49 years. In an analysis of cancer incidence among nearly 48,000 human immunodeficiency virus (HIV)-seropositive people from North America, Europe, and Australia, the adjusted annual incidence of cerebral NHL fell significantly from 1.7 per 1,000 during the period 1992–1996 to 0.7 per 1,000 during the years 1997–1999, indicating a substantial reduction in risk with the introduction of highly active antiretroviral therapy [30].

Ionizing Radiation The only established environmental risk factor for CNS tumors is ionizing radiation. Radiotherapy (RT) for cancer, including prophylactic CNS irradiation as part of the treatment for childhood leukemia, increases the risk of CNS tumors in young people. The predominant tumor types are meningiomas and high-grade astrocytomas [10, 11]. There is also evidence supporting radiation related to diagnostic imaging, including CT scanning, as a risk factor [15, 63, 64], but the evidence regarding high background radiation is less strong.

Nonionizing Radiation There is much less evidence that exposure to nonionizing radiation is a risk factor for brain tumors. Studies of occupational exposure to electromagnetic fields are heterogeneous, and the absence of a dose–response relationship in most studies makes the results hard to interpret. Epidemiological studies of exposure to radiofrequency emissions from the use of mobile telephones suggest that a large risk over a short time of use is unlikely, but there is insufficient evidence regarding the possibility of increased risks that are relatively small or related to longer follow-up periods [48, 50, 51].

Carcinogens Intra-CSF (intrathecal) methotrexate with a cumulative exposure >70 mg/m^2 is associated with an increased risk of meningioma (RR 35.6 adjusted for radiation exposure) [11]. Since N-nitroso compounds (NOCs) were found to be potent experimental carcinogens more than 30 years ago, a succession of epidemiological studies has investigated the hypothesis that exposure to preformed NOCs or their precursors can cause brain tumors in humans. Studies have been most consistent for cured meat consumption but have often depended on un-validated data [23–25, 65]. Tobacco smoke is a potent source of NOCs and polycyclic aromatic hydrocarbons (PAHs), among other carcinogens, but there is little evidence to associate smoking by parents or patients [55, 56], alcohol intake [58], and coffee or tea drinking [59] with CNS tumors. There is some evidence that parental exposure to pesticides is a risk factor for childhood CNS tumors [27], but there has been little consistency in studies of other parental occupations [28].

Fetal Growth Rate, Weight, and Stature There is some evidence that increased birth weight or fetal growth rate is associated with enhanced risk for all brain tumors [31] and pilocytic astrocytoma [32]. Greater adult stature [33] and obesity [34, 35] are associated with enhanced risk.

Epilepsy and Head Injury Raised risks of glioma in association with a history of epilepsy have been found in several studies of children [66] and adults [64, 65]. It seems likely, however, that this reflects at least in part the fact that epilepsy can be an early symptom of a brain tumor, especially low-grade astrocytomas of childhood [66]. There is little consistent evidence that head injury is a risk factor for CNS tumors [67–69].

Protective Effects Many studies have found a protective effect of prenatal vitamin or folic acid supplements against childhood brain tumors, though with limited consistency regarding particular supplements [36]. There is a growing body of evidence that past history of allergies, asthma or eczema [37–43], or certain common viral infections [36, 40, 42] are protective against glioma and meningioma. This may indicate a role for immunological factors in the etiology of CNS tumors. The apparent protective effect of female reproductive hormones is consistent with the generally lower incidence of glioma in women compared with men [46, 47]. High levels of physical activity [35] and the presence of diabetes [44, 45] have been found protective.

14.2.8 Predisposing Genetic, Familial, and Endogenous Conditions

An appreciable proportion of AYAs with CNS tumors may be associated with predisposition syndromes that in some instances may not be diagnosed until the CNS tumor presents. Their recognition is critical as the predisposing condition may:

- Determine the diagnostic process.
- Affect the prognosis for the tumor.
- Play a part in treatment selection.
- Provide novel genetically determined approaches for therapy.
- Be the presenting symptom of a previously unrecognized genetic disease and provide an opportunity for participation in important tumor-related research, which, with current rates of progress, may influence treatment options in the foreseeable future. The range of currently recognized predisposing genetic conditions is listed in Table 14.3 [70–82].

14.2.9 Genetic Factors

The possible effects of common heritable variants on the risk of glioma started to be investigated over 20 years ago, though it was only with the advent of genome-wide association studies (GWAS) for glioma around 2009 that reproducible results began to emerge [54]. By the end of 2013, eight independently significant germ-line single nucleotide polymorphisms (SNPs) had been identified in five GWAS; of these, some appeared to contribute to glioma risk in general, whereas others were limited to particular histological or molecular subtypes [54]. Since then, GWAS have proliferated, and a recent genome-wide complex trait analysis indicated that one quarter of variation in glioma risk is associated with common SNPs that are in linkage disequilibrium with functional variants, with the proportion being very similar for glioblastoma and non-glioblastoma tumors [83].

Of course, SNPs implicated in glioma etiology may in fact be irrelevant to tumors of adolescents and young adults, but a recent analysis of data from the multinational CEFALO study found that several SNPs previously associated with adult glioma risk may also be associated with risk of childhood brain tumors [84]. This suggests that brain tumors in children and adults – and thus also in AYA – may share common genetic risk factors and similar etiological pathways [84]. Particular interest has developed in the possible involvement of telomere maintenance in predisposition to, and initiation of, gliomas, as with many other cancers, especially as inherited variants in some telomere-related genes influence glioma risk [85].

14.2.9.1 Neurofibromatoses

Neurofibromatosis Type 1 (NF1)

NF1 is associated with visual pathway glioma and other tumors of the CNS [86–90]. About 20 % of NF1 cases are associated with low-grade glioma which are almost always pilocytic astrocytomas, the most common locations for them being the visual pathways, cerebellum, and brain stem [91]. They can occur anywhere in the central nervous system. Their frequency in early childhood affecting the visual pathways is classical and justifies visual screening during early childhood. Their treatment, where visual function is progressively affected or seriously threatened, is by chemotherapy, vincristine and carboplatin or

Table 14.3 Syndromes associated with CNS tumors

Syndrome (gene)	Associated CNS tumors
Ataxia-telangiectasia (ATM)	Medulloblastoma
Constitutional Mismatch Repair Deficiency Syndrome (MSH2, MSH6, MLH1, PMS2)	Astrocytoma
	Glioblastoma
	CNS primitive neuroectodermal tumor
	Medulloblastoma
Familial adenomatous polyposis (APC)	Astrocytoma
	Medulloblastoma
	Ependymoma
	Pineoblastoma
Carney complex (PRKAR1A)	Schwannoma (psammomatous melanotic)
Cowden syndrome (PTEN)	Dysplastic gangliocytoma of cerebellum
	Meningioma
DICER1 syndrome (DICER1)	CNS primitive neuroectodermal tumor (specifically medulloepithelioma)
	Pineoblastoma
	Pituitary blastoma
Fanconi anemia (FANCD1/BRCA2, FANC-N, or PALB2)	CNS primitive neuroectodermal tumor
	Medulloblastoma
Hereditary retinoblastoma (RB1)	Pineoblastoma
Li–Fraumeni Syndrome (TP53)	Astrocytoma
	High-grade glioma (diffuse astrocytoma, anaplastic astrocytoma, glioblastoma)
	Choroid plexus tumor
	CNS primitive neuroectodermal tumor
	Medulloblastoma
Neurofibromatosis type 1 (NF1)	Glioma (brain stem, neuraxial)
	Pilocytic astrocytoma/optic pathway glioma
	Diffuse astrocytoma
	Glioblastoma
	Malignant peripheral nerve sheath tumor
	Neurofibroma
Neurofibromatosis type 2 (NF2)	Glioma
	Astrocytoma
	Ependymoma
	Meningioma
	Neurofibroma
	Schwannoma
	Vestibular schwannoma
Nevoid basal cell carcinoma syndrome (PTCH/SUFU)	Astrocytoma
	Craniopharyngioma
	Medulloblastoma (desmoplastic subtype)
	Meningioma
	Oligodendroglioma
Rhabdoid tumor predisposition syndrome (SMARCB1)	Atypical teratoid/rhabdoid tumor
	Malignant peripheral nerve sheath tumor
Rubinstein–Taybi syndrome (CREBBP)	Medulloblastoma
Schwannomatosis (SMARCB1)	Schwannoma
Tuberous sclerosis complex (TSC)	Subependymal giant cell astrocytoma
Von Hippel–Lindau (VHL)	Hemangioblastoma (intracranial, spinal)

vinblastine alone being the most commonly used drugs. New biological markers of the MAP kinase pathway are underdevelopment and in trial; antiangiogenic drugs may effectively reverse neurological signs, but sustained use is associated with vascular risks. Radiotherapy, while effective, is potentially damaging to vascular structures within the radiation field and is generally avoided or used with highly focused techniques. Where surgical removal is not possible, the tumors can be seen to grow, arrest, and then in some cases involute or even regrow, during childhood and adolescence. This growth pattern may be derived from growth characteristics of the normal brain. Benign tumors associated with NF1 are generally seen to burn themselves out by the end of adolescence, remaining static or indeed involuting. There is an association between NF1 and high-grade glioma; their treatment is complicated by enhanced radiosensitivity linked to the NF1 genotype, which can lead to encephalopathy or late vascular damage. As a consequence, surgery and chemotherapy or biologically targeted therapy would be recommended before considering radiotherapy.

Neurofibromatosis Type 2 (NF2)

NF2 is a genetic condition where mutations in the NF2 gene leads to abnormalities of the gene product, a protein called merlin. This protein is made in the nervous system, particularly in specialized cells that wrap around and insulate nerves (Schwann cells) where it is thought to control cell shape, cell movement, and communication between cells. Merlin also functions as a tumor suppressor protein, which prevents cells from growing and dividing too fast or in an uncontrolled way. This shortened protein cannot perform its normal tumor suppressor function in cells permitting cells, especially Schwann cells, to multiply too frequently and form noncancerous tumors, characterized by the presence of acoustic neuromas or auditory nerve sheath schwannomas, causing hearing difficulties. Other clinical features include skin nodules or plaque-like lesions, cafe au lait patches, mono- or polyneuropathies, and visual loss due to cataracts or post lenticular opacities. In addition there is high risk of intracranial meningioma, affecting 18–58 % of patients [92], astrocytomas and ependymomas in about 3 % of patients [90]. When present in the AYA age group, they may represent the more aggressive version of the disease, the Wiseheart type, which present in childhood are progressive and reduce life expectancy compared to the adult presentation [93].

14.2.9.2 Meningiomas

Multiple meningiomas are also a feature of NF2, occurring earlier in life than sporadic meningiomas, and are usually WHO grade 1 tumors. There is no increased frequency of atypical or malignant meningiomas, although they are more frequently fibroblastic [94].

14.2.9.3 Schwannomas

NF2-associated schwannomas are WHO grade 1 tumors that differ from sporadic schwannomas by presenting at an earlier age and at multiple sites (e.g., bilateral vestibular schwannomas occurring in the third decade of life). The role of antiangiogenic drugs bevacizumab is currently under investigation and extended use to inhibit tumor progression/development [95]. They affect multiple cranial and spinal nerves, predominantly sensory (5th and 8th), although motor roots such as the 12th are reported. They may present as either multilobular tumors or as multiple schwannomatous tumorlets with potential to progress to schwannomas. Vestibular schwannomas may entrap several cranial nerves, exhibiting high-proliferative activity.

14.2.9.4 Astrocytomas/Gliomas

The overwhelming majority (80 %) of gliomas associated with NF2 are intramedullary, either within the spinal cord or the cauda equina. A further 10 % affect the medulla. Up to 75 % of these gliomas are ependymomas, frequently multiple, the remainder being diffuse or pilocytic astrocytomas.

14.2.9.5 Neurofibromas

Although these occur, they are frequently found to be schwannomas upon review. Plexiform neurofibromas are not seen in NF2.

14.2.9.6 Von Hippel–Lindau Syndrome

This is an autosomal dominant disorder caused by mutation in the VHL antiangiogenic tumor suppressor gene on chromosome 3p, with an incidence of between 1:36,000 and 1:45,500. Diagnostic criteria are based upon:

- Capillary hemangioblastoma in the CNS or retina
- The presence of one of the typical VHL-associated tumors
- A previous family history

Among 83 subjects in a genetic register for VHL disease in North West England, cerebellar hemangioblastoma affected 60 % and was the presenting manifestation in 35 % [96]. Hemangioblastoma was diagnosed at a mean age of 30 years (range 15–56 years), so a sizeable proportion of diagnoses must have been at age 15–29 years. Spinal hemangioblastoma occurred in 14 % of subjects, at slightly more advanced ages. Of 86 people with a CNS hemangioblastoma in the regional cancer registry, 13 % were on the VHL register. Ependymomas and choroid plexus papillomas have been reported in association with VHL, probably mediated through the loss of suppression of the pro-angiogenic hypoxia inducible factor (HIF 1a) when the VHL gene is mutated.

14.2.9.7 Capillary Hemangioblastoma

A WHO grade 1 tumor of stromal cells and abundant capillaries, an uncertain histogenesis, and a preferential cerebellar location, capillary hemangioblastoma has been reported in the brain stem, spine, and, rarely, supratentorially. When associated with VHL, these tumors are frequently multiple in number. They occur with increasing frequency during development and with the peak incidence occurring in the thirties. The success of surgical resection (though repeated resection of cerebellar tumors can carry significant morbidity) means that life-limiting tumor problems of VHL often relate to malignancy at other sites (e.g., renal cell carcinoma), justifying surveillance at regular intervals.

14.2.9.8 Tuberous Sclerosis Complex (TSC)

This is a genetic condition where two thirds are sporadic new mutations and about one third are inherited as an autosomal dominant disorder with an estimated incidence of 1:5,000–10,000. The mutations inhibit the function of TSC1 and TSC2 protein synthesis although up to 25 % phenotype cases have no recognizable mutations. TSC2 mediates the cellular energy response to control cell growth and survival [97, 98]. TSC phenomena (Table 14.4) can affect any organ; however, the brain and skin affects up to 80 %. The other organ phenomena manifest at different times in life, i.e., cardiac rhabdomyomas occurring in infancy, growing, and then involuting within the first year; SEGAs present symptomatically or on brain imaging as part of diagnostic screening during childhood and grow during adolescence. Renal angiomyolipoma have been detected on surveillance imaging during childhood but generally present clinically in third and fourth decade and beyond, while the lymphangioomatosis (LAM) of the lung predominantly affects females and presents in the third and fourth decades [99].

14.2.9.9 Subependymal Giant Cell Astrocytoma (SEGA)

For this chapter SEGA are the relevant focus, individuals with either type of TSC are estimated to have a 5 % risk of SEGA by age 30 years [100]. SEGAs are typically WHO grade 1 tumors that arise in the wall of the lateral ventricles either a singular or less frequently multiple tumors and are composed of large ganglioid astrocytes. Malignant transformation even at relapse is not reported. Recently published guidelines recommend surveillance imaging which is diagnosing the development of SEGAs and other TSC phenomena earlier during childhood. Worsening epilepsy and raised intracranial pressure due to obstruction of the lateral/third ventricles are common presenting symptoms; occasionally, massive spontaneous hemorrhage can occur. The currently preferred treatment is surgical resection, when possible, which is often achievable in solitary tumors when they grow to a size that threatens CSF circulation from lateral to third ventricles given the tendency of solitary lesions

Table 14.4 Tuberous sclerosis complex (TSC)

Updated diagnostic criteria for TSC, 2012[a]
A. Genetic diagnosis criteria
The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of TSC. A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation for which the effect on protein function has been established by functional assessment [101–103]. Other TSC1 or TSC2 variants whose effect on function are less certain do not meet these criteria and are not sufficient to make a definite diagnosis of TSC. Note that 10–25 % of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC or has any effect on the use of clinical diagnostic criteria to diagnose TSC
B. Clinical diagnostic criteria
Major features
1. Hypomelanotic macules (≥3, at least 5-mm diameter)
2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias[b]
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)[c]
11. Angiomyolipomas (≥2)[b]
Minor features
1. "Confetti" skin lesions
2. Dental enamel pits (≥3)
3. Intraoral fibromas (≥2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas
Definite diagnosis: two major features or one major feature and ≥2 minor features
Possible diagnosis: either one major feature or ≥2 minor features

[a]Modified from Northrup and Kruger [104]
[b]Includes tubers and white matter cerebral radial migration lines
[c]A combination of the two major clinical features (LAM and angiomyolipoma) without other features does not meet criteria for a definite diagnosis.

to be located near to formina of Monro, the fenestrations between the two ventricles.

The recent observation that Mechanistic Target of Rapamycin (mTOR) inhibitors shrink SEGAs and subsequent trials have led to licensing of the mTOR inhibitor (everolimus) for this purpose in childhood is opening this group of patients to new approaches to management. In considering the selection of surgical versus medical management of SEGAs, balancing the risks of treatment-related neurotoxicity is critical, given the inherent cognitive consequences of TS due to cortical lesions and associated epilepsy. The mTOR inhibitors are mild immunosuppressants; mouth ulcers are reported as the commonest side effect.

14.2.9.10 Li–Fraumeni Syndrome

Li–Fraumeni syndrome (LFS) is an autosomal dominant disorder; its population incidence is unknown, although 108 families with TP53 germline mutations were reported from 1990 to 1996 [105]. Diagnostic criteria are (1) occurrence of sarcoma before age 45 years, (2) at least one first-degree relative with any tumor before age 45 years, or (3) a second-degree relative (or first) with cancer before 45 years or a sarcoma at any age [106–108]. Brain tumors are a recognized component of LFS [109, 110]. In a cohort study of 28 LFS families with germ-line TP53 mutations, the risk of CNS tumors at age 15–29 years was 32 times that in the general population [111]. The spectrum of CNS tumors associated with LFS reflects the age incidence of other tumors in the AYA population, with astrocytomas predominating [105]. The mean age at presentation of a CNS tumor in patients with LFS is 25.9 years – the third youngest age category. Sarcomas (mean age 16.7 years) and adrenal tumors (mean age 4.7 years) present earlier in life. Multiple tumors in those with LFS are well recognized; prior CNS irradiation may confer additional risk.

Of those CNS tumors reported to be associated with LFS, the age-incidence pattern is preserved, with childhood embryonal (PNET), ependymal, and choroid plexus tumors arising in childhood and the astrocytic tumors (low-grade, anaplastic glioblastoma, oligoastrocytoma, and gliosarcoma) arising in the AYA and adult years.

14.2.9.11 Multiple Endocrine Neoplasia

Pituitary tumors are a frequent component of multiple endocrine neoplasia (MEN) type 1. In a multicenter series of 220 affected members of 98

MEN type-1 families, 30 % had a pituitary tumor [112]. These tumors were nearly always diagnosed before age 40 years.

14.2.9.12 Cowden Disease

This is an autosomal dominant condition where the population incidence is unknown; it is thought to have a relatively high rate of novel mutations and a variable severity of phenotype, making its hereditary pattern obscure. Diagnostic criteria include multiple trichilemmomas (benign skin appendage tumors; 85 %), thyroid tumors (70 %), malignant breast tumors (30 %), oral papillomatosis, cutaneous keratoses, hamartomatous soft-tissue tumors, and benign breast tumors. The CNS manifestation of this condition is dysplastic gangliocytoma of the cerebellum (L'hermitte–Duclos disease), which is a diffuse enlargement of the cerebellum [113]. The histology is a WHO grade 1 lesion consisting of large neuronal cells expanding the granular and molecular layers. It is unclear whether this is a hamartomatous or neoplastic lesion because of its proliferation index and the absence of progression. However, recurrence has occasionally been noted, and they may develop in adults with previously normal magnetic resonance imaging scans. Other CNS features include megalencephaly (20–70 %), heterotopic gray matter, hydrocephalus, mental retardation, and seizures [114].

14.2.9.13 Lynch Syndrome (LS)/ Mismatch Repair Syndrome (MMR)/Biallelic MMR (BMMR-D)/Turcot Syndrome/Gardner Syndrome

This group of syndromes describes associations between colonic polyps and brain tumors. The precise features overlap and are being increasingly investigated through case collection and intensive study. Their importance is twofold: first a patient is diagnosed with a brain tumor and one of these associated conditions may be eligible for targeted treatment for the specific genetic mutation as research emerges; secondly they may be the proband for a familial cancer predisposition affecting the extended family.

LS, MMR, and BMMR–D are a group of autosomal dominant and possibly autosomal recessive disorders caused by mutations in DNA mismatch repair genes, e.g., MLH1, MSH2, MSH6, and PMS2. MMR corrects single base-pair mismatches and small insertion–deletion loops that arise during replication. Moreover, the MMR system is involved in the cellular response to a variety of agents that damage DNA and in immunoglobulin class switch recombination.

Lynch Syndrome (LS) and Mismatch Repair Syndrome (MMS) Heterozygous germ-line mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* cause LS which is characterized by coexistence of primary colorectal polyps and tumors and gliomas. The gliomas (high-grade astrocytomas or medulloblastoma) almost always occur before age 25 years and are associated with families with hereditary nonpolyposis colorectal cancer (HNPCC) endometrium carcinoma and other malignancies, occurring on average in the fourth and fifth decades of life [115]. Notably, LS-associated tumors display somatic loss of the remaining wild-type *MLH1*, *MSH2*, *MSH6*, or *PMS2* allele and evidence of microsatellite instability. In the Dutch HNPCC registry and in a Finnish study of 50 HNPCC families, the risk of a brain tumor was four to six times that of the general population [116, 117].

Biallelic Mismatch Repair Deficiency (BMMR–D) [118] This is a syndrome where heritable biallelic (homozygous) mutations in any of the MMR genes result in a different clinical syndrome characterized by gastrointestinal tumors, skin lesions, brain tumors, and hematologic malignancies. This recently described and under-recognized syndrome can present with adenomatous polyps leading to early-onset small bowel and colorectal adenocarcinoma. An important clue in the family history that suggests underlying BMMR–D is consanguinity. Other clinical features include café au lait spots in HNPCC and congenital hypertrophic retinal pigmented epithelium. Interestingly, pedigrees of BMMR–D patients typically show a paucity of Lynch syndrome cancers, and most parents are unaffected. Therefore, a family history of cancers is often noncontributory. Detection of BMMR–D can lead to more appropriate genetic counseling and the implementation of targeted

surveillance protocols to achieve earlier colonic tumor detection that will allow surgical resection. A trial of a checkpoint inhibitor (pembrolizumab) in colorectal tumors associated with BMMR–D and those without BMMR–D showed preliminary favorable outcome in BMMR–D patients suggesting a new target for treatment linked to genotype [119]. This experience suggests a parallel approach in brain tumors with this heritable association that should be explored.

Turcot Syndrome In families with medulloblastoma and other features of familial adenomatous polyposis (FAP), mutations have been found in the *APC* gene. People who may have Turcot syndrome can have a mutation in the *APC* gene associated with FAP or the *MLH1* gene or the *PMS2 gene*. Where a gene mutation is found, other family members may also be diagnosed with Turcot syndrome if they are tested and have the same gene mutation. However, some families that appear to have Turcot syndrome may not have a detectable gene mutation.

Gardner Syndrome This is a group of autosomal dominant (due to mutation in the APC gene on chromosome 5q, often considered a variant of familial adenomatous polyposis) and possibly autosomal recessive disorders, in which there is coexistence of familial adenomatous polyposis (FAP), associated colonic polyps, and characteristic bone lesions and brain tumors. The characteristic nonmalignant lesions include sebaceous cysts, epidermoid cysts, fibromas, desmoid tumors, and osteomas, usually found on the jaw. Most of the brain tumors are medulloblastomas, but gliomas also occur [115]. In the Johns Hopkins FAP registry, the relative risk for any brain tumor in the first 30 years of life was 23, and the corresponding relative risk for medulloblastoma was 99 [120].

14.2.9.14 Other Conditions with Increased Risk of CNS Tumors

People with Down syndrome have a reduced overall risk of CNS tumors, although the risk of intracranial GCTs is increased [121]. Gorlin syndrome is strongly associated with medulloblastoma, and germ-line mutations in the INI1 gene are associated with atypical teratoid rhabdoid tumors, although both of these associations occur almost exclusively in early childhood and are therefore not applicable to the age focus of this chapter [122–125].

Finally, there are reported medulloblastomas presenting in patients with ataxia-telangiectasia, a syndrome that is characterized by cerebellar degeneration and DNA repair defect and is associated with an increasing number of specific gene mutations within the AT gene complex, making the patient particularly vulnerable to ionizing RT [126–129].

14.2.9.15 Familial Aggregation of Brain Tumors

The risk of a brain tumor is approximately doubled in first-degree relatives of brain tumor patients [130]. Relative risks are similar for glioma in first-degree relatives of glioma patients [64] and for meningioma when a first-degree relative also has meningioma [131]; however, the risk of low-grade glioma in first-degree relatives may be considerably higher [131]. The absence of excess risk among spouses of brain tumor patients indicates genetic rather than environmental origins for familial aggregations [132]. Many familial aggregations of CNS tumors are attributable to the aforementioned syndromes, especially NF1 and NF2,Turcot/Mismatch Repair Syndrome, LFS, VHL disease [133], and MEN1. In other instances, however, there is no evidence of a brain tumor predisposition syndrome or germ-line TP53 mutation [134], and explanations are, therefore, awaited.

14.3 Presentation, Assessment, Treatment, and Outcome in CNS Tumors in AYAs

14.3.1 Clinical Presentation

The most common concerns among AYAs with cancer are prolonged periods of illness prior to the ultimate diagnosis. This is particularly true for those who present with brain tumor and is corroborated by epidemiological evidence [135]. The spectrum of tumors and their common locations in AYAs,

together with the implications of functional anatomy, mean that symptomatology is governed by:

- Symptoms of raised intracranial pressure due to obstructive hydrocephalus or large tumor mass with midline shift
- Specific symptoms due to neurological dysfunction of brain regions involved with the tumor, including the primary site of the tumor and areas where metastatic disease exists [136] (Fig. 14.10)

The UK HeadSmart Be Brain Tumor Aware campaign [137] was designed to amplify the impact of evidence-based clinical guidelines [138] directed at the profession and the public, seeking to reduce the total diagnostic interval (TDI). The campaign did raise awareness of signs and symptoms among pediatricians, nationally. The UK public became aware of the campaign; the TDI reduced from 14 weeks (median; mean 35 weeks), prior to the publication of clinical guidance document, to a TDI of 7 weeks (median; mean 22 weeks), 2 years after the launch of the awareness campaign. TDI data was collected for a representative sample of patients up to 16 years of age by the network of UK brain tumor treatment centers. The reduction in TDI observed was least pronounced in the adolescent age group. The tumor types with the greatest proportion of prolonged delays were low-grade glioma, intracranial germ cell tumor, optic pathway glioma, and craniopharyngioma. The anatomical sites showing the greatest reductions were midline supratentorial tumors and cerebellar tumors, and the age group showing the least change was the adolescent age group (12–16 years) (see Fig. 14.11). The interaction between age (12–16 years),

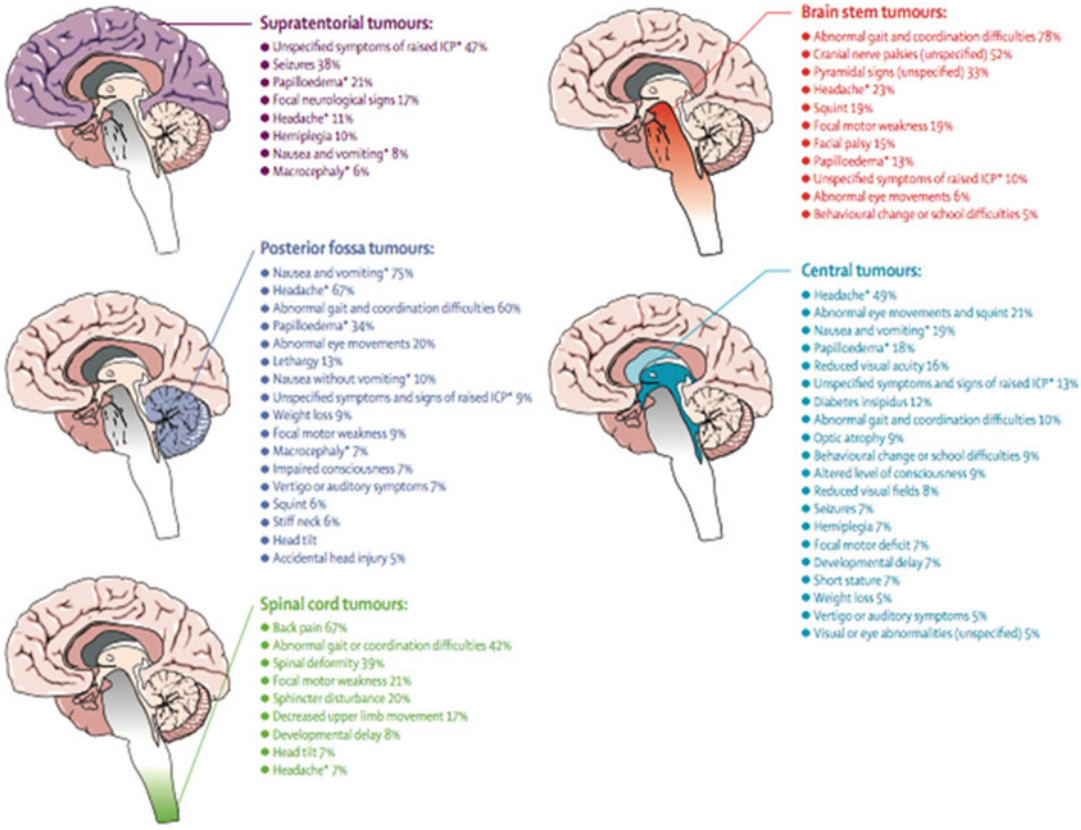


Fig. 14.10 CNS tumor presentation. *Symptom or sign ranked by frequency caused by raised intracranial pressure (*ICP*) [136]

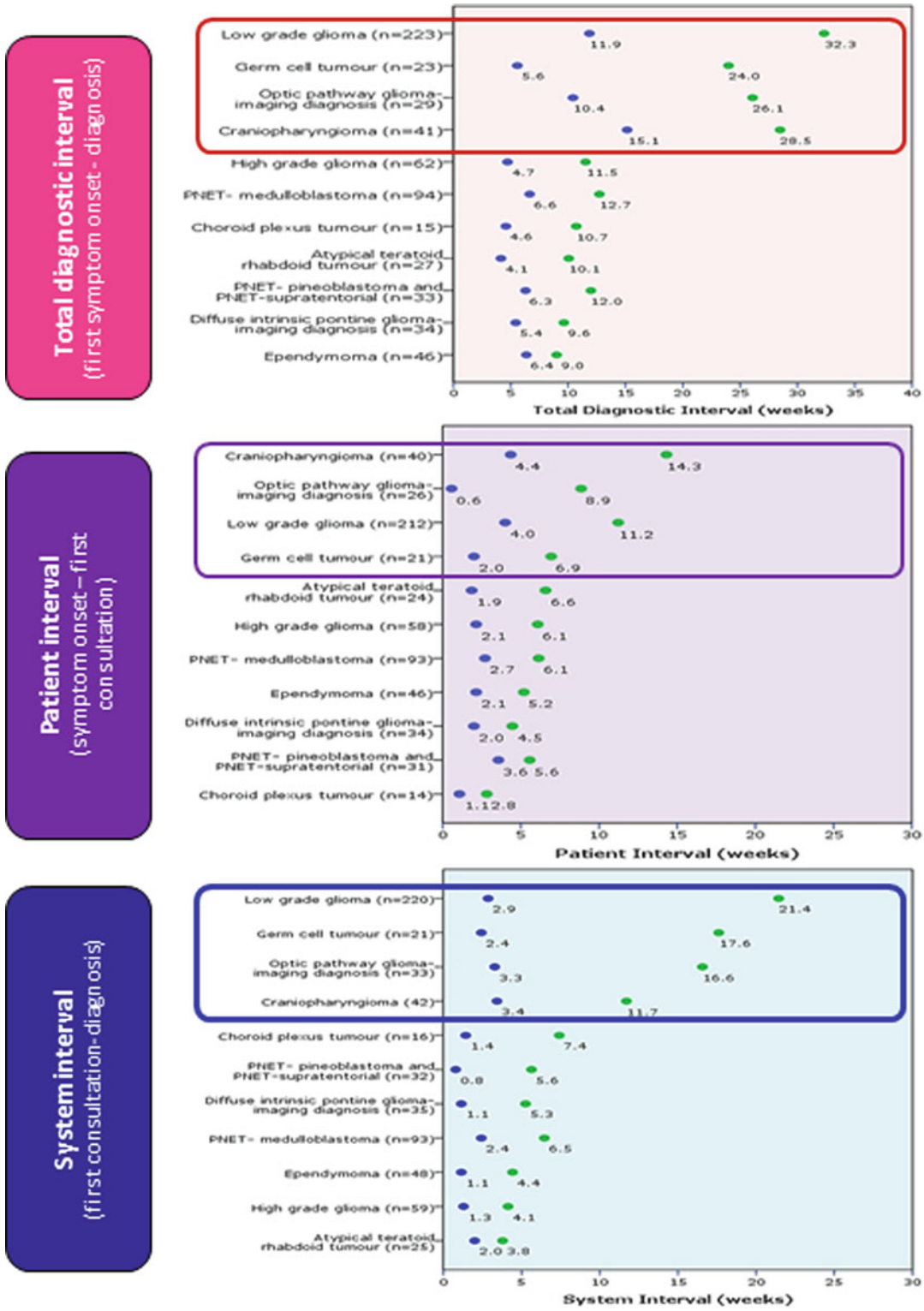


Fig. 14.11 Diagnostic intervals for pediatric brain tumor referrals (age <18, UK 2011–2013 HeadSmart dataset). Data ranked by differences between median (*blue*) and mean (*green*)

midline supratentorial tumors, and intracranial germ cell tumors highlights a particular challenge for the adolescent age group if delays are to be further reduced. The overall success of this program using public awareness techniques is worthy of consideration.

14.3.2 AYA Neuro-oncology Team Models

AYA neuro-oncology teams straddle pediatric and adult practice and are evolving in parallel with AYA models of cancer care in other leukemia and solid tumor types. The difference is the focus on clinical neuroscience, which strongly influences clinical presentations, diagnostic processes, treatment planning and delivery, and rehabilitation, especially where focal neurological deficits occur as well as the need to consider the cognitive and endocrine consequence of the tumor and its treatment (Figs. 14.12 and 14.13).

In the UK, the National Institute for Health and Care Excellence (NICE) issued guidance in 2005, "Improving Outcomes in Children and Young People with Cancer" [139], which provides clear standards for service delivery. The key principles are:

- Care is centered on principal (childhood cancer) treatment centers, supported by designated local hospitals.
- An AYA-specific multidisciplinary team works out of each group or treatment center alongside cancer site-specific teams.
- There needs to be an AYA psychosocial team that provides an umbrella over services.
- Young people must have unhindered access to age-appropriate facilities and support and should have choice about their care.

Similarly in 2006 NICE (UK) issued guidance for adult patients with brain and central nervous system tumors [140]. The key principles are:

- All patients' care should be coordinated through a designated multidisciplinary team (MDT).

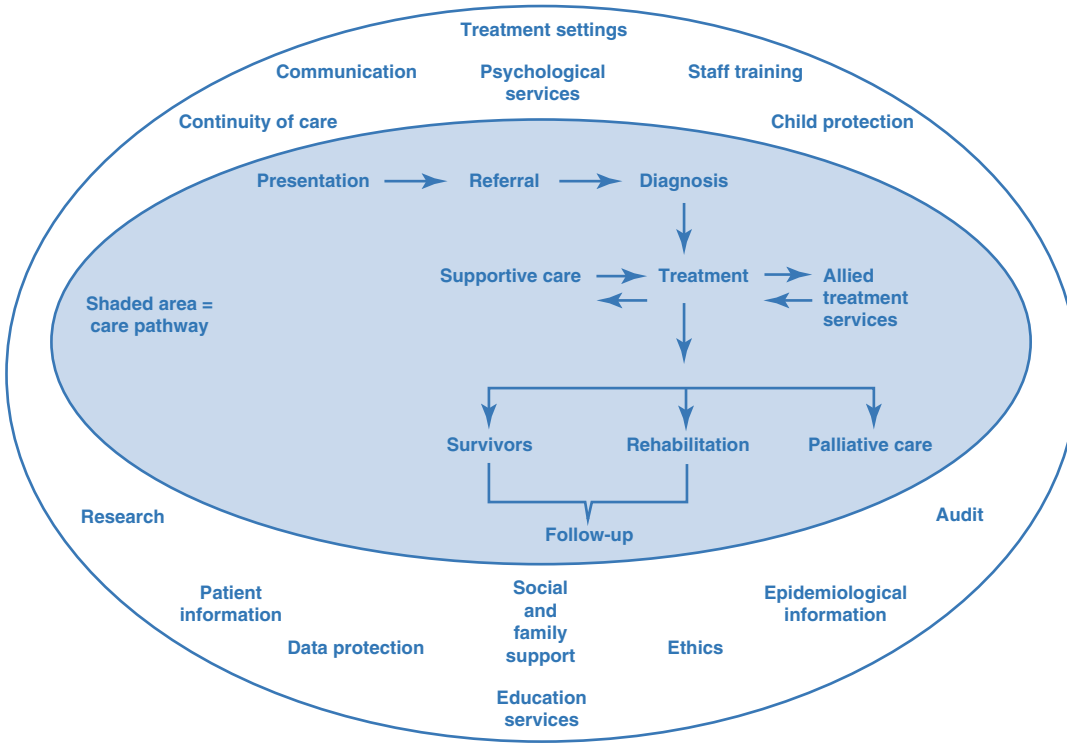


Fig. 14.12 The care pathway for children and young people with cancer and its wider context [139]

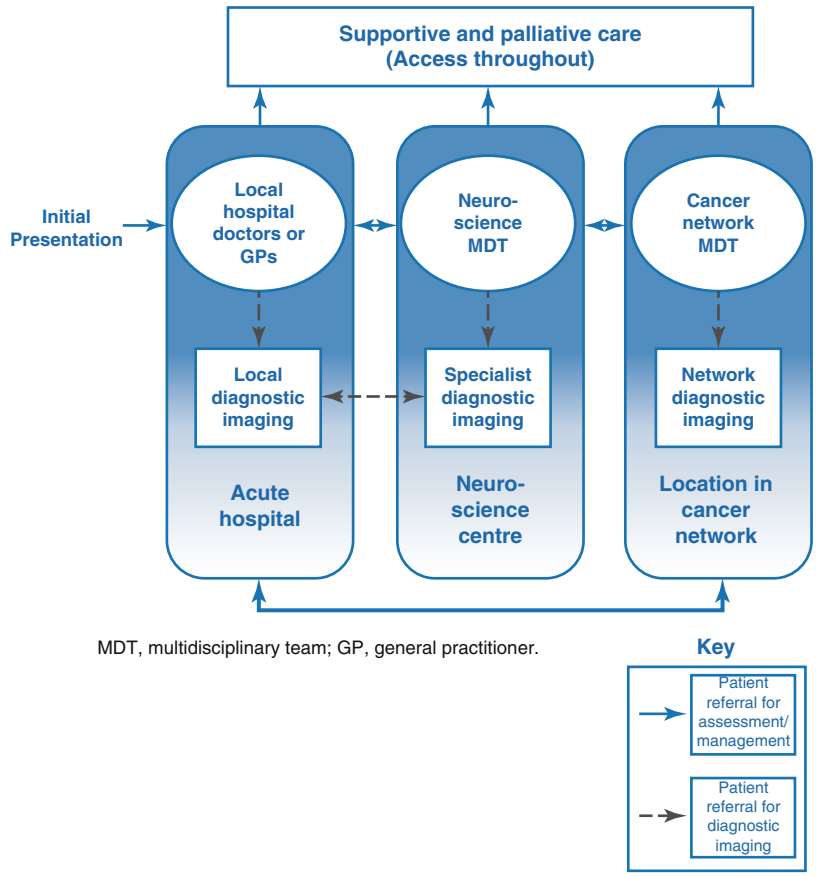


Fig. 14.13 Care pathway for adults with brain tumors [140]

- All patients should have face-to-face contact with healthcare professionals to discuss their care at critical points in their care pathway and be provided with high-quality written information to support this.
- All patients should have a clearly defined key worker.
- Patients should have ready access to specialist care services as appropriate.
- Palliative care specialists should be core members of the neuroscience MDT and of the cancer network MDT.

In the UK, national clinical trial research networks have been established by the National Institute of Health Services Research (NIHR) [www.crn.nihr.ac.uk] which are performance managed to optimize recruitment cancer patients to clinical trials as part of an all-disease research strategy. Internationally different models of care for AYA neuro-oncology are developing; the UK principles are being used here as an illustrative example in a public health system.

These examples of models of management of the AYA brain tumor patient at the interface between pediatric and adult neuro-oncology practice pose challenges for multidisciplinary team working. In the author's regional specialist center, the weekly multidisciplinary meeting must discuss and decide on treatments for ~40–60 patients per week involving four regional hospital teams connected by a video conference technology. The meeting takes place over 2 h; patients are presented with the oldest first and the youngest last. In the first 90 min, up to 60 patients are discussed, aged 90+ to 18 years; in the last 30–40 min, 5–10 patients are discussed aged 18–0 years. These diagnostic and treatment planning meetings are now complemented by AYA multi-professional meetings, where each patient's psychosocial and rehabilitation needs are discussed and planned for. The time funded for

specialist staff in this way is starting to transform the experience for the young patients presenting with brain tumor problems and being managed across the pediatric to adult service gap.

14.3.3 Neurosurgery

14.3.3.1 Pediatric and Adult Neurosurgical Services

CNS tumors in adolescence present neurosurgeons with difficulties similar to those found in the pediatric and young adult populations. Clinical management in this age range creates specific patient-management concerns, although tumor management is approached with the same inventory applied to specific tumors in any age range. Neurosurgery has three roles to play in the management of brain tumors: (1) reduction of raised intracranial pressure, (2) making a diagnosis, and (3) contributing to therapy. These will now be discussed.

14.3.3.2 Management of Raised Intracranial Pressure

Raised intracranial pressure demands surgical intervention to reduce mass effect and brain distortion, which may need to be achieved urgently. Preoperative treatment with high-dose steroids and, in emergencies, mannitol infusions, contributes to the control of raised pressure, while preparation for surgery is in progress. Surgical treatment is required for large tumors, cysts, and those obstructing cerebrospinal fluid (CSF) pathways. With acute hydrocephalus, CSF diversion may be necessary with external drainage as a temporary measure or third ventriculostomy or ventriculoperitoneal shunting for a more permanent solution. Although concern exists about the dissemination of malignant cells, it is generally overridden by the need to deal with long-term hydrocephalus. In medulloblastoma and posterior fossa ependymoma, there may be a need for temporary external drainage of CSF, but a long-term shunt may be avoided after tumor resection. Reduction of intracranial pressure by tumor debulking may stabilize the patient's clinical condition and allow other oncological therapies, even for tumors that are not completely resectable.

14.3.3.3 Making the Diagnosis

Histological and genetic examination of tumor tissue is an essential part of establishing a tumor diagnosis in the brain, as it is for other sites. On the whole, surgery to biopsy or otherwise achieve tissue diagnosis is straightforward in intracranial lesions, though carrying a small risk of intracranial hemorrhage and other serious complications A variety of techniques can be used, including stereotactic, endoscopic, or open biopsy sampling (see Fig. 14.14), as well as obtaining tissue at the time of tumor resection. The risks of these techniques vary. Stereotactic biopsy, for instance, has mortality and morbidity rates of less than 1 % and less than 5 %, respectively, in supratentorial tumors, and a very high positive diagnostic rate. As the contribution of molecular genetic information to therapy decisions

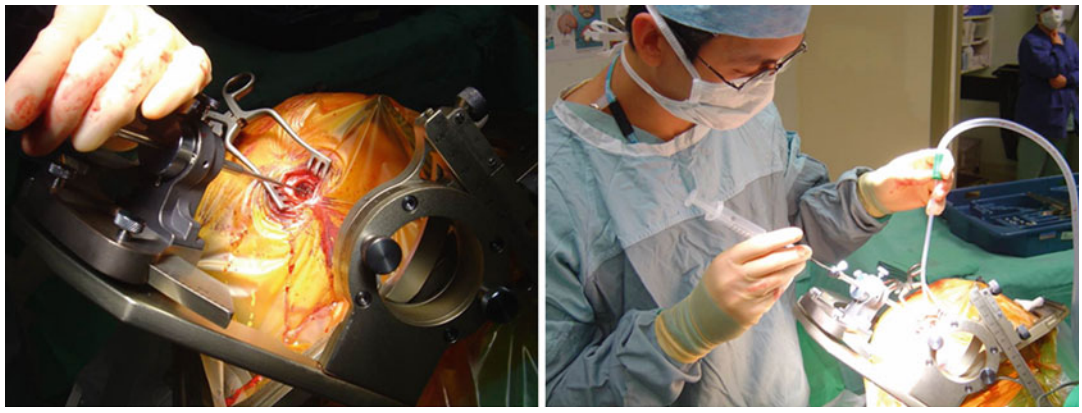


Fig. 14.14 Craniotomy burr hole and stereotactic biopsy

increases, biopsy for material to allow genetic analysis is becoming of increasing importance, even for unresectable tumors.

14.3.3.4 Surgical Approaches: Midline Supratentorial Tumors

Midline tumors are more common in the adolescent age range than later in life and present major neurosurgical management difficulties. Their diagnosis may be made by examination of tumor markers [α-fetoprotein (αFP), β-human chorionic gonadotropin (βHCG), and placental-like alkaline phosphatase] in either the blood or CSF, and if these tumor markers are found, then diagnostic surgery may be avoided [141]. If pineal region tumors present with obstructive hydrocephalus, then operative CSF diversion allows the opportunity to take CSF for tumor marker analysis. If, rather than performing a ventricular peritoneal shunt, a third ventriculostomy is considered via a neuro-endoscopic procedure, then an opportunity arises to visualize a pineal tumor from the third ventricle and, indeed, perform an endoscopic biopsy procedure. If blood and CSF markers are negative, then it is necessary to obtain a biopsy sample of pineal tumors to determine their histology, which has great influence on their further management. Stereotactic biopsy in the pineal region is not without risk in view of the deep situation of the pineal region, and the proximity, in particular, of veins, which together with the chance of lesions "bouncing off" biopsy cannulae, raises the possibility of the procedure failing to provide a tissue diagnosis. Pineal region tumors may, in their own right, cause localized problems, e.g., gaze abnormalities, and require excision. Open resection may be undertaken through supratentorial (suboccipital) or infratentorial (supracerebellar) approaches depending on tumor location.

14.3.3.5 Surgical Approaches: Brain Stem

The brain stem is not difficult to biopsy with stereotactic techniques, but there is a higher risk of morbidity. Imaging diagnosis, while still a standard practice, was accepted as there was no alternative to radiotherapy for treatment, and despite extensive trials no chemotherapy agents were shown to work. Recent research has identified new biomarkers which will be evaluated in future trials as targets for therapy and/or markers of prognostication. A recent consensus accepted that biopsy was justified as part of biocharacterization studies [142–144].

14.3.3.6 Surgical Approaches: Other Sites

Surgical resection proceeds on the general principle of achieving maximal safe resection with minimal neurological damage. Tumors in noneloquent brain areas, e.g., frontal or temporal pole, may be safely resected with a margin, whereas tumors in eloquent areas, e.g., primary speech areas or motor strip, must be resected more cautiously in order to avoid serious neurological disability which may even preclude further oncological therapy. Eloquent-area tumors can be safely debulked as long as resection remains within the central tumor areas and avoids surrounding brain. However, many of the higher-grade tumor, e.g., glioblastoma or medulloblastoma, have a highly infiltrative phenotype with even "complete" surgical resection leaving substantial amounts of infiltrative tumor cells within apparently normal brain parenchyma. Pre- and intraoperative image guidance with computed tomography or magnetic resonance imaging (including functional mapping of eloquent areas), intraoperative ultrasound, or even intraoperative magnetic resonance scanning may be of help. Other modern techniques introduced to aid maximal safe resection include awake craniotomy, which may be appropriate for young adults able to cope with the psychological aspects of this procedure. Cortical bipolar stimulation and neuropsychological testing intraoperatively allow more surgical confidence in resecting close to eloquent brain areas. 5-Aminolevulinic acid (Gliolan™) can also be given preoperatively for suspected high-grade gliomas, leading to accumulation of fluorescent protoporphyrin IX specifically in tumor cells, which can be visualized as pink fluorescence under blue light at operation, allowing easier identification of potentially occult tumor areas and better differentiation between tumor and normal brain.

Surgery aimed at maximal safe resection has a therapeutic role in most tumor types, save perhaps for lymphoma, craniopharyngioma, or GCTs. Tumors encountered in adolescence may be a problem increasingly as a result of previous medical interventions such as the use of CNS irradiation for other tumors. Meningiomas and other malignant tumors occur in this age range, presenting particular difficulties. Malignant tumors are difficult to treat in their own right, but benign tumors such as meningiomas are particularly complex because they may be multiple and may occur within previous radiotherapy fields, which not only provokes field change within the dura, making complete resection difficult, but limits subsequent radiation doses due to tissue tolerance limits. Radiation-induced meningiomas are also more likely to be of atypical (WHO grade II) or meningiosarcoma (WHO grade III) subtypes, making their behavior more aggressive and recurrence much more likely.

Surgery plays an important role in relieving patients of symptoms linked to tumor bulk. In pilocytic astrocytoma, those arising in the cerebellum in particular and at other sites, the balance of risk versus benefit is determined by the anatomical location of its eloquence for function. Predicting tumor behavior in pilocytic astrocytoma is increasingly understood to be linked to age and location, as yet there are no informative biomarkers. Selecting patients for nonsurgical therapy is best done by careful multidisciplinary discussion weighing up risk and benefits. In hypothalamic–visual pathway tumors, surgery is seldom indicated to save vision; debulking of large tumors can sometimes be achieved [144].

In grade 2 glioma, rational discussion should be had with the patient outlining that malignant transformation of the "low-grade" tumor to a high-grade "cancerous" tumor is almost inevitable, but this may not occur for many years, with the median time to transformation for isocitrate dehydrogenase type 1 (IDH-1) mutant tumors of approximately 7 years, but of only 1 year for IDH-1 wild-type low-grade gliomas. Biopsy to establish this status is an option, but MR spectroscopy may soon be able to determine this based on the accumulation of the onco-metabolite 2-hydroxyglutarate. Surgical resection and oncological therapy carry significant risks and will clearly interfere with the quality of life of the patient in their young adult years. Surveillance with MRI is an option, avoiding the immediate risks of treatment, but the risk of transformation remains and may occur without warning. However, the ideal treatment is macroscopic complete resection, which probably produces a better outcome but is limited by the eloquent position of many tumors. Subtotal resection is often employed; although even 90–99 % resections will not prevent malignant transformation, bulk reduction does improve progressive symptomatology in the short to medium term.

Surgery for higher-grade astrocytomas has never been subjected to a randomized controlled trial in young patients to compare resection versus biopsy sampling (one small RCT in the elderly showed benefit for resection over biopsy), but surgeons generally attempt the most complete resection possible where deemed reasonable, based on several large post hoc retrospective analyses that seem to show benefit if resection can extend to at least 90 % of enhancing material. A phase III randomized placebo controlled trial [145] showed a modest but significant benefit for the insertion of carmustine-eluting Gliadel™ wafers, allowing direct local delivery of chemotherapy bypassing the blood–brain barrier. Open surgery also allows for implantation of therapeutic agents such as gene therapy [145–151].

Following primary surgery there is sometimes a role for a second open operation. Postoperative MRI imaging as soon as possible following surgery (certainly less than 48 h) is critical to assess tumor residuum (as well as allowing accurate planning for radiotherapy), and resectable tumor may be suitable for reoperation. A pilocytic astrocytoma or ependymoma in the cerebellum might well be reoperated if a resectable residuum were found on imaging. Recurrent higher-grade tumors are resected more than once depending on their response to adjuvant therapies, patient performance, and overall prognosis. In addition, surgery has a role in symptom control in a palliative setting, the control of raised intracranial pressure,

and the resection of symptomatic metastatic tumors in selected cases, as appropriate.

14.3.4 Radiotherapy

Radiotherapy (RT) is the main adjuvant therapy in CNS tumors where either surgical resection is not possible or incomplete or, in malignant tumors, where dissemination or recurrence is predictable. The great advantage of RT is that it can be delivered safely to the whole brain and spinal cord at doses that are known to carry acceptable acute and long-term risks in the vast majority of AYA patients. Stereotactic radiosurgery may have a role in certain situations to defined small recurrent/residual tumors, being particularly used for recurrent meningiomas.

14.3.4.1 Balancing the Risk and Benefits of RT in AYA Patients

In pediatric neuro-oncology, the known radiosensitivity of the developing brain has led to a range of trials attempting to minimize radiation dose and distribution to uninvolved neural tissue. This includes studies to reduce the radiation target size [152] as well as using multimodality therapy to reduce the necessary radiation dose [153]. The endocrine consequences of craniospinal irradiation (CSI) in this group are considerable and include secondary hypothyroidism, growth hormone deficiency, and, in girls, either precocious puberty or incomplete pubertal development, as well as risking infertility from irradiation of the hypothalamus, pituitary, and ovaries. Irradiation to the vertebrae will result in failure of these bones to grow during the adolescent growth spurt, causing loss of up to 5 cm in truncal height; this is unresponsive to growth hormone therapy. Other well-recognized side effects of radiation for brain tumors include hearing and vision loss, vasculopathy, radiation necrosis, and radiation carcinogenesis.

The same balance of risks concerning efficacy versus toxicity must be considered for the AYA population, although there is very limited radiation toxicity data that specifically addresses this age cohort. Most research that includes children and adolescents demonstrates trends suggesting that neurocognitive toxicity of conventional RT doses in AYA patients is somewhat mitigated due to the protective effect of neural maturation. Similarly, due to their age, many young adults have overcome the critical hormonal milestones of adolescence. The risk of ovarian radiation from spinal fields remains an important consideration however. If an ultrasound or MRI reveals ovaries will be exposed to exit dose from photon CSI, oophoropexy may be performed to move the ovaries outside the treatment field. Alternately, the absence of exit radiation dose with proton CSI may make such a procedure unnecessary (PMID: 24940532). Radiation vasculopathy is a dynamic, poorly understood process impacting both large and small vessels of brain tumor survivors; its risk is enhanced in patients with NF1. Although there is a suggestion that younger age is a risk factor among pediatric cohorts [152], the risk may plateau at some yet-defined age. The risk of radiation CNS necrosis likewise may inversely proportional to age. However, a provocative case report speculates that the adolescent spinal cord might in fact be particularly sensitive to chemoradiotoxicity [154]. It is widely accepted that the incidence of radiation-induced second tumors is higher in children than adults. This is thoroughly documented in both radiobiologic and empiric data. One exception to this general rule is the radiation carcinogenesis of breast cancer, where irradiated adolescents and young adults may be at higher risk than younger children [155]. As with many radiation late effects, emerging dosimetric data suggest that this too might be reduced through the use of newer radiation techniques [156].

14.3.5 Chemotherapy and Targeted Drug Therapy

The outcome for AYA patients with brain tumors will depend upon developments in drug therapy aimed at either killing cancer cells or modifying tumor biology. Existing drugs in use are primarily chemotherapeutic agents aimed at attacking the tumor cell during division, leading to cell death. Current experience has identified roles for

chemotherapy in most types of brain tumor. As in extracranial malignancies, chemotherapy or biological therapy can assist with multidisciplinary treatment through:

1. Tumor shrinkage to optimize surgical resectability (e.g., GCTs, ependymoma, and low-grade glioma) has been recommended as a strategy in clinical trials.
2. Adjuvant treatment to complement reduced dose/field RT (e.g., medulloblastoma germinoma).
3. Treatment or prevention of leptomeningeal tumor, IT therapy, is increasingly being used in this role at relapse and in selected tumors at the time of diagnosis (e.g., lymphoma, medulloblastoma, pineal PNET, and GCT).
4. Targeted drug therapy can target specific cellular pathways connected with cell growth mechanisms (e.g., bevacizumab in acoustic neuroma in NF2; everolimus in TSC).

However, these roles for drug therapy are limited in their effectiveness by the difficulties of drug access imposed by the blood–brain barrier.

14.3.5.1 Special Considerations for Chemotherapy in CNS Tumors in AYA Patients

Drugs that penetrate the blood–brain barrier have the capacity to produce neurotoxicity as a dose-limiting side effect, which may compound other treatment-related neurotoxicities (e.g., methotrexate and RT). The use of chemotherapy, especially in high doses, in patients with CNS tumors carries additional hazards linked primarily to the infectious risks of ventriculo- or lumbar-peritoneal shunts and central venous lines and frequent episodes of fever, which cause difficulties in discriminating between shunt infections and febrile neutropenia. A recent publication analyzing tolerance of chemotherapy in patients with medulloblastoma showed that patients ages 10–20 years were more likely to suffer toxicity and require modifications in treatment than individuals 5–10 years of age [157]. The reasons for this observation are not clear. However, parameters for drug dosing (body weight versus surface area) during adolescence have not been the focus of research; the relative portion of red marrow and therefore resilience to cytotoxic side effects change considerably during adolescent growth; the brain is growing and maturing, and neural plasticity is reducing; psychologically the maturing adult psyche is changing, and tolerance of symptoms coupled with increasing empowerment changes consent and tolerability of toxic treatments. Together these data suggest that AYA patients would benefit from a modification of the aggressive chemotherapy regimens often utilized in children. Furthermore, great care needs to be applied where optimized doses of chemotherapy at limits of tolerance are combined with optimized doses of radiotherapy designed to limits of tolerance; serious irreversible neuro-toxicity can be encountered [158].

14.3.6 Symptom Control

The AYA patient with a brain tumor is frequently suffering from both acquired neurological disabilities and side effects of the various treatment modalities. Successful delivery of combined care requires close attention to all aspects of symptom control and integration of rehabilitation both at home and in the hospital. Symptoms of raised intracranial pressure are common at presentation and are treated with corticosteroids preoperatively. However, prolonged postoperative use of steroids leads inevitably to the development of Cushing's syndrome and worsening disability due to weight gain, proximal myopathy, personality disorder, metabolic disturbance, striae, acne, and facial and body disfigurement, not to mention the increasing nursing burden for the parents and care providers. If it is not possible to treat the cause of the raised intracranial pressure (e.g., ventricular shunting or ventriculostomy, surgical debulking of the tumor, RT, or chemotherapy), steroids should be used only in short courses of 3–5 days to assess effectiveness while minimizing the risks of severe side effects. Such an approach requires close cooperation by the clinical team, particularly since the transient neurological improvements that occur with short-term steroid use are sometimes grasped by patient, family, and doctor alike as a sign of a treatment effect, in otherwise very difficult circumstances [159, 160] (Fig. 14.15).

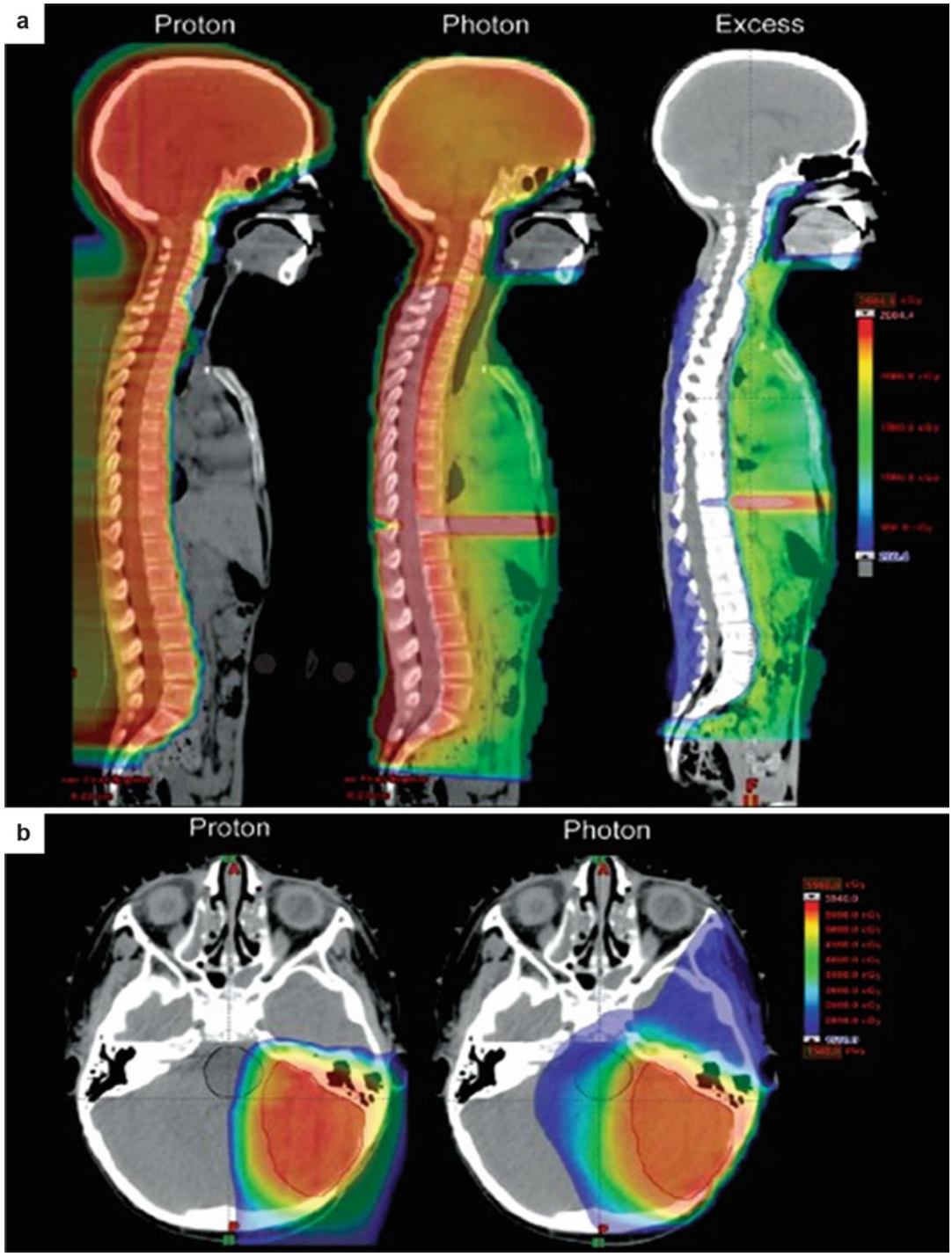


Fig. 14.15 Proton, photon, and net dosing comparisons. (**a**) Comparative craniospinal radiation dosing between proton dosimetry, photon dosimetry, and net dosing to non-brain tissue. (**b**) Comparison of proton and photon dosimetry for posterior fossa tumor

14.3.7 Integrated Care

Integrated care, as described, is a major undertaking. It requires great care in communication with adolescents to secure initial and ongoing consent to treatment, rehabilitation, and social and personal development. Furthermore, there are the inevitable risks of reactive depression; staff with special skills in liaison, counseling, and family support are essential. Access to rehabilitation resources, transportation, educational support, and communication with peers at home can, individually or collectively, make the difference between a young person completing the proposed treatment or rejecting it altogether.

14.3.8 Intracranial Germ Cell Tumors (GCTs): A Model Tumor of AYA Neuro-oncology Practice – Historical Perspectives [161]

We have elected to discuss the progress made in GCTs as a model AYA tumor because their incidence peaks in the age range; the literature reports improved outcomes from multidisciplinary management. In the previous edition of this book, this chapter had an extensive literature review as the basis for recommendations for care. This was based upon a wide variety of sources of evidence including institutional studies, registry reports, phase 2 trials, and some pilot phase 3 studies. There were different philosophies active globally driving strategies in this very rare tumor type, the higher population incidence in Asia fuelling very important reports of surgically led clinical experiences. This has led to a series of international workshops which have just recently, in 2015, published their first consensus [**Consensus Statements**] which has successfully summarized the state of knowledge at this time [161].

Historically, combined treatment approaches evolved from two reports. The earliest by Wara et al. [162] concluded that germinoma was radiocurable, but the metastatic recurrence risk was such that CSI was recommended. Another report, by Jennings et al. [163], reviewed the literature for 399 cases and concluded that anatomical staging was critical to identify high-risk patients with metastases and suggested that NGGCTs could benefit from additive chemotherapy. These two very early reports set the scene for two decades of evolution of clinical practice, resulting in current therapies. The Japanese studies from institutional sources explored a variety of approaches to classifying diagnoses both clinically and histologically; they explored the role of primary- and second-look surgery and primary and adjuvant radiotherapy and identified the serious late effects of the tumor and its treatment upon quality of life. European national and collaborative studies explored the role of radiotherapy alone, combined chemotherapy, and radiotherapy in GGCTs and NGGCTs, respectively, demonstrating that combined approaches in NGGCTS, in particular, were associated with significant improvements in survival. Clarification of diagnostic criteria has been complicated by the very limited biopsy material obtained from these deep-seated tumors and the diverse histological subtypes of NGGCTs featuring malignant and nonmalignant variants. The emergence of an early consensus on the value of classifying patients into marker positive (secreting) versus marker negative (nonsecreting) categories permitting a nonsurgical diagnostic approach in the secreting tumor types which has been shown to offer reduced risks of surgically acquired brain injury at the time of diagnosis.

14.3.8.1 Intracranial GCTs: Tumor Origins

Intracranial germ cell tumors (GCTs) are a heterogeneous group of tumors that arise from primordial germ [2]. They typically arise from midline structures, the pineal gland and suprasellar region being the most common locations. They only rarely arise from other locations (Table 14.5). They account for <20% of all GCTs; their histological appearance in the brain is identical to that seen in other anatomical sites. GGCT (germinoma) is the most common subtype and, according to SEER data, comprises two thirds of CNS GCTs in individuals 15–29 years of age [6]. GGCTs have a syncytiotrophoblastic subtype that secretes low levels of βHCG. Nongerminomatous germ cell tumors (NGGCTs)

Table 14.5 Anatomic location of CNS germ cell tumors in patients <45 years of age, United States SEER, 1975–1999

	Number	% of total	Male	Female
Pineal	113	54	107	6
Pituitary	21	10	11	10
Ventricle	11	5	9	2
Cerebrum	10	5	7	3
Brain overlapping	7	3	5	2
Brain stem	3	1	3	0
Cranial nerve	3	1	1	2
Olfactory nerve	1	0	1	0
Frontal lobe	1	0	0	1
Spinal cord	2	1	0	2
Brain NOS[a]	38	18	21	17
Total	210			

[a]Not otherwise specified

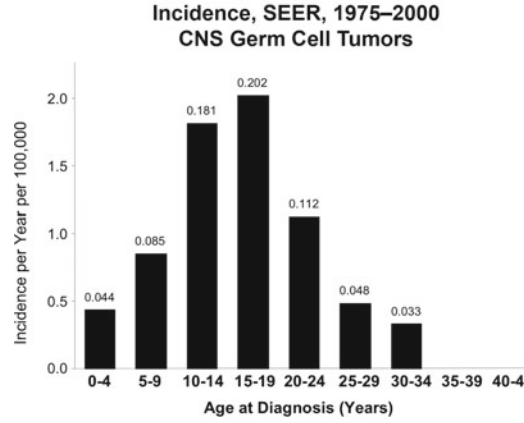


Fig. 14.16 Incidence of intracranial germ cell tumors, United States SEER18, by age [5]

account for one third of CNS GCTs in the 15–29-year age group [6]. The WHO classification includes embryonal carcinoma (EC), yolk sac tumor (YST), choriocarcinoma (CC), teratoma (immature, IT; mature, MT), and teratoma with malignant transformation (MalT) and mixed GCTs (MGCT). Frequently, NGGCTs secrete higher levels of αFP (YST and MGCT) or βHCG (CC and MGCT). This classification is complex, and improved terminology has been identified as a priority for international consensus [161] (**Consensus Statements 1**, **19 and 20**).

At the time of diagnosis, 5–10 % of GCTs, predominantly germinomatous germ cell tumors (GGCTs) occur as "bifocal" disease located in both the pineal region and the suprasellar region. It is assumed that bifocal disease represents simultaneous development of the tumor in two sites rather than due to local dissemination. GCTs do disseminate to leptomeninges, 19 % of germinoma patients showed dissemination at diagnosis in the International Society of Pediatric Oncology (SIOP) CNS GCT 96 trial [164].

14.3.8.2 Epidemiology of CNS GCTs

According to SEER data, intracranial GCTs are seen predominantly in infants and AYAs, with a peak incidence between 10 and 20 years of age (Fig. 14.16). The incidence of intracranial GCTs in AYAs is more than three times more frequent than in females (male/female ratio of 3.6:1); in infants the reverse is true, with females having a higher incidence (Fig. 14.16). SEER data for all subtypes of CNS GCTs at any age show a marked male predominance in the pineal location (male/female of up to 18:1) and no gender predilection for a pituitary location.

The rarity of these tumor types spanning the AYA age range justifies identifying specialist centers for their multidisciplinary management within health systems. The centers should seek to obtain, store, and share samples for biological research so as to contribute to international collaborations that are active. Their purpose is to refine treatment approaches directed at enhancing outcomes for both survival and quality of survival [161] (**Consensus Statements 2–5 and 32**).

Early reports identified that the timing and male preponderance of these tumors developed as a response to endogenous surges of sex hormone around puberty [165]. Intracranial GCTs are more common in Japan, where the incidence is five- to eightfold greater than that seen in the United States, the only predisposing condition being Down syndrome [166].

14.3.8.3 Clinical Diagnosis of CNS GCTs

The first challenge is their clinical presentation and the associated risk of delays in diagnosis.

The HeadSmart project identified that both the adolescent age range and midline supratentorial tumors including germ cell tumors were associated with the longest delays [137]. Endocrine presentations being a focus of interest, especially as their evolution clinically is gradual and endocrine functions are lost at time diagnosis of diagnosis, are generally considered to be irrecoverable. Panhypopituitarism represents a threat to long-term survival over and above the risk of tumor recurrence [166–171]. Recovery of vision however can occur if raised intracranial pressure is relieved and early drug treatment started to reduce tumor bulk and associated brain tissue invasion/compression.

14.3.8.4 Tumor Markers and Pathology of CNS GCTs

Experience over the past decades has now clarified the interrelationship between histology and tumor markers justifying a marker-driven diagnostic approach that is now accepted in clinical trials. Patients presenting with typical midline tumors in the third ventricle and/or pineal region should have tumor markers measured in blood and CSF as a matter of urgency. The lumbar CSF sample is preferred although ventricular CSF diversion offers an opportunity to obtain both CSF samples and endoscopic biopsy. If the markers are below the threshold, then a biopsy is necessary by whatever technique the surgeon considers safest and appropriate. If tumor markers show elevated AFP (EU 25 kU/L; Unites States 10 kU/L), βHCG (>50 IU/L) or raised placental alkaline phosphatase, then a secreting nongerminomatous germ cell tumor can be diagnosed and treatment started based upon this. Germinomas secrete αFP or βHCG in low quantities, while the majority of NGGCTs secrete these tumor markers in substantial amounts, embryonal carcinoma being the exception [172–174]. The thresholds for Europe and United States have been quoted, but they vary in other continents [161]. In many Japanese studies, more complex interpretations of diagnostic criteria are adopted by different groups. These biochemical markers are also particularly valuable for monitoring disease response [161, 175, 176] (**Consensus Statements 7–12**).

14.3.8.5 Surgical Management of Intracranial GCTs

Surgery is directed at controlling intracranial pressure, obtaining tissue for diagnosis, and debulking tumors where the benefits are justified.

14.3.8.6 Management of Raised Intracranial Pressure

Intracranial GCTs frequently present with obstructive hydrocephalus necessitating urgent CSF diversion which may be necessary before a biochemical diagnosis can be made [161] (**Consensus Statement 13**). If at all possible, CSF samples for βHCG and α-fetoprotein should be taken at this time [161] (**Consensus Statement 14**). Endoscopic third ventriculostomy where possible is the preferred surgical intervention for obstructive hydrocephalus [161] (**Consensus Statement 15**); an initial placement of an external ventricular drain is favored over a permanent ventricular shunt [161] (**Consensus Statement 16**).

14.3.8.7 Obtaining Samples for Diagnosis

If tumor markers do not exceed threshold for secreting tumor classification, then surgical biopsy is required regardless of imaging features [161] (**Consensus Statement 17**). Where tumor marker thresholds are exceeded, then tumor biopsy is not required, and a diagnosis of NGGCT can be made [161] (**Consensus Statement 18**).

14.3.8.8 Debulking Tumor Surgery

Where mature or immature teratoma without malignant transformation is diagnosed and complete surgical resection is feasible, then complete surgical resection is recommended [161] (**Consensus Statement 21**). For malignant NGGCTs with residual disease after nonsurgical therapy, complete surgical resection should be undertaken before completion of therapy [161] (**Consensus Statement 27**).

14.3.8.9 Nonsurgical Therapy GGCT

Based upon current knowledge, patients with GGCT should receive radiotherapy to maximize their chances of cure. For localized GGCT, focal radiotherapy alone is insufficient, and therefore,

radiotherapy should at least include the cerebral ventricles (whole ventricular radiotherapy) [161] (**Consensus Statements 22 and 23**). Chemotherapy is an effective strategy to reduce the dose of radiotherapy for localized GGCT [161] (**Consensus Statement 24**).

14.3.8.10 Nonsurgical Therapy NGGCT

All patients with malignant NGGCT should receive a combination of chemotherapy and radiotherapy to maximize their chance of cure [161] (**Consensus Statement 25**). For patients with metastatic NGGCTs, craniospinal radiotherapy should be included in the treatment plan [161] (**Consensus Statement 26**).

14.3.8.11 Clinical Follow-Up

Tumor markers should be used for clinical follow-up of all intracranial GCTs and should be used whether they were positive at diagnosis or not [161] (**Consensus Statement 28**).

14.3.8.12 Management at Relapse

All patients with symptomatic radiological or marker-detected relapse should be fully restaged and assessed before considering management options [161] (**Consensus Statement 29**). GGCTs are salvageable with further treatments which are under examination [161] (**Consensus Statement 30**). Relapsed malignant NGGCTs can be treated with curative intent, where appropriate, using high-dose chemotherapy with hematopoietic stem cell rescue, combined with surgery and additional radiotherapy where feasible [161] (**Consensus Statement 31**).

14.3.8.13 Late Effects

More information is needed to better understand the interrelationship between tumor and treatment effects of the late effects for this tumor group at this age. Future research should include studies of quality of life; GGCTs are salvageable with further treatments which are under examination and development [161] (**Consensus Statement 33**). Monitoring the consequences of the tumor itself, associated with hydrocephalus, surgery, chemotherapy, and radiotherapy, is an essential component of long-term follow-up for these patients; GGCTs are salvageable with further treatments which are under examination and development [161] (**Consensus Statement 34**).

14.3.8.14 Molecular Studies

Molecular studies are yet to be translated into clinical practice [177]. Paradoxically, however, the intracranial GCT group with inferior outcomes, namely, NGGCTs, are the exact cohort of patients that the US and European trial groups are advocating avoiding up-front surgical approach when serum or CSF markers are negative, and hence there are few bio-specimens available for molecular studies. Furthermore, where neurosurgical biopsy is undertaken, specimens are often small with limited material leftover for research after diagnostic studies have been completed. In contrast, the Japanese approach, where up-front surgery is regularly performed, has allowed the creation of two large consortia for bio-specimen collection, led by Koichi Ichimura (Tokyo, Japan) and Ching Lau (Houston, United States) [178]. Furthermore, banking of tumors and associated samples was recently strongly recommended as part of a consensus process in order to support molecular studies of intracranial GCTs [161]. Associated bio-specimens, such as serum/plasma, CSF, and constitutional DNA, are also important, as this material may contain an accurate readout for molecular changes in the tumors themselves, which may assist future noninvasive diagnosis and risk stratification [161]. Recent advances include descriptions of whole-exome sequencing (WES) studies [178, 179] which have identified somatic mutations in KIT and RAS, which were mutually exclusive. Novel germ-line mutations have also been described [180] that may illuminate potential genetic predispositions to this disease. Further work will be required to identify recurrent mutations that are associated with treatment response and outcomes. With regard noninvasive diagnosis, specific short nonprotein-coding RNAs, termed microRNAs, are known to be dysregulated in all malignant GCTs [181], and the same microRNAs have been shown to be elevated at diagnosis in serum [182, 183] and CSF [184] from patients with extracra-

nial and intracranial malignant GCTs, respectively. They may offer future utility for noninvasive diagnosis and risk stratification in this disease.

14.4 Late Effects

14.4.1 Endocrine

Tumors in the common GCT regions frequently damage the hypothalamic–pituitary axis, necessitating hormone replacement therapy before initial diagnostic surgery, where indicated, or during immediate antitumor management. It is unusual for these endocrine deficits to improve after completion of treatment; indeed surgery and RT may make them worse.

14.4.2 Neurological

Focal neurological deficits affecting ophthalmic function at presentation frequently regress with initial steroids and commencement of antitumor treatment. Surgical resection may not improve these symptoms, thus justifying consideration of neoadjuvant chemotherapy or RT. CSI may also be associated with cataracts, even at low dose. Moreover, the combination of cisplatin and CSI can also lead to hearing loss.

14.4.3 Cognitive/Health State

Assessment of these measures is becoming increasingly easy now that a battery of generic and specific questionnaire methodologies have been developed for use in children and young people [185, 186]. Adult oncology has already developed this type of measure for evaluating outcomes in order to assist with a selection of preferred palliative drug strategies. Their use in children and AYA populations is lagging. Where attempts have been made to measure cognitive and health-state outcomes in survivors of GCTs in recent eras, the burden of morbidity has been low; indeed they have compared favorably to normal populations in some cases. This lack of recent evidence of true adverse cognitive outcomes, coupled with the possibility that combined chemotherapy and RT may have a deleterious impact on health state compared to RT alone, further justifies trials of combined treatments aimed at measuring QoL as primary outcome measures.

14.4.4 Quality of Life Reports

QoL for survivors is of great importance for this group of patients with increasingly curable tumors. Factors determining adverse QoL outcomes are becoming better understood. Tumor growth and infiltration of brain tissue, particularly in the neurohypophyseal region, cause local neurological damage and may lead to permanent endocrine, visual, and behavioral consequences. Certainly, primary surgery was seen to aggravate these symptoms as well as threaten further neurological damage and life itself in the early era of this literature review. RT has been widely implicated in causing long-term neurocognitive damage based upon experience in medulloblastoma and leukemia [187]. Chemotherapy, on the other hand, has developed a reputation for minimal neurotoxicity compared to these other modalities. However, a preliminary report reports results of health-state and behavior measurements in survivors of the SIOP PNET3 study at a median of 7 years after completion of treatment that indicate a lower health-state scores for those who received combined chemotherapy and CSI as compared to those treated with CSI alone [187]. The most common long-term complications after diagnosis and treatment of GCTs were endocrine disturbances, especially in patients with suprasellar tumors. Interestingly, most of these endocrinopathies were present at the time of diagnosis or following surgery, although radiation could be implicated in a subset of patients [188–191]. Other common long-term sequelae include neurocognitive defects, which in most cases were mild [188, 190–193], ophthalmologic abnormalities, with Parinaud's syndrome seen in pineal region tumors and

visual impairment seen in suprasellar tumors, hearing loss, and radiation-induced second tumors. Future trials for GCTs should aim at improving survival while minimizing long-term sequelae of therapy.

14.5 Survival Rates for Other CNS Tumors: United States SEER and European Data

There are many reports of survival from CNS tumors in clinical series that include AYAs, but population-based results are relatively scarce. International comparisons are complicated by the diversity of age groups and calendar periods, but survival was probably somewhat higher in the United States than in the UK and Southern and Central Europe. The especially high survival in the Nordic countries may be an artifact resulting from inclusion of a higher proportion of nonmalignant tumors. Survival in Eastern Europe was somewhat lower than elsewhere. No population-based survival data from developing countries are available for this age group. Five-year survival of children and young adults aged 0–34 years ranged from 9 to 44% in two Chinese and two Thai cancer registries during the 1980s and 1990s [194], indicating substantially lower survival among AYAs than in developed countries. Survival rates from well-equipped treatment centers in developing countries, however, are comparable with those achieved in developed countries [195, 196].

Figure 14.17 shows the 5-year relative survival rate of the major CNS tumors in the United States as a function of age at diagnosis during 2000–2010. AYAs had a better survival than either younger or older patients for several CNS cancers: glioblastoma and anaplastic astrocytoma, ependymoma, medulloblastoma/PNET, and sellar region tumors. Low-grade astrocytoma, primary CNS lymphoma, and meningioma had a progressively worse survival rate with increasing age. The survival rate for germ cell tumors was relatively independent of age over the pediatric to middle-aged adults that it occurred.

Figure 14.18 depicts the change in 5-year brain-tumor-specific survival since 1976 in AYAs and younger and older patients. In AYAs, brain stem tumors have shown little improvement in

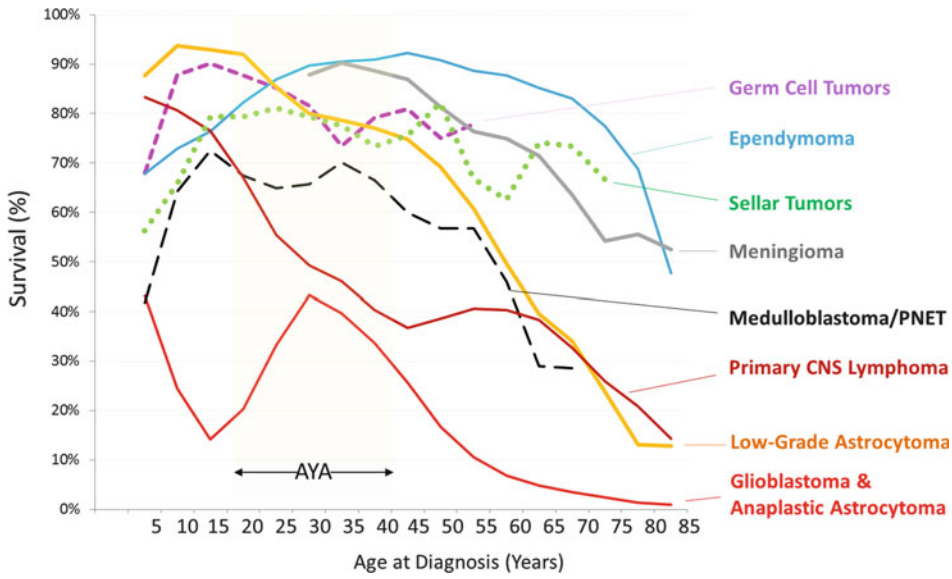


Fig. 14.17 A 5-year relative survival of patients with invasive CNS tumors, 2000–2010, United States SEER18, by anatomical region and age [197]. The curves are two 5-year moving averages. Ages with <10 patients are not shown

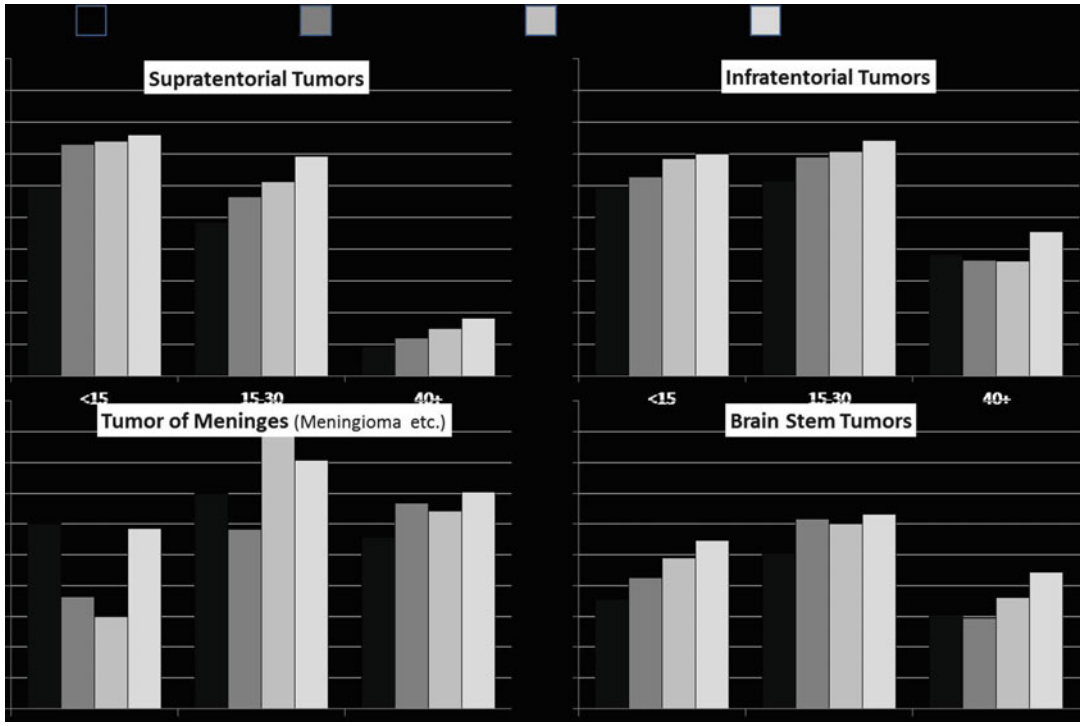


Fig. 14.18 A 5-year tumor-specific survival of patients with invasive CNS tumors, by 9-calendar-year intervals, 1976–2011, United States SEER9 by anatomical region and age [197]

the 5-year relative survival and in comparison with younger and older patients with brain stem tumors.

14.6 Research Priorities

A recent UK consensus process involving public partnership managed by the James Lind Alliance identified the top 10 priorities for research which are applicable to any age:

1. Do lifestyle factors (e.g., sleep, stress, diet) influence tumor growth in people with a brain or spinal cord tumor?
2. What is the effect on prognosis of interval scanning to detect tumor recurrence, compared with scanning on symptomatic recurrence, in people with a brain tumor?
3. Does earlier diagnosis improve outcomes, compared to standard diagnosis times, in people with a brain or spinal cord tumor?
4. In second recurrence glioblastoma, what is the effect of further treatment on survival and quality of life, compared with best supportive care?
5. Does earlier referral to specialist palliative care services at diagnosis improve quality of life and survival in people with a brain or spinal cord tumor?
6. Do molecular subtyping techniques improve treatment selection, prediction, and prognostication in people with a brain or spinal cord tumor?
7. What are the long-term effects (physical and cognitive) of surgery and/or radiotherapy when treating people with a brain or spinal cord tumor?
8. What is the effect of interventions to help carers cope with changes that occur in people with a brain or spinal cord tumor, compared with standard care?
9. What is the effect of additional strategies for managing fatigue, compared with standard

care, in people with a brain or spinal cord tumor?
10. What is the effect of extent of resection on survival in people with a suspected glioma of the brain or spinal cord?

The partnership between patient's caregivers, clinicians, and researchers developed this consensus and ranking of the priorities for research highlighting the comprehensive challenge of seeking to improve outcomes for patients with brain tumor [198].

Conclusions

This chapter has focused on neuro-oncology as it applies to AYAs by identifying clinical problems, relevant clinical and scientific data and how they apply to the emerging subspecialty of neuro-oncology. Central to this theme is the need to assist the young adult patient as he or she moves through the health system, coping with the shock of diagnosis and its implications for the future. In this, it is important that the teams caring for them acknowledge the individualized pathway through adolescence which is driven by the brain's state of development. The historical lack of progress in outcomes for this age group challenges the AYA neuro-oncology teams and trial networks to prioritize inclusion of young adults in relevant trials, seeking improvements in individualized patient care. The progress reported in intracranial germ cell tumor with the new global consensus on the management of intracranial germ cell tumors will accelerate new trials to investigate new approaches compared against this established standard. The overall priority is to develop clinical teams with comprehensive understanding of the AYA patient with brain tumor so that they can offer care that is increasingly focused upon their specialized needs and based upon the most recent evidence. Improvements in survival and its quality are parallel priorities for this group of patients and their families and friends.

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Soft Tissue Sarcoma

15

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Abstract

Soft tissue sarcomas represent a very heterogeneous group of mesenchymal malignant tumors that may occur at any age. Some histotypes are typically of a given age and rare in others, but as a whole group, soft tissue sarcomas are tumors bridging the pediatric and adult settings: adolescents and young adults are therefore age groups in which the soft tissue sarcoma family represents a subgroup of relatively frequent tumors. Managing these malignancies in patients in this age bracket poses various clinical problems, partly because different therapeutic approaches have been sometimes adopted by pediatric and adult oncologists, even though they were dealing with the same condition. In addition, whether the biology and clinical behavior of a given histotype is the same in patients of different ages remains to be seen. The treatment of adolescent and young adult patients with soft tissue sarcomas is particularly complex and necessarily w and requires adequate expertise. Cooperation between pediatric oncologists and adult oncologists is of critical importance to improve the quality of the treatment as well as the research programs dedicated to young patients with these diseases.

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15.1 Introduction

Soft tissue sarcomas (STS) are a very heterogeneous group of over 50 subtypes of nonepithelial extraskeletal malignancies that are classified on a histogenic basis according to the mature tissue they most resemble. Given the diversity of subtypes, further subdivided by grades, there is quite a spectrum of markedly different biologies, demographics, and clinical behaviors. Some subtypes are low-grade sarcomas that remain localized and slow growing and have virtually no cause-specific mortality. However, high-grade STS display local aggressiveness, propensity to metastasize and lethality. STS can arise, generally as a painless, enlarging soft tissue mass, anywhere in the body; three-quarters occur in the soft tissue of the extremities, 10 % each in the trunk wall and retroperitoneum, less commonly in the head and neck region and occasionally intraparenchymally. In addition to their high mortality rate, they cause a relatively high burden of morbidity, due to deforming surgery, chemotherapy- and radiation-induced complications, and secondary cancers [1].

STS occur at any age, but a shift occurs in adolescence/early adulthood from the predominant rhabdomyosarcoma of childhood to a mixture of several "adult-type" STS. The term "non-rhabdomyosarcoma soft tissue sarcomas (NRSTS)" is a term favored by pediatric oncologists, though of course >97 % of sarcomas treated by other oncologists are "NRSTS." Certain subtypes are particularly typical of adolescents and young adults [2–4, 93], and sarcoma is in many regards a quintessential adolescent and young adult (AYA) cancer. Although only 6 % of all cancer is diagnosed between the ages of 15 and 40, 18 % of all STS is diagnosed in the AYA age range. The orthopedic surgeons and radiation oncologists who are often involved in multidisciplinary sarcoma care treat both children and adults, and the field of STS oncology is not "owned" by either pediatric or medical oncology.

15.2 Classification and Pathology

The histologic classification of STS is based on their morphologic resemblance to one of the constituent mesenchymal tissues in the different developmental stages, and there are almost 100 subtypes of STS. Historical clinical trials have "lumped" all STS together. Recently, more advanced immunohistochemical techniques, cytogenetics (both traditional and targeted hybridization techniques), and even microarray techniques are increasing the precision of the diagnosis. Hopefully, this will allow better prognostication and development of risk-based and targeted therapeutics. Genomic and expression profiling studies suggest that sarcomas can be divided into four major genetic groups: (a) sarcomas with specific translocation [5] (Table 15.1), (b) sarcomas with specific activating or inactivating mutations, (c) sarcomas with 12q13-15 amplification, and (d) sarcomas with a complex genomic profile [6, 7]. Most of sarcomas typical of childhood fall in the first group, whereas more than 50 % of the adult-type sarcomas are encompassed in the last category.

Table 15.1 Translocation and fusion genes in soft tissue sarcomas

Ewing sarcoma	t(11;22)(q24;q12)	EWS-FLI1
	t(21;22)(q22;q12)	EWS-ERG
		EWS-AFT1
Clear-cell sarcoma	t(12;22)(q13;q12)	EWS-WT1
Desmoplastic small round cell tumor	t(11;22)(q13;q12)	EWS-CHN
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	TAF2N-CHN
		TLS-CHOP
	t(9;17)(q22;q11)	TLS-ATF1
		PAX3-FKHR
Myxoid liposarcoma	t(12;16)(q13;p13)	PAX7-FKHR
Angiomatoid fibrous histiocytoma	t(12;16)(q13;p11)	SYT-SSX1,2
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	
	t(1;13)(p36;q14)	COL1A1-PDGFB
		ETV6-NTKR3

STS have been notoriously difficult to account for accurately in cancer registries. Traditionally registry classification schemes are categorized by organ site, as adult tumors are predominantly epithelial malignancies of each organ. Soft tissue sarcomas then are only counted when they occurred in a connective tissue (vessel, nerve, muscle, fibrous tissue). This likely underestimates the number of STS, which can occur within or in close proximity to an organ. Alternatively, the International Childhood Cancer Classification pediatric classification scheme, which is used for the AYA site recode in the Surveillance, Epidemiology, and End Results (SEER) registry, recognizes and divides STS by histology but reflects the predominance of rhabdomyosarcoma (RMS) in children by only having three other subgroups: fibromatous (fibrosarcoma, peripheral nerve, and other fibrous), Kaposi sarcoma, and other STS (specified and unspecified).

In 2013, the World Health Organization (WHO) classification of STS was rewritten for the first time in 11 years [8]. The new inclusion of malignant peripheral nerve sheath tumor (MPNST), dermatofibrosarcoma protuberans (DFSP), and gastrointestinal stromal tumor (GIST) in STS classification rather than nervous system, skin and gastro-intestinal tract classification respectively, is particularly important in the AYA age range where these tumor types are quite common. Table 15.2 outlines the incidence and classification of the most common AYA soft tissue sarcomas by WHO classification and AYA site recode. Note that neither the SEER nor the WHO classification includes phyllodes tumor of the breast, mesothelioma, or any of the non-leiomyosarcoma STS of the uterus (endometrial stromal tumor, mixed Mullerian tumor, etc.), and they are not included in the figures or discussion. The natural history and treatment of extraosseous Ewing sarcoma, osteosarcoma, and chondrosarcoma are comparable to their more common presentation in the bone and are discussed in Chap. 12. Lastly, Kaposi sarcoma is included in SEER and WHO classifications but is a distinct STS in epidemiology, etiology, treatment, and outcome and dramatically skews calculations and conclusions and, unless otherwise noted in the text or figures, is not included in reference to "soft tissue sarcoma (STS)."

STS may be classified also according to their grade of malignancy. Tumor grade is determined by a combined assessment of histological features: degree of cellularity, cellular pleomorphism or anaplasia, mitotic activity, and degree of necrosis. Different histotypes with the same grade of malignancy could display the same clinical behavior. In general, low-grade tumors may have local aggressiveness but a low tendency to metastatic spread. High-grade tumors have a more invasive behavior with a high propensity to metastasize (in particular to the lung). Some histotypes (i.e., rhabdomyosarcoma, but also synovial sarcoma, alveolar soft-part sarcoma, and angiosarcoma) are usually considered as being high grade independently from their mitotic index, necrosis, and cellularity.

Different grading systems (generally three-grade systems) have been defined over the years by pediatric and adult oncologists for predicting clinical course and prognosis and defining a risk-adapted treatment. The most frequently used grading systems for adult sarcomas are the National Cancer Institute (NCI) system and the French Federation of Cancer Centers (FNCLCC) system [9]. The Pediatric Oncology Group system is similar to the NCI system but accounts for tumors found exclusively in childhood [10].

15.3 Epidemiology

Overall, STS are rare: with an annual incidence of around 5/100,000 persons of all ages, they account for <1 % of all cancer in the United States. Like many cancers, STS incidence increases exponentially with age. Rates in the AYA age range start at 1.4/100,000 for 15–19-year-olds and rise gradually to 3.4/100,000 in 35–39-year-olds. A total of approximately 2,900 STS are diagnosed in AYAs each year in the United States.

In contrast to this rising incidence with increasing age, STS become a less common

Table 15.2 Subtypes of soft tissue sarcoma

Subtype	ICD-O-3	ICCC and AYA subgroup	WHO subgroup	Rate in AYAs (per million)	Percent of total STS in AYAS
Kaposi sarcoma	9140	Other, Kaposi	Vascular	5.6	19.8
Dermatofibrosarcoma protuberans	8832–3	Fibromatous	Fibroblastic	5.0	17.7
Liposarcoma	8850–5, 8857–8, 8860	Other, specified	Adipocytic	2.3	8.1
Sarcoma NOS/undifferentiated/ spindle cell/giant cell/small cell (non-bone site)	8800–3, 8805	Other, unspecified	Tumor of uncertain differentiation	2.3	8.1
Leiomyosarcoma	8890–1, 8893–6	Other, specified	Smooth muscle	2.3	8.0
Synovial sarcoma	9040–3	Other, specified	Tumor of uncertain differentiation	2.1	7.2
Rhabdomyosarcoma (RMS)	8900–2, 8910, 8912, 8920	RMS	Skeletal muscle	1.5	5.1
Malignant peripheral nerve sheath tumor (non-CNS site)	9540, 9560–1, 9571	Other, specified	Nerve sheath	1.3	4.7
Gastrointestinal stromal tumor	8936	–	GIST	1.1	3.8
Fibromatous/fibroblastic	8811, 8821–24	Fibromatous	Fibroblastic	1.1	3.8
	8825	Other, specified			
Fibrohistiocytic	8830, 8835, 9252	Fibromatous	Fibrohistiocytic	1.0	3.5
	9251	Other, specified	Fibrohistiocytic		
	8836	Fibromatous	Tumor of uncertain differentiation		
Hemangiosarcoma/vascular STS	9120, 9125, 9130, 9133, 9170	Other, specified	Vascular	0.8	2.9
Epithelioid	8804	Other, specified	Tumor of uncertain differentiation	0.5	1.8
Other:	8991	RMS	Tumor of uncertain differentiation	0.5	1.8
Embryonal sarcoma	8840	Other, specified			
Myxosarcoma	8842				
Ossifying fibromyxoid tumor	8982				
Malignant myoepithelioma	8990				
Malignant mesenchymoma	9044				
Clear-cell sarcoma, not of kidney	9580				
Malignant Granular cell tumor					
DSRCT	8806	Other, unspecified	Tumor of uncertain differentiation	0.5	1.6
Solitary fibrous tumor/ hemangiopericytoma	8815	Fibromatous	Fibroblastic	0.3	1.0
	9150	Other, specified			
Alveolar soft-part sarcoma	9581	Other, specified	Tumor of uncertain differentiation	0.3	1.0
Total				28.5	100 %

proportion of all cancers (Fig. 15.1). Whereas in children under 15, STS account for nearly 7 % of cancer, this percent drops to 5 % of cancer in the third decade and 3 % in the fourth decade. Across the AYA age spectrum, histotypes of STS change as well (Fig. 15.2). SEER data from the period 2000–2011 shows DFSP to be the most common non-Kaposi STS among 15- to 39-year-olds, followed by liposarcoma, sarcoma not-otherwise specified (NOS), leiomyosarcoma, fibromatous sarcoma, synovial sarcoma (SS), RMS, and MPNST.

Between 2000 and 2011, the incidence of STS was nearly the same between females and males. However there are marked differences in incidence by race: for all categories (RMS, fibromatous, and other STS), AYA blacks have the highest rate, followed by non-Hispanic whites, then Hispanics, Asians, and American Indians/Natives (Fig. 15.3). The incidence of STS in AYAs has not changed dramatically in the last 36 years; the one particular rise in incidence is the rising rate in AYA males of "other STS" (non-fibromatous and non-RMS), which has increased from 1.0/100,000 to 1.5/100,000 (Fig. 15.4).

The epidemiology of Kaposi sarcoma bears particular note: it is still the most common STS in AYAs, although its incidence has dropped to nearly the incidence of the pre-AIDS epidemic of the 1990s. It is almost exclusively seen in males, and the rate in black AYAs is three times that in non-blacks (Fig. 15.3).

Concerning survival, in the SEER 2000–2011 registry, the 5-year overall survival (OS) rate for STS in AYAs averages 73 % with substantial differences according to the histology, the grade of malignancy, and the stage of the disease [3]. Compared to other ages, AYAs with RMS have worse survival than younger patients, and AYAs with Kaposi sarcoma have worse survival than older patients. A fascinating trend is seen in examining STS survival by sex. Specifically between the ages of 10 and 45, the overall 5-year survival is worse in males than females; in both younger and older ages, males have better survival (Fig. 15.5). Notably, for AYAs with STS, especially those with "other STS," there has been no improvement in survival for the last 25 years. For AYAs age 15–39, 5-year cause-specific survival rates for STS in 2003–2010 were 76.2 %, little better than 75.0 % in 1976–1984, whereas survival for those <15 has improved from 71.7 to 76.6 % and for those over 40 has increased from 51.9 to 62.0 % (Fig. 15.6).

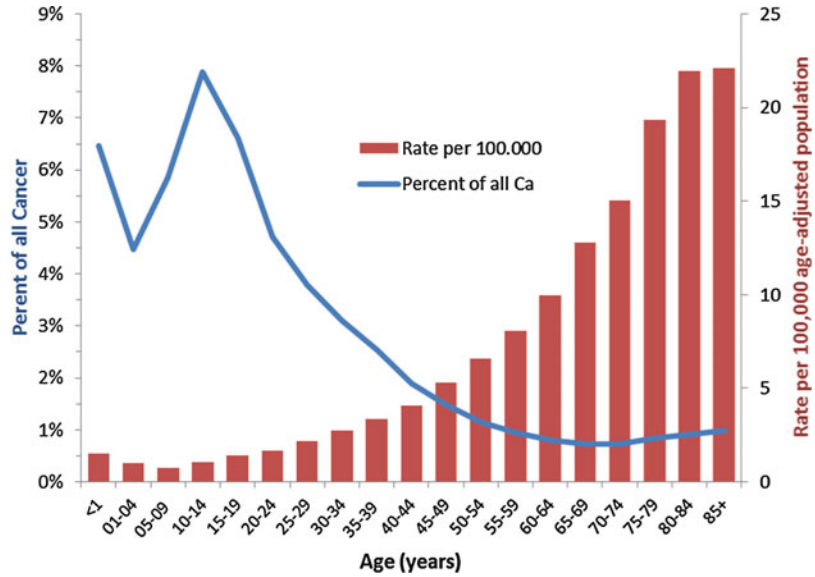


Fig. 15.1 Incidence of soft tissue sarcoma as a percent of all cancer (*left axis*) and rate per 100,000 and age-adjusted to the 2000 US standard population (*right axis*), by age, SEER 18, 2000–201

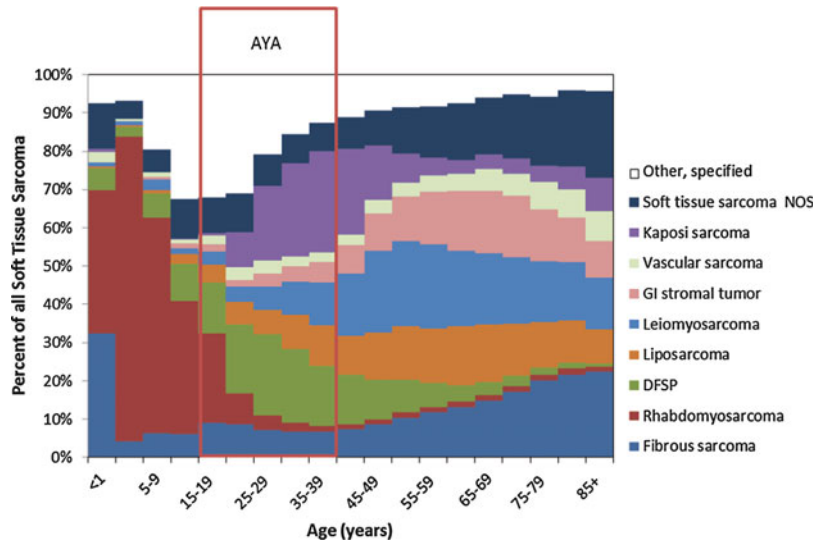


Fig. 15.2 Distribution of soft tissue sarcoma subtypes within 5-year age intervals from birth to age 85+, SEER 18, 2000–2011. *NOS* not otherwise specified, *GI* gastrointestinal, *DFSP* dermatofibrosarcoma protuberans

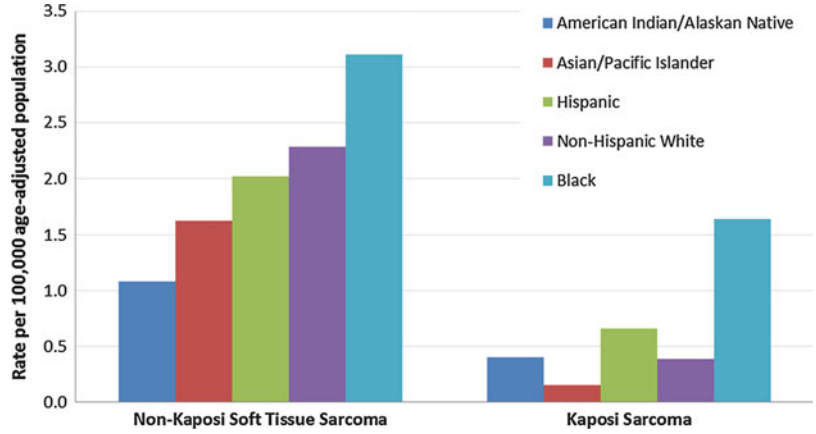


Fig. 15.3 Incidence of non-Kaposi soft tissue sarcoma (*left*) and Kaposi sarcoma (*right*) in AYAs age 15–39 according to race/ethnicity, SEER 18, 2000–2011

15.4 Etiology

For most STS subtypes, the pathogenesis remains unknown and there are few well-established risk factors [11]. Ionizing radiation clearly causes sarcomas, and chemical carcinogens (herbicides, polyvinyl chloride, and arsenic) have been associated with the development of some type of sarcomas, but the etiological relationship remains unclear. HHV8 is known to be the causative agent for Kaposi sarcoma. Although they cumulatively cause few of all STS, several genetic predispositions are well described. Neurofibromatosis type 1 increases the lifetime risk of MPNST to approximately 10 % and appears to increase the rate of RMS as well [12, 13, 97]. STS is one of the defining tumors of Li-Fraumeni syndrome, and survivors of hereditary retinoblastoma have a cumulative risk of developing a postradiation STS of 13.1 % [14]. Finally, there are several described germline mutations associated with GIST predisposition (particularly Carney-Stratakis syndrome) [15]. Those with genetic conditions are predisposed to develop tumors at a

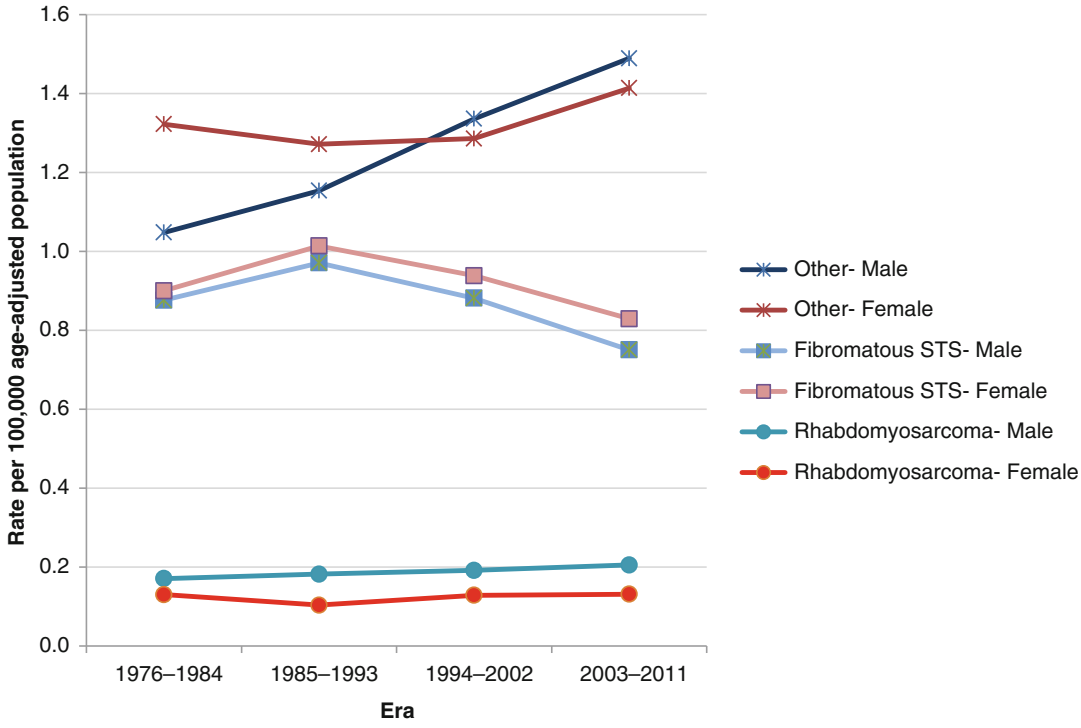


Fig. 15.4 Change in the incidence rate of soft tissue sarcoma in AYAs age 15–39, by sex and subtype, as a function of era of diagnosis, SEER 18, 1976–2011. Fibromatous STS = International Childhood Cancer Classification of fibromatous soft tissue sarcoma (STS) including dermatofibrosarcoma protuberans, solitary fibrous tumor, fibromatous, fibroblastic, and fibrohistiocytic sarcomas. Others= all non-Kaposi, non-fibromatous, and non-rhabdomyosarcoma STS

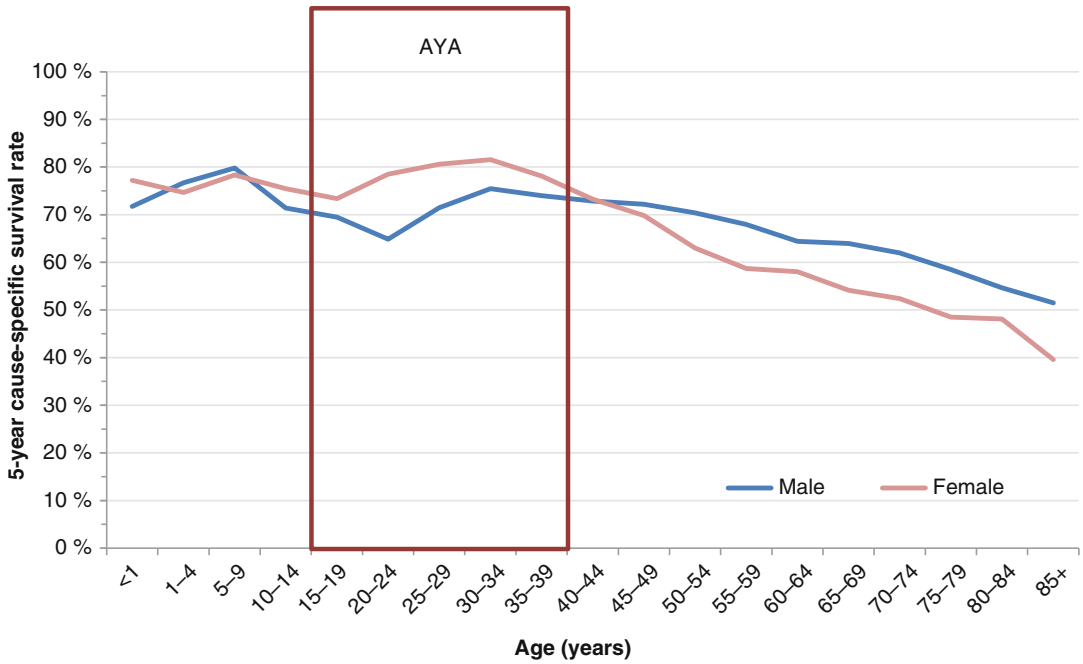


Fig. 15.5 A 5-year cause-specific survival of soft tissue sarcoma by sex, as a function of age, SEER 18, 2000–2011

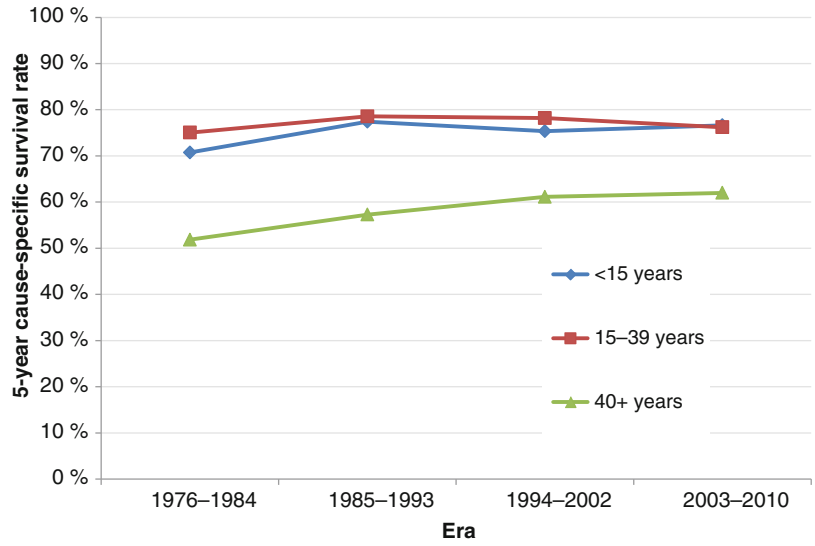


Fig. 15.6 Change in 5-year cause-specific survival rates of soft tissue sarcoma for those aged <15, 15–39, and 40+ at diagnosis, as a function of era, SEER 18, 1976–2010

younger age, so that the proportion of adolescents and young adults with STS with a genetic predisposition is probably higher than in older adults [16].

15.5 Diagnosis

15.5.1 Clinical Presentation

The initial signs and symptoms in patients with STS may vary and depend on the site of origin and tumor extension, as well as on the different degree of malignancy along histotype and tumor grade. An enlarging painless mass is the most common presentation. In 15- to 29-year-olds, about one-third of STS originate in the extremities. For example, for SS, the clinical presentation is often a slow-growing mass in the soft tissues of the lower extremity, especially around the knee. However, STS can arise anywhere in the body. RMS may occur also in sites in which striated muscle tissue is normally absent: the head and neck region represents the most common location for RMS, and the symptoms vary from proptosis, cranial nerve palsy, or nasal obstruction; hematuria may be present in RMS of the genitourinary tract; ascites and intestinal obstruction can occur with retroperitoneal tumors.

For low-grade STS, growth rate may be indolent, and sometimes the diagnosis is done after removing a small swelling that has existed for several years. The clinical presentation is very different among the different entities included in this group of tumor: e.g., MPNST are generally axial (trunk, head-neck region) and aggressiveness disease; epithelioid sarcomas present typical features such as peculiar superficial distal location like hand and fingers, indolent growth, and tendency for lymph node involvement; desmoplastic small round cell tumors (DSRCT) usually present as rapidly growing and large abdominal masses, generally disseminated at the time of diagnosis, with peritoneal seeding.

15.5.2 Diagnostic Procedures

In the case of suspected lesions, three diagnostic levels need to be evaluated: (a) the histological diagnosis, (b) the definition of locoregional extension, and (c) the staging of the disease to detect regional or distant metastases.

Pathological assessment is necessary to define the histological diagnosis. The initial biopsy has the aim to define the diagnosis but also should provide enough material for immunochemistry, cytogenetics, biological studies, and central pathology review for patients to be included in multicentric clinical trials. In the case of a large and deep soft tissue mass, biopsy should be always the initial surgical procedure, in order to avoid inadequate surgery. Open biopsy (incisional biopsy) or core needle biopsy (Tru-Cut, guided by ultrasound or computed tomography [CT] scan) is preferred to fine-needle aspirates that could establish the presence of malignancy but rarely identify the subtype or provide the tissue required for additional studies. In any case, the initial biopsy should be carefully planned by an experienced surgeon, taking into account the possible subsequent definitive surgery that must include the scar and the biopsy tract. For example, in STS of the extremities, the incision must be longitudinal to the limb and not traverse multiple compartments; very careful hemostasis must be ensured to minimize the risk of postsurgical hematoma and need for drains.

Local extent of disease is determined by CT scan or magnetic resonance imaging (MRI), the latter appearing to be superior in defining soft tissue extension.

The diagnostic workup is completed by staging investigations, aimed to detect regional and distant metastases. Since distant metastases mainly occur to the lung, chest CT scan is the most important exam. Abdominal ultrasound or CT scan may be used to identify abdominal metastases, while technetium bone scan can be required to detect bone metastases (for patients with aggressive and high-grade STS) [17, 64, 72]. Positron emission tomography is increasingly used, though its role remains not well defined in STS [18].

15.5.3 Staging

An adequate stratification of the patients is necessary for a risk-adapted therapy. However, as in grading, pediatric and medical oncologists have not used the same systems, making comparison of risk and prognosis difficult. The pediatric Intergroup Rhabdomyosarcoma Study (IRS) postsurgical grouping system [19] supplements the pretreatment clinical tumor-node-metastases (TNM) classification [20], categorizing patients into four groups based on the amount and extent of residual tumor after the initial surgical procedure. Group I includes completely excised tumors with negative microscopic margins (also called R0 resection); group II indicates grossly resected tumors with microscopic residual disease (R1 resection) and/or regional lymph nodal spread; group III includes patients with gross residual disease after incomplete resection (R2 resection) or biopsy sampling; group IV encompasses patients with metastases at onset [19]. According to the TNM classification, T1 are those tumors confined to the organ or tissue of origin, while T2 lesions invade contiguous structures; T1 and T2 are further classified as A or B depending on whether tumor diameter is $\leq$ or >5 cm, respectively. Regional node involvement is defined as N0 or N1 and the status of distant metastases at onset as M0 or M1 [20].

However, adult oncology groups have generally utilized other systems: the Musculoskeletal Tumor Society Staging System requires the accurate definition of compartmentalization and the American Joint Committee on Cancer Staging System combines TNM definitions and histological grading [21].

15.6 Treatment Management and Outcome

The treatment of patients with STS is complex and necessarily multidisciplinary, requiring evaluation and management by a team with adequate expertise and experience and the ability to enroll on clinical trials (NCCN guidelines 1.2015). Treating patients outside of a referral center has been identified as an independent risk factor for nonadherence to treatment guidelines [22] which

has in turn been seen to increase treatment cost, risk of recurrence, and mortality in STS [23].

15.6.1 Surgical Aspects

The approach to surgical resection of soft tissue sarcoma (STS) is focused on achieving an adequate resection margin. The goal of the orthopedic or surgical oncologist, regardless of the anatomic location of the tumor, is ideally to achieve a negative resection margin, which can be defined as grossly complete removal of the tumor with a surrounding rim of normal tissue, with no macroscopic tumor visible and no microscopic tumor cells present at the edge of the resected specimen. The ability to achieve a negative margin resection for STS, and the quality and quantity of the resected tissue surrounding the actual tumor mass, is largely determined by the tumor size and location, proximity of the tumor to critical structures that would lead to unwanted morbidity if removed en bloc with the tumor and the experience of the surgeon.

Any discussion of surgical margins requires an understanding of the local biology of STS as well as the concept of compartmentalization in the extremities as popularized by [24]. Sarcomas must be removed with a rim of surrounding normal tissue in order to achieve a negative resection margin. This is critical to avoiding local tumor recurrence because STS do not have a true capsule; instead as they grow, they compress the surrounding tissues into a reactive "pseudocapsule" that does not provide an actual barrier to tumor extension and actually contains malignant cells (Fig. 15.7). Beyond the "pseudocapsule" and surrounding the STS is a zone of variable distance that may look normal to the eye of the surgeon but which contains subclinical or microscopic disease and has been termed the "inflammatory" or "reactive" zone. If one could identify the extent of this zone and thereby the furthest possible extent of microscopic tumor cells beyond the main tumor mass, then placing the surgical margin beyond that point, through normal tissue, would always provide not just a negative resection margin but a locally curative one too, since no residual tumor cells would be left behind which could subsequently grow and account for a local tumor recurrence. There is currently no objective test which can identify the local extent of the microscopic disease within the "reactive" zone, although the presence of "peritumoral edema" that is often seen to surround STS on MRI scans may reflect areas at risk for harboring microscopic disease, that should either be resected at the time of surgery or be included in the radiotherapy field if treatment will involve combined management with preoperative radiation, although this is not a universally accepted practice [25, 26].

Compartmentalization is based on fascial boundaries which generally act as impenetrable and predictable barriers to tumor growth. For instance, the superficial investing fascia in the extremities and the superficial fascia of the trunk or abdominal wall provide a barrier to deep tumor spread. Similarly, the superficial investing fascia in the extremities joins the deep intermuscular septae and defines muscular compartments which also act as barriers to local tumor spread. For STS that originate within a muscular compartment, tumors may grow longitudinally along fascial planes but typically cannot grow in a radial

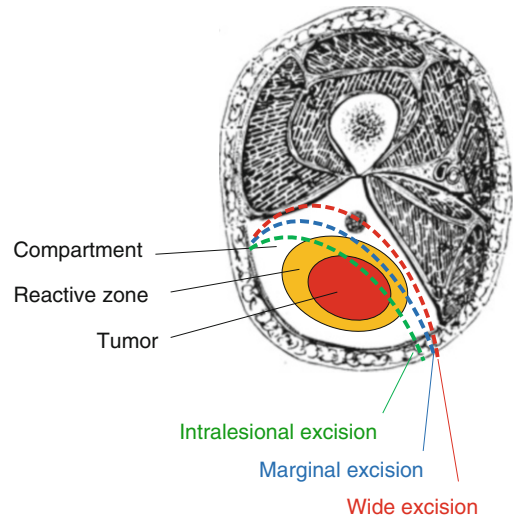


Fig. 15.7 Tumor, reactive zone and compartment, and type of resection, according to Enneking definition (The Authors thank Luna Boschetti for the picture)

pattern beyond the fascia which acts as a barrier to local growth. However, there are a number of locations in the extremities where fascial compartments do not exist, most frequently at areas of flexor creases such as the axilla, antecubital fossa, inguinal canal, and popliteal fossa, and in these anatomic sites, it is often difficult to achieve a "wide" resection margin around an STS, such that adjuvant therapy is often required as part of the treatment plan.

The concept of fascia and compartments as barriers can be utilized to define different types of resection margins [24]. For instance, Enneking defined a "wide" resection margin as having either an intact fascial boundary (even if directly adjacent to or within a few millimeters of the tumor) or an adequate surrounding layer of tissues which would indicate that the tumor was removed with an intact pseudocapsule, reactive zone, and some additional normal tissue. Defining a fascial boundary is relatively straightforward; however, defining where the normal layer is situated beyond the reactive zone surrounding a STS is more challenging. As a result, local management of extremity STS historically necessitated entire compartment resections, and even more radical resections including amputations were commonplace to avoid local tumor recurrences.

With better local imaging by MRI which allows improved definition of local tumor extent, as well as the introduction of radiation as a commonly utilized treatment modality as part of combined management for the local control of STS, more conservative and function preserving surgery for STS is now possible. Generally, a 1–2 cm layer of normal tissue surrounding an STS (e.g., 1 cm for low-grade and 2 cm for high-grade tumors) is considered to represent an adequate wide margin and should provide local control in >90% of cases following surgical resection alone [27, 28]. However, the majority of STS cannot be resected with a "wide" margin and therefore require combined management with (neo)adjuvant radiation or (neo)adjuvant chemotherapy or both. For extremity STS that require combined surgery and radiotherapy due to less than wide resection margins, a randomized clinical trial comparing preoperative and postoperative radiation by the Canadian Sarcoma Group showed that although preoperative radiation was associated with a higher risk of early postoperative wound healing complications, it was also associated with better long-term functional outcomes for patients due to less soft tissue fibrosis, pain, stiffness, and limb edema as well as less radiation-associated fractures [29, 30]. In that study, the rate of local and systemic control was identical in both treatment arms. A more recent phase 2 study of Image-Guided Intensity Modulated Radiation Therapy (IMRT) by the Toronto Sarcoma Group showed that this newer modality for delivery of preoperative radiation was safe and could diminish the risk of wound complications compared to conventional preoperative radiation yet maintain a low risk of local tumor recurrence as well as good limb function [31]. The use of preoperative radiation is becoming more commonplace and is likely the optimal approach for combined management of extremity STS as well as other difficult anatomic sites for most patients and is particularly useful in children and adolescents as it limits both the dose of radiation and the treatment volume [32].

Today, surgical resection margins are typically defined as R0 (negative margin), R1 (microscopically positive margin), and R2 (grossly positive margin). Gross positive (R2) margins are associated with unacceptably high rates of local recurrence. R0 does not differentiate between a true wide resection as defined by [24] where surgery alone is adequate, and a close but negative margin where the addition of radiation has been well documented to decrease the risk of local tumor relapse [33, 34]. Even in the setting of a microscopically positive margin (R1), the risk of local tumor relapse is significantly lower if adjuvant radiation is combined with surgery. A common anatomic scenario that can result in an R1 margin is when an STS is situated directly abutting a major motor nerve, blood vessel, or bone where resecting one of these structures would introduce significant morbidity for the patient. In this setting, planning for a very close margin of resection, such as using epineurium, vessel adventitia, or periosteum, in combination with preoperative radiation in order to save a critical structure has

been shown to be safe [35, 36] even if the final margin ends up microscopically positive. The same studies also defined other situations in which resection of STS with positive margins (e.g., following a prior unplanned excision elsewhere or an unexpected positive margin during primary resection) leads to high rates of local recurrence and metastasis and therefore much worse outcomes for patients. Although much of this data is derived from the management of extremity STS, it likely applies to management of STS of other anatomic sites, including the head and neck, thorax, retroperitoneum and pelvis. For management of patients with retroperitoneal STS in particular, a consensus statement has recently been published by a transatlantic working group [37] that leads to initiation of a randomized clinical trial comparing surgery with or without preoperative radiation for patients with previously untreated nonmetastatic disease who are 18 years of age and over (EORTC 62092-22092 – STRASS clinical trial).

The pediatric approach to the management of STS has been quite different and focused on the role of chemotherapy, largely because of the chemosensitivity of rhabdomyosarcoma, soft tissue Ewing sarcoma/PNET, and possibly synovial sarcoma. In addition in pediatric patients, there is the added objective of trying to minimize the use of radiation in this young population. High-dose radiation in the extremity of a growing child can be complicated early on by growth arrest related to radiation of the growth plate, joint stiffness related to fibrosis, and bone osteopenia and weakness with subsequent risk of fracture. More importantly, and in the longer term, there is a time-dependent cumulative risk for development of secondary radiation-induced malignancies including sarcomas and even carcinomas, as well as other chronic health disorders depending on the location of the radiation including obesity, pulmonary, thyroid, and cardiac dysfunction [38]. As a result, most pediatric patients with any type of high-risk STS (i.e., large and high-grade tumors) tend to be treated with chemotherapy, even if they have an “adult” histologic type of tumor, in the hope that it will facilitate resection and minimize the need for radiotherapy. However, in the setting of inadequate surgical resection margins, radiation should still be utilized to enhance local tumor control.

Synovial sarcoma spans both the pediatric and adult age groups, and owing to the pediatric approach, most adults with high-risk synovial sarcoma have been offered preoperative chemotherapy over the past decade as part of their treatment (Fig. 15.8).

15.6.2 Rhabdomyosarcoma

RMS is a distinct entity and clearly differs from other soft tissue sarcomas in regard to its natural history and its sensitivity to therapy: (a) it is one of the typical embryonal tumor of childhood, composed by cells resembling normal fetal skeletal muscle; (b) it is always characterized by high-grade malignancy, local invasiveness, and a marked propensity to metastasize, to the point that all RMS patients should be assumed to have micrometastatic disease at diagnosis and therefore need to be treated with systemic therapy; (c) it is generally characterized by good response to chemotherapy (80–90 % response rate) and radiotherapy.

RMS cells can be recognized by the expression of myosin and MyoD protein family antigen. Classically, two histological subtypes of RMS have been distinguished, the favorable embryonal subtype and the unfavorable alveolar subtype [39]. A third form, pleomorphic RMS, needs to be considered separately from other RMS subtypes (it is very rare in the pediatric population, occurring typically at an age older than 50 years, and it is probably more close to an adult sarcoma such as malignant fibrous histiocytoma or high-grade spindle-cell sarcomas than to other RMS subtypes typical of children). Cytogenetic and molecular analyses are of critical importance to define the diagnosis of RMS subtype. Most alveolar RMS (80–85 %) display a consistent genetic abnormality, that is, the reciprocal chromosomal

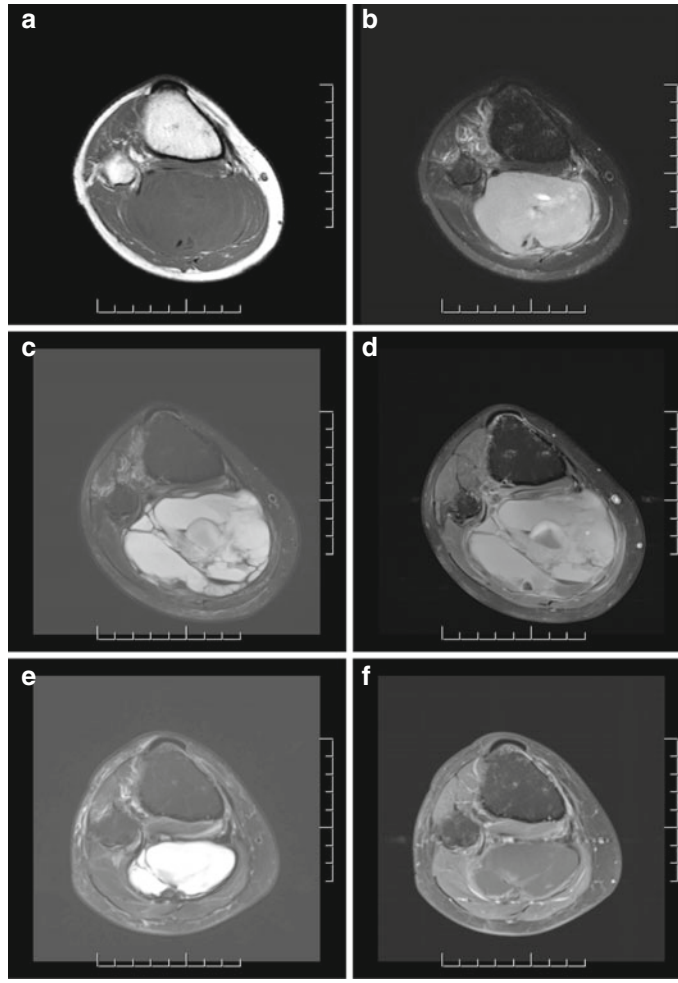


Fig. 15.8 A 28-year-old male with synovial sarcoma in the proximal calf/popliteal fossa. At diagnosis, (**a**) axial T1-weighted MRI image and (**b**) axial T2-weighted image with fat suppression show a large solid STS involving the superficial and deep posterior calf compartments and extending into the popliteal fossa with involvement of the neurovascular bundle. Following preoperative chemotherapy, (**c**) axial T2 with fat suppression and (**d**) axial T1 with fat suppression and gadolinium MRI images demonstrate interval enlargement and development of multiloculated cystic components with fluid levels, suggestive of hemorrhage and necrosis. Some rims of enhancement are seen on the post-gadolinium images. The patient received preoperative radiation following initial chemotherapy. (**e**) Axial T2 with fat suppression and (**f**) axial T1 with fat suppression and gadolinium MRI images show interval reduction in size of the lesion with less peripheral enhancement from gadolinium. Limb sparing surgery necessitated excision of the posterior tibia nerve as well as resection and reconstruction of the posterior tibia vessels. The final pathology report revealed 95 % treatment-induced necrosis. The patient remains alive without evidence of disease 2 years following treatment

translocations t(2;13) (q35;q14) or t(1;13) (p36;q14), generating the *PAX3* or *PAX7–FOXO1* chimeric protein. Embryonal RMS lacks a tumor-specific translocation but generally exhibits recurring abnormalities such as loss of heterozygosity on the short arm of chromosome 11 (11p15.5), which may act by inactivating tumor-suppression genes. A pattern of association between histotypes and clinical features has been described (i.e., the alveolar histotypes are more frequently localized at the extremities and in the trunk, and it is more typical of adolescents and young adults than of children). Recently, some controversies have emerged regarding the histopathological diagnosis of alveolar RMS: patients with alveolar histology but lacking the fusion gene *PAX3* or *PAX7–FOXO1*(fusion gene-negative alveolar RMS) would have a genomic profile and a clinical course more similar to those of embryonal RMS than those of fusion-positive alveolar cases [40, 41]. These findings would suggests that a biological characterization would be better than the currently used histological assessment in classifying RMS subtype and predicting prognosis, and they will be probably incorporated in future risk stratification.

During the past 30 years, the 5-year overall survival (OS) rates of pediatric RMS have improved dramatically from 25 to 30% to approximately 70% [42–44, 46, 47, 51]. These results are due largely to the development of treatment approaches that are (a) multidisciplinary (including surgery, radiotherapy, and in particular multiagent effective chemotherapy), (b) risk-adapted (prognostic factors are used to stratify treatment: more intensive therapy improves cure rates in those patients with less favorable disease, whereas those with more favorable findings avoid overtreatment and side effects without jeopardizing survival), and (c) cooperative multi-institutional trials able to enroll a large number of patients. Historically, these trials included subjects up to the age of 18 or 21 years; however, in recent years, pediatric collaborative groups have raised the upper age limit of their RMS protocols to 30 years and more.

Currently, the two main cooperative groups dedicated to RMS are the Soft Tissue Sarcoma Committee of the North-American Children's Oncology Group (COG) and the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG), which involves most of the European countries and others (e.g., Argentina, Brazil, Israel). Other European countries join the German CWS (Co-operative Weichteilsarkomen Studie) group.

The treatment approach of the different cooperative groups is built along similar lines, but differences still exist. RMS is a very heterogeneous disease, and the prognosis depends on multiple factors, including histological subtype, primary tumor site and size, lymph node involvement, and distant metastasis. For example, patients with alveolar histology continue to have less than optimal outcome, and most patients with distant metastasis do not achieve long-term cure. With the recognition of the different prognostic factors, the risk assignments (to decide the treatment's intensity) became more complex but also more careful. The recent EpSSG protocol identifies low-, standard-, high-, and very high-risk groups (with 8 subgroups) for localized patients, plus the group of metastatic RMS cases [48, 65] (Fig. 15.9); the COG protocol describes three groups (low, intermediate, and high risk) and 17 subgroups, but the definitions do not cover the same subsets of patients (e.g., the EpSSG high-risk group grossly corresponds to the IRS-V intermediate-risk group) [49]. Among the other variables used in the risk stratification, the patient's age has also emerged as a factor significantly influencing survival: in various series, patients over 10 years of age have been reported to have a worse prognosis than younger children [50].

Treatment strategy for RMS is necessarily based on a multimodal approach. An optimal local treatment is essential, because local progression or recurrence continues to be the primary causes of treatment failure. Nevertheless, it is possible to state that multiagent chemotherapy is the mainstay of the treatment and should be definitely given to all patients. The reliable chemosensitivity of RMS has led to an evolution in the role of local therapies: surgery has evolved over the years from being the primary

treatment modality to just one component of a multidisciplinary approach and from an aggressive surgical approach to more conservative, organ-sparing procedures. As time of diagnosis, surgery with risk of anatomic or functional impairment is not recommended and biopsy should be performed. Tumors considered unresectable at diagnosis can be conservatively and completely resected in a large percentage of cases after tumor shrinkage achieved by primary chemotherapy. Similarly, the efficacy of chemotherapy may reduce the proportion of patients for whom radiotherapy is indicated (or the doses used) and thus reduce the risk of radiation-related sequelae, in particular for younger patients (fibrosis, bone and soft tissue hypoplasia, neuroendocrine dysfunctions, second tumors) [51]. Radiotherapy is often omitted in embryonal RMS after initial complete resection, but it is still recommended in many cases (i.e., alveolar RMS, inadequate resection, large tumors). Radiotherapy is generally delivered to the pretreatment tumor volume with doses generally ranging between 40 and 55 Gy, using three-dimensional conformal techniques.

The backbone of RMS treatment is intensive alkylating-based multidrug chemotherapy given for at least 6–9 months. A large number of different chemotherapeutic regimens have been tested over the years within cooperative randomized trials. In many protocols, the addition of various drugs to the gold standard VAC (combination of vincristine, actinomycin D, and cyclophosphamide, used in North America) and IVA regimen (which differs in the choice of the alkylating agent, i.e., ifosfamide in the place of cyclophosphamide, used in Europe) did not show clear advantage compared to the standard combinations.

In the recent EpSSG RMS 2005 trial, the role of doxorubicin has been evaluated in a randomized trial using the IVADO regimen (IVA plus doxorubicin) [52], administering early the maximum dose intensity of doxorubicin, compared to standard IVA. Preliminary results did not show any advantage for the addition of doxorubicin

Risk group	Histotype	IRS group	Nodal involvement	Tumor site	Size and Age	% of cases	Overall survival
A	Embryonal	I	N0	Any	Favorable	6%	95%
B	Embryonal	I	N0	Any	Unfavorable	6%	90%
C	Embryonal	II-III	N0	Favorable	Any	18%	88%
D	Embryonal	II-III	N0	Unfavorable	Fav	9%	85%
E	Embryonal	II-III	N0	Unfavorable	Unfavorable	27%	60%
F	Embryonal	II-III	N1	Any	Any	8%	60%
G	Alveolar	I-II-III	N0	Any	Any	20%	60%
H	Alveolar	I-II-III	N0	Any	Any	6%	50%

- IRS (Intergroup Rhabdomyosarcoma Study) Group: group I, complete resection; group II, microscopic residual disease after initial surgery; group III, macroscopic residual tumor after surgery (or biopsy)
- Tumor site: favorable = non-parameningeal head-neck (i e, orbit), non-bladder/prostate genitourinary (i e, paratesticular, vagina); unfavorable = parameningeal, extremities, GU bladder-prostate, abdomen, trunk
- Size and Age: favourable= tumor size <5cm and age <10 years; unfavourable= size >5 cm or age ≥10 years

Fig. 15.9 Risk stratification, estimated percentage of patients, and estimated overall survival according to the European Pediatric Soft Tissue Sarcoma Study Group: (EpSSG) RMS 2005 protocol

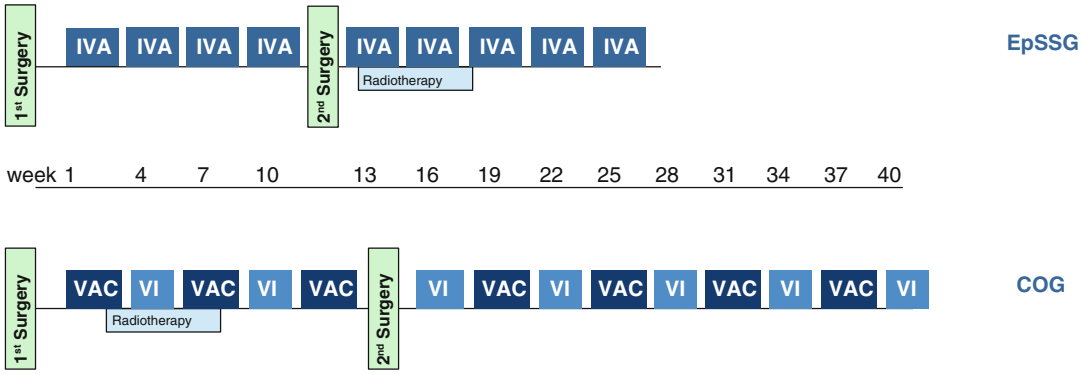
but a higher toxicity [53]. The trial remains open for a second randomization, to evaluate the role of maintenance therapy with low-dose continuous chemotherapy: patients with localized RMS who are in complete remission after 6-month chemotherapy are randomized to receive or not maintenance therapy with oral cyclophosphamide plus vinorelbine (which has shown activity in RMS) [54].

The most recent COG trials for localized RMS explored the role of camptothecin derivatives. In the COG D9803 study conducted between 1999 and 2005, the addition of topotecan to VAC failed to show benefit [46]. In the subsequent COG ARST0531 study conducted between 2006 and 2012, patients with localized standard-risk RMS have been randomized to receive 14 courses of VAC versus VAC alternating with vincristine-irinotecan (VI). As in other previous randomized trial adding new regimens to VAC, the addition of VI did not improve outcome; however, as there was minor hematologic/infective toxicity and a lower dose of alkylating agents, COG has decided that the VAC/VI regimen will be used in future trials as the comparator arm (Fig. 15.10) [55].

A less toxic regimen (VA, vincristine plus actinomycin D, without alkylating agents) is used in a very selected subset of patients with low-risk characteristics, i.e., completely resected small tumor, embryonal histology, paratesticular and vagina sites, and age <10 years. Since age over 10 years is an adverse prognostic variable, the VA is generally not recommended in adolescents and young adults.

The outcome of patients with metastatic disease at diagnosis remains poor (about 30 % survive) even with the use of very intensive treatments [56], including in the past high-dose chemotherapy followed by reconstitution with peripheral blood stem cells [57]. New drugs and new approaches are needed for these patients, as well as for when disease recurs. COG strategy currently includes a "dose-compression" approach for metastatic patients (full-dose chemotherapy administered with a shorter interval between doses, e.g., 1–2 weeks instead of the usual 3 weeks) and the investigation of the role of different target agents: for example, temsirolimus is considered one of the more promising new drugs for RMS.

Age over 10 years is considered an adverse prognostic variable in RMS. A recent Italian study analyzed the clinical features and outcome of adolescents (76 patients 15–19 years old) treated in pediatric trials from 1988 to 2005, in comparison with children (567 patients aged



IVA: vincristine 1.5 mg/m²/cycle, actinomycin D 1.5 mg/m²/cycle, ifosfamide 6 g/m²/cycle
VAC: vincristine 1.5 mg/m²/cycle, actinomycin D 1.5 mg/m²/cycle, cyclophosphamide 1.2 g/m²/cycle
VI: vincristine 1.5 mg/m²/day 1 and 8, irinotecan 50 mg/ mg/m²/day 1-5

Fig. 15.10 Current backbone treatment in pediatric rhabdomyosarcoma trials for the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) and the North-American Children's Oncology Group (COG)

0–14) [58]. During the study period, age was not considered a factor for stratifying treatment and therefore adolescents received the same treatment as children. The study found that the adolescent subgroup had a significantly higher prevalence of unfavorable features, including alveolar subtype, nodal infiltration, and metastases at diagnosis (Table 15.3). Moreover, the diagnosis of RMS was significantly "delayed" in adolescents: the median time elapsing between first symptoms and diagnosis doubled in 15–19-year-old patients as compared to 0.14-year-olds. Age below 15 years correlated with a better survival (5-year overall survival 68.9 % vs. 57.2 %), but the outcome was very similar between 10–14- and 15–19-year-olds, suggesting that a 10-year-old cutoff may be more appropriate than distinguishing between children and adolescents (i.e., using a cutoff around 14–15 years of age) for the purpose of attributing different risk factors. Notable, this study also reported that the number of patients actually enrolled in the Italian pediatric protocols as compared with the number of cases expected to be diagnosed in Italy was 90 % for children and 27 % for adolescents [58]. Another Italian study confirmed that the symptom interval was longer in adolescents than in children with soft tissue sarcomas (1.5, 2.6, and 2.7 months in 0–9, 10–14, and >15-year-old patients) but showed also an association between longer symptom interval and higher mortality [59].

15.6.2.1 Rhabdomyosarcoma in Adults

Although RMS is a typical tumor of childhood, it can occur in adults, albeit rarely. Scanty information is available on clinical and biological findings of adult RMS. All studies, however, highlight a poorer outcome than in children, with OS in the range of 20–50 % [60–62]. These findings raised questions as to whether adult RMS is biologically the same as childhood RMS. The pleomorphic subtype should be considered apart, being more similar to other soft tissue sarcoma subtypes in adult than to RMS. However, an inferior outcome for adults remains even when pleomorphic cases are excluded from analyses. A recent study compared the clinical features and outcome of 1,071 adults (age >19 years) and 1,529 children (age ≤19 years) with RMS registered in the Surveillance, Epidemiology, and End Results (SEER) database [63, 83]. This study showed that adults were more likely to have adverse prognostic variables (alveolar histology, unfavorable site) and confirmed the far worse prognosis for adult RMS (5-year OS: 26.6 % vs.

Table 15.3 Children and adolescents with rhabdomyosarcoma: comparison of various clinical findings and outcomes in Italian prospective clinical trials conducted by the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) Soft Tissue Sarcoma Committee (STSC) from 1988 to 2005

	Children (0–14 years)	Adolescents (15–191 years)
No.	567	76
Observed/expected cases	0.9	0.27
Symptom interval	4.86 weeks	8.43 weeks
Clinical characteristics		
Alveolar subtype	32.6 %	47.4 %
N1	23.3 %	39.1 %
M1	17.8 %	30.7 %
Outcome		
Response to chemotherapy[a]	73.8 % CR and major PR	81.1 % CR and major PR
5-year PFS	64.3 %	48.1 % ($p=0.0237$)
5-year OS	68.9 %	57.2 % ($p=0.006$)

Bisogno et al. [58]

N1 nodal involvement, *M1* distant metastases, *PFS* progression-free survival, *OS* overall survival

[a]Response to chemotherapy at week 9, after 3 courses of chemotherapy

60.5 % in children) regardless of the variables known to influence survival garnered from experience of treating children [63, 83]. Despite the limits of such an analysis including the absence of detailed information on received treatment, these findings support the unsatisfactory survival rates in adults being related to factors other than clinical presentation, such as the delivered treatment.

A role for treatment in explaining the different outcomes is supported by another study from the Istituto Nazionale Tumori in Milan of 171 patients >18 years (age range 19–83) with embryonal and alveolar RMS where treatment modalities have been analyzed and patients have been stratified according to the degree to which they had been treated appropriately, based on current treatment guidelines for childhood RMS (assigning a score to each patients) [32, 62]. The study showed overall results (5-year OS 40 %) similar to those of other published series. Only 39 % of patients had been treated in line with the pediatric protocols: noteworthy, in this subset of patients, the adults' outcome was not too far from the figures for pediatric series (i.e., 5-year OS was 61 % and increased to 72 % for patients with embryonal RMS) [62] (Fig. 15.11). Moreover, the overall response to chemotherapy was 85 %, substantially different from that observed in other adult sarcomas and in the same range as the rate for pediatric RMS.

These findings support two main considerations: first, chemotherapy is active in adult RMS (as in childhood) and adult patients would fare better if treatments used were closer to those used in children pediatric patients; second, adults with RMS are sometimes not treated adequately. It remains to be clarified what prevents adults from receiving proper treatment. Adults may tolerate intensive treatments originally developed for children less well (e.g., the neurotoxicity associated with vincristine may be more frequent and more severe in adult patients). Another factor may be the lack of familiarity of treating teams with this diagnosis. In any case, efforts should be made to improve the number of adults patients with RMS who receive treatment according to the same principles used in pediatric patients. New strategies of cooperation between pediatric and adult oncologists are needed. Pediatric cooperative groups have raised the upper age limits for their protocols, but this may really help only if adult groups can be included in the project too, since adult physicians may not hear about such trials or might be reluctant to enroll their patients in trials in which they themselves have no part. An interesting result recently comes from Italy, where the goal of developing a protocol for adult RMS based on pediatric-like strategy (Fig. 15.12) has been achieved by the Italian Sarcoma Group (ISG) and the Italian Rare Tumor Network (mainly concerned with adult oncology), in cooperation with the pediatric cooperative group Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) Soft Tissue Sarcoma Committee (STSC).

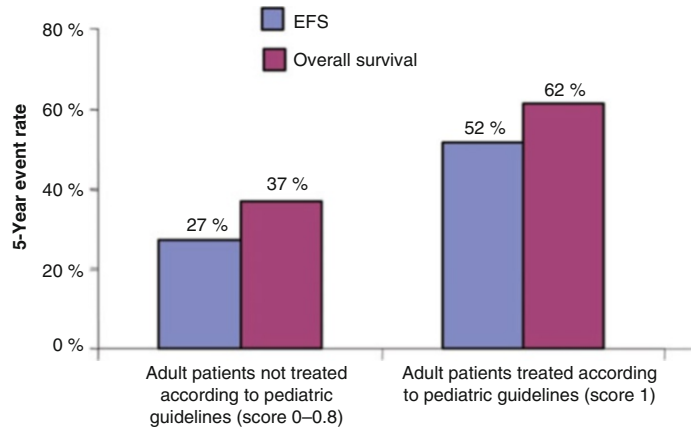


Fig. 15.11 Rhabdomyosarcoma in adults: 5-year outcome as a function of "pediatric versus adult treatment." Data from Ferrari et al (2003) *EFS* Event-free survival

15.6.3 Synovial Sarcoma

Synovial sarcoma (SS) is a typical STS subtype crosses pediatric and adult ages, and there is sometimes an uncertainty about the "*intellectual property*" of this tumor, which is often "claimed" by both pediatric and medical oncologists [17, 64, 72].

The biological hallmark of SS is the t(X;18)(p11.2;q11.2) chromosomal translocation (and the SYT-SSX transcript in its various forms). SS is generally considered a high-grade sarcoma that is locally invasive and has a propensity to metastasize, regardless of how it is graded in terms of tumor differentiation, mitoses, and necrosis [48, 65]. The prognosis for synovial sarcoma patients depends mainly on the feasibility of surgical resection, tumor size and site, and any metastases, but the optimal treatment remains to be determined [17, 64, 72]. As for other STS of adult age, the standard treatment for localized disease is surgery. A general agreement has not yet been achieved regarding the role of adjuvant treatments. Postoperative radiotherapy has a well-defined role to improve local control after less-than-compartmental resection. In the case of locally advanced disease, the radiotherapy sandwich technique (preoperative chemotherapy and radiotherapy, then surgery followed by further chemotherapy and a possible boost of irradiation) may be useful for shrinking the tumor and making it resectable. More open questions still exist regarding the role of chemotherapy, given that the rarity of the tumor hinders the adequate accrual for a randomized trial. Over the years, completely different strategies have been developed in pediatric oncology protocols as compared to the adult setting. Practically speaking, in European centers, a patient aged 16 years old, enrolled in pediatric trials, was treated very differently from a 22-year-old patient. Given the relatively high rates of response to chemotherapy documented in pediatric SS series (i.e., approximately 60 %, which is higher than is usually reported for adult STS), pediatricians tended to consider SS as a chemosensitive disease and mutated their approach from the management of RMS: SS was considered as an "RMS-like" tumor (in Europe at least), and patients were treated with the same protocols designed for RMS, thus giving adjuvant chemotherapy to the majority of patients, even in cases of completely excised small tumors [17, 64, 66–73]. On the contrary, adult patients with SS were generally treated like the other adult STS (generally thought to be poorly chemosensitive) and the treatment focused on local control: adjuvant chemotherapy was rarely utilized in adults and only in the recent years it has been somewhere proposed for high-risk patients (local invasiveness, large size, deep localization) [74–82] (Table 15.4). The most effective strategy remains unclear. Published series report better outcome in pediatric series than in adult studies, but all the known adverse prognostic factors are reported more frequently in adults (large size, local invasiveness, unresectability, proximal sites). Moreover, age per se has been suggested as a probable prognostic indicator. In a pediatric multicenter retrospective analysis published some years ago, 5-year OS was 80 %, but the risk

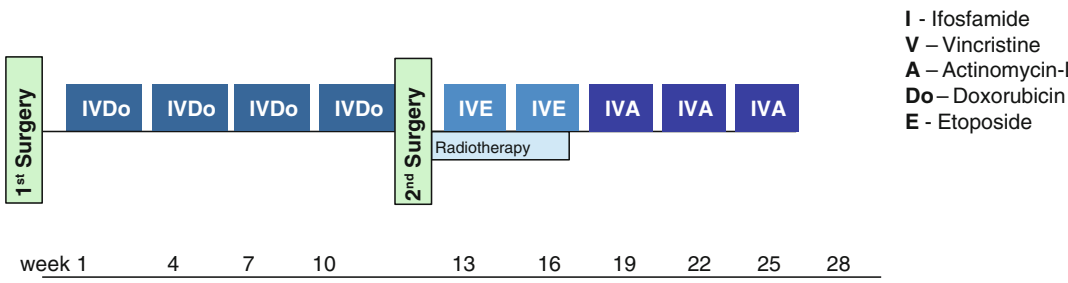


Fig. 15.12 Italian protocol for adult rhabdomyosarcoma developed by the Italian Sarcoma Group (ISG) and the Italian Rare Tumor Network in cooperation with the pediatric cooperative group Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) Soft Tissue Sarcoma Committee (STSC)

Table 15.4 Most important series on synovial sarcoma published by pediatric or adult oncology groups in the last 10–15 years

Pediatric series	
Okcu et al. [67] multicenter study (MDACC, SJCRH, INT Milan, CWS)	219 pts <20 years (study period 1966–1999) 5-year OS 80 % 84 % received chemotherapy; 60 % response rate to chemotherapy
Brecht et al. [68] CWS, AIEOP-STSC	150 pts <18 years (1975–2002), groups I–II (initial gross resection) 5-year OS 89 %, nearly all patients treated with chemotherapy identification of low-risk patients (group I, ≤5 cm) for which chemotherapy might be omitted
Ferrari (2009) AIEOP-STSC	115 patients <20 years (1979–2005) 5-year OS 76.9 %, nearly all patients received chemotherapy worse outcome for axial sites vs. limbs (OS 55.1 % vs. 84.0 %
Brennan et al. [70] UK CCLG	77 patients <18 years (1991–2006) 5-year OS 76 % prognostic factors: T stage and IRS group
Orbach et al. [71] SIOP-MMT	88 patients <18 years (1984–2003) 5-year OS 85 % omission of radiotherapy in many cases
Ferrari et al. [17, 64, 72] European join series	Critical reappraisal of staging investigations in relation to the rate of metastases at diagnosis 258 patients (1988–2005) Tumor diameter to warrant more accurate radiological investigations (e.g., lung CT scan)
Ferrari et al. [17, 64, 72] AIEOP-STSC	Salvage rates and prognostic factors after relapse 44 relapsing cases (1979–2006), 10-year survival 21 % Variables influencing survival: timing and type of relapse, complete surgery
Stanelle and Christison-Legay [73] MSKCC	111 patients <21 years (1970–2010) 5-year OS 73 %, tumor size was the main factor in discriminating survival risk "…the role of radiotherapy and chemotherapy for synovial sarcoma warrants future study…"
Ferrari et al. [86] EpSSG	138 patients <21 years (2005–2012) with nonmetastatic disease 5-year EFS 81.9 %, OS 90.7 % – no metastatic relapse in 24 low-risk patients (completely resected tumor ≤5 cm) treated with surgery alone Response to chemotherapy 55.2 %, including major and minor responses Collaborative prospective studies are feasible on a European scale, with excellent treatment compliance
Comparison pediatric versus adult series	
Ferrari et al. [66] INT Milan	271 patients of all ages (46 <17 years) (1973–2002) 5-year OS 64 % Adjuvant chemotherapy improve outcome
Sultan et al. [63, 83] SEER (1983–2005)	Epidemiological series, 1,268 cases (213 ≤18 years) 5-year cancer-specific survival: 83 % versus 62 % ($p<0.001$) in children/adolescents versus adults Multivariate analysis: significantly higher mortality for adults after adjusting for other variables
Adult series	
Lewis et al. [74] MSKCC	112 adult patients (1982–1996), 5-year mortality rates 25 %, 37 % were treated with adjuvant chemotherapy "…no evidence of survival benefit for adjuvant chemotherapy…"
Trassard et al. [75] French Sarcoma Group	128 patients with nonmetastatic disease (1980–1994) 5-year DSS 62.9 %, "…we failed to observe a significant improvement in patient's outcome when chemotherapy was used…"
Spurrell et al. [76] Royal Marsden Hospital, London	104 patients (1978–2003) with advanced disease median survival 22 months, response rate to doxorubicin plus ifosfamide – 59 % "…synovial sarcoma is a chemosensitive tumor…"
Eilber et al. [77] MSKCC and UCLA	101 patients (1990–2002) "…ifosfamide-based chemotherapy was associated with an improved 4-year DFS (88 % vs. 67 %, p 0.01) in high-risk, extremity synovial sarcoma and should be considered in the treatment of such patients"

(continued)

Table 15.4 (continued)

Guadagnolo et al. [78] MDACC	150 patients (1960–2003) 5-, 10-, and 15-year OS – 76 %, 57 %, and 51 %. "Synovial sarcoma is adequately controlled at the primary site by conservation surgery and radiotherapy…"
Canter et al. [79] MSKCC	255 patients (1982–2006), preoperative nomogram to predict the risk of disease-specific death. 5-, 10-, and 15-year DSS – 72 %, 60 %, and 53 %, "…survival benefit to chemotherapy… This nomogram may improve decision-making with regard to selecting patients most likely to benefit from neoadjuvant/adjuvant chemotherapy"
Italiano et al. [80] French Sarcoma Group	237 patients (1974–2006), 5-year OS 64.0 % chemotherapy had no significant impact on survival "…wide surgical excision with adjuvant radiotherapy remains the cornerstone of treatment… …chemotherapy should not be delivered outside a clinical trial setting…"
Palmerini et al. [81] Rizzoli Institute	250 patients (1976–2006), chemotherapy given to 48 % of patients with localized disease 5-year OS 76 % for localized disease "…the role of adjuvant chemotherapy remains unproven…"
Al-Hussaini et al. [82] University of Toronto	87 adults (plus 15 pediatric patients) (1986 and 2007) chemotherapy given 13.8 % of adults (and 87 % of children); 5-year OS – 80.3 % "evidence for a well-defined role of chemotherapy to improve survival remains elusive…"

MDACC M.D. Anderson Cancer Center, *SJCRH* St. Jude Children Research Hospital, *INT* Istituto Nazionale Tumori Milan, *CWS* Co-operative Weichteilsarkomen Studie (German Soft Tissue Sarcoma Cooperative Group), *AIEOP-STSC* Associazione Italiana Ematologia Oncologia Pediatrica – Soft Tissue Sarcoma Committee (Italian Cooperative Group), *UK CCLG* United Kingdom Children's Cancer and Leukaemia Group, *SIOP-MMT* International Society of Pediatric Oncology – Malignant Mesenchymal Tumor Committee, *EpSSG* European Pediatric Soft Tissue Sarcoma Study Group, *SEER* Surveillance, Epidemiology, and End Results, *MSKCC* Memorial Sloan-Kettering Cancer Center, *UCLA* University of California Los Angeles, *OS* overall survival, *EFS* event-free survival, *DSS* disease-specific survival, *CT* Computed Tomography

of event increased 0.06 times for every 1 year increase in age [67].

A more recent epidemiological SEER study on 1,268 cases showed a progressively worsening outcome with age: cancer-specific mortality rates were 34 and 16 % in adults and children, respectively [63, 83]. It is noteworthy that the adults' outcome remained consistently worse than the children's, even after adjusting for the different prognostic variables (tumor size, site, and stage), suggesting that factors other than a difference in the incidence of unfavorable clinical variables might be involved in this unsatisfactory outcome [63, 83]. The hypothesis that the different treatment outcomes might correlate, to some degree at least, with the different usage of chemotherapy would be supported by the retrospective study by the Istituto Nazionale Tumori in Milan, which compared pediatric and adult cases (for a total of 271 cases), and found that those who received adjuvant chemotherapy (administered to 80 % of the children but only to 20 % of the older patients) appeared to have better outcomes (metastases-free survival was 60 % in patients given chemotherapy and 48 % in those who were not) [66]. Being a retrospective study, this finding was far from a demonstration of efficacy of adjuvant chemotherapy in SS though may be interpreted as suggestive of a role for it. In the SEER study, data on treatment were not available. However, further interesting findings emerged analyzing the different decades of patient's age [63, 83]. The widest survival gap was observed between the first and the second decades: SS rarely occurs in children younger than 10 years of age (only 2.5 % of the cases in the SEER series), but when it occurs, tumors have favorable clinical features (e.g., extremity primaries, small tumors) and the outcome was excellent, suggesting a unique favorable biology/clinical history of SS in prepubertal patients. Conversely, survival rates were the same in the group of adolescents/young adult (10–18- vs. 19–29-year-old patients), while a survival gap emerged around the age cutoff of 30 years (Fig. 15.13) [63, 83]. Whether these differences in outcome might be related to biological variables or to historically different treatment approaches adopted in pediatric versus adult

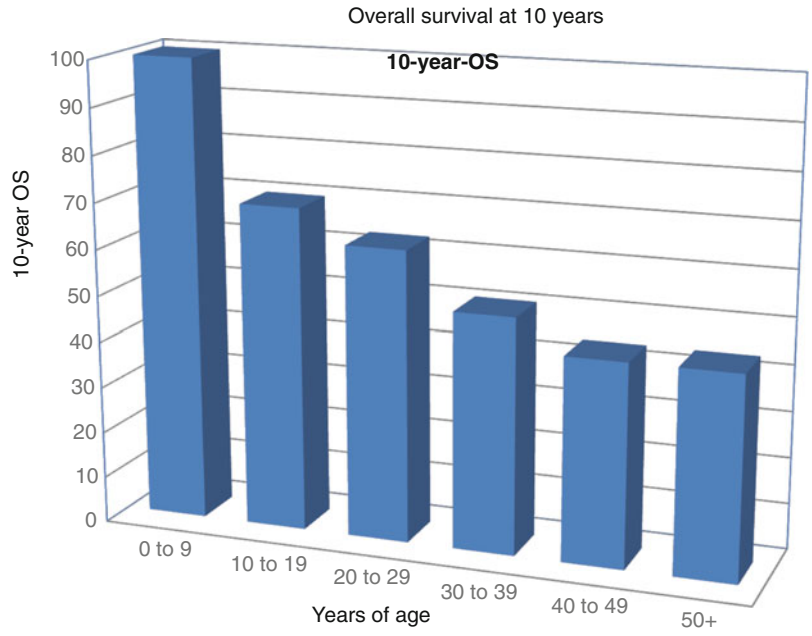


Fig. 15.13 Cancer-specific mortality by the age bracket in the Surveillance, Epidemiology, and End Results (SEER) series (1,268 cases) (Courtesy of Dr. Iyad Sultan, Department of Pediatric Oncology, King Hussein Cancer Center, Amman, Jordan)

patients remains unclear. However, it may be noted that in the most recent adult series published by major referral institutions or cooperative groups (e.g., the Memorial Sloan-Kettering Cancer Center and the French Sarcoma Group, the Rizzoli Institute) [77, 79–81], the survival rates of adult patients (5-year disease-specific survival rates in the range of 70 %) were not too far from the outcome reported by pediatric groups, though chemotherapy was used in a lower proportion of cases. Perhaps, it might be hypothesized that the worse outcome of adult SS reported in epidemiological analyses related to a different access to care (e.g., different enrollment in clinical trials, different access to referral institutions) [17, 64, 72].

Despite of the historical differences in the treatment strategy adopted in the pediatric and in the adult world, the situation has now changed to some degree, and clinical approaches have tended to converge toward a common strategy. If literature review on adult SS shows a lack of consensus on the role of chemotherapy (Table 15.4), nowadays many adult oncologists, definitely not all, tend to recommend chemotherapy for SS patients, in particular in the setting of neoadjuvant therapy, recognizing that SS may be quite different from other adult STS (with a younger age at onset, greater metastatic potential, and possible greater chemosensitivity) [84, 85].

On the other hand, pediatric oncologists have drawn from adult experiences and shifted from an "RMS-like" strategy in favor of a treatment approach that suggests the use of chemotherapy (the ifosfamide-doxorubicin chemotherapy remaining the standard regimen) according to the patient's risk stratification, based on tumor size, site, and stage [48, 65]. On the basis of an Italian and German study that identified a subset of low-risk patients (with completely resected tumors under 5 cm in size) with a very low risk of metastases [68] and therefore suggested that the use of chemotherapy in all cases, regardless of prognostic stratification (as developed in previous pediatric European trials), might be considered as overtreatment, in 2005 the EpSSG developed a new protocol dedicated to SS, with the omission of adjuvant chemotherapy in low-risk cases [48, 65] (Fig. 15.14). The results of this trial (138 patients <21 years treated between 2005 and 2012) have been recently published [86].

Firstly, the EpSSG protocol demonstrated that collaborative prospective studies on a rare tumor as SS are feasible even on a European scale, with

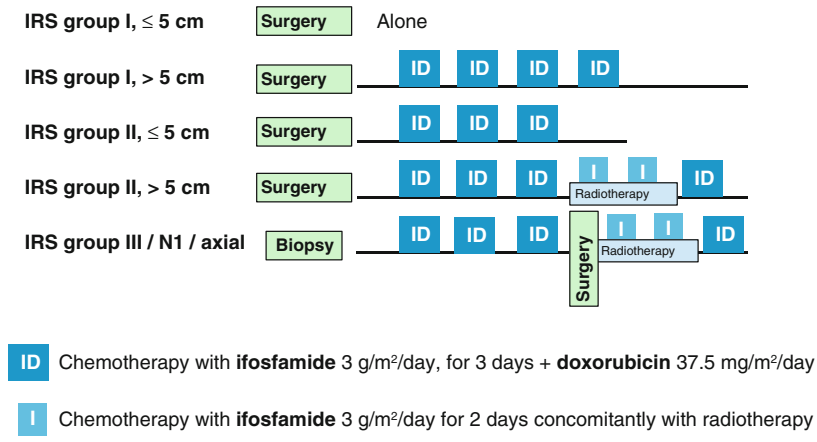


Fig. 15.14 The risk-adapted treatment program for synovial sarcoma in the EpSSG NRSTS 2005 trial

excellent treatment compliance (major protocol deviation was reported in <5 % of cases). The EpSSG in fact includes 15 different countries, with 131 centers. Other major findings of the study were (a) satisfactory overall results (5-year EFS and OS 80.7 % and 90.7 %, respectively), with higher survival rates than those previously published by pediatric groups; (b) in patients with measurable disease, response to chemotherapy was 55.2 % (22.4 % with complete remission and major partial remission, plus 32.8 % of minor remission), but it also described 97 % with "no progression"; (c) 24 low-risk patients were treated with surgery alone, and only 2 local relapses (and no metastatic relapses) were observed; though the number of cases was relatively small and caution is needed, this finding might suggest that adjuvant chemotherapy might be safely omitted for such patients without jeopardizing their outcome [86]. However, EpSSG authors themselves concluded that "it is clear that the number of patients in each of the risk groups would be too small to undertake a randomized clinical trial (e.g., to ascertain the role of adjuvant chemotherapy)" and "this emphasizes the need to create opportunities for larger, international, prospective projects. In view of the peak age range for the occurrence of SS, pediatric oncologists should collaborate with oncologists treating adult patients with SS to develop cooperative studies spanning different ages, integrating the same treatment concepts regardless of age" [86]. Very recently, preliminary steps in the direction of a European pediatric-adult common protocol have been already taken. Future trials should incorporate investigations on the role of new target therapies, at least in relapsing patients [87], and should improve the collaborations between oncologist and biologists to improve the understanding of the biology of SS, with the aim of reaching consensus on stratification and hopefully identify new pathways and new targets for novel therapies [88]. As an example, two subsequent French studies have recently reported that a 67-gene signature related to chromosome integrity, mitotic control, and genome complexity, called CINSARC (complexity index in sarcoma), could predict the risk of metastatic spread; those studies suggested differences in genome instability between adult and pediatric cases and hypothesized a potential role for this biomarker in explaining differences in outcome between children and adults [89, 90]. A broader international cooperation may be essential also for generating enough tumor samples to confirm this finding and lead to further age-related biological studies.

15.6.4 Adult-Type Soft Tissue Sarcomas

This group of tumors includes a heterogeneous variety of different entities that are generally regarded to have uncertain responsiveness to chemotherapy. The histologic spectrum of STS originating more commonly in the adult population

differs significantly from those in the pediatric population. The three most common subsets of adult-type STS include liposarcomas, leiomyosarcomas, and undifferentiated pleomorphic sarcomas, previously classified as malignant fibrous histiocytomas.

These tumors are rare in children and adolescents. Pediatric oncologists often called them "non-rhabdomyosarcoma soft tissue sarcomas" (NRSTS) [2, 91–93]. The term *non-rhabdomyosarcoma* STS reflects the fact that most of the experience gained on the treatment of pediatric NRSTS has been based on principles deriving from the management of rhabdomyosarcoma, which is a clearly distinct entity. But times have changed, and both the North-American Children's Oncology Group (COG) and the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) are currently carrying out clinical trials specifically tailored to NRSTS (also drawing insight from the numerous reports on adult sarcomas).

Adult STS are malignant tumors by definition; however, their destructive local behavior and their tendency to develop distant metastases are correlated to the different degree of malignancy along histotype and tumor grade. Clinical course may widely vary, from rapidly growing tumor with lung metastases at onset to tumors with indolent growth rate, being diagnosed after removing a small swelling that has existed for several years. As a general view, it is possible to say that low-grade tumors are often locally aggressive, but unlikely to metastasize, while high-grade tumors are more aggressive and have a strong propensity to metastasize, particularly to the lung. Different histotypes with the same grade of malignancy may display the same clinical behavior. Other histotypes differ significantly for their natural history.

The important prognostic factors that help predict clinical behavior remain grade, size, and depth of the tumor in relation to the investing fascia and extent of disease at presentation. These factors form the basis for the AJCC staging system (Soft tissue sarcoma. In: Edge SB, Byrd DR, Compton CC). Stages 1 and 2 represent primary STS that are either small (<5 cm), low grade, and/or superficial to the investing fascia portending a favorable biology and clinical behavior. These are therefore treated with margin-negative resection with or without adjuvant radiation therapy resulting in 5-year survival rates of >80%. Stage 3 patients are defined as "high-risk" primaries given their size (>5 cm), high grade, and deep location with an approximately 50% risk of recurrence/metastases and death within 5 years, when treated with local treatments including surgical resection and radiation therapy [92, 95, 96]. Stage 4 disease with obvious distant metastatic disease continues to remain a challenge with 5-year survivals ranging between 10 and 20%, influenced mostly by the biology of the tumor coupled with the possibility of gross total metastasectomy.

Similar considerations may be applied to adult-type STS when occurring in pediatric age: the prognostic variables predicting survival in adult patients (tumor resectability, tumor size, depth, grade of malignancy, and histotype) are relevant also for pediatric patients [12, 97]. Population-based studies reported epidemiological differences in the incidence of the different histotypes according to ages, but not major clinical differences for the group of adult-type STS. Inferior survival was seen for patients over 50 years of age as compared to children with same disease, while no major differences in outcome were observed under the age of 50 [2, 93].

15.6.4.1 Chemotherapy for Advanced/Metastatic Disease

A relatively recent paradigm shift in systemic therapy for adult-type STS recognizes that more than 50 different subtypes of STS are indeed heterogeneous in their clinical behavior and therapeutic sensitivity, e.g., synovial sarcoma and angiosarcoma myxoid liposarcomas are far more sensitive to standard chemotherapy compared to near-resistant ones like alveolar soft-part sarcoma, clear-cell sarcoma, and gastrointestinal stromal tumor (GIST). More contemporary clinical trials have therefore concentrated on specific histology-based accrual rather than the traditional mixed bag of STS where many of the 50 subtypes were underrepresented. Acknowledging this variability, anthracyclines (doxorubicin) with or without ifosfamide continue to remain the front-line systemic

therapy for most STS. Both these agents have shown some evidence of dose response [98]. The EORTC recently reported on a randomized trial comparing single-agent doxorubicin at 75 mg/m^2 to a dose-intensive combination of doxorubicin (75 mg^2) plus ifosfamide (10 g/m^2) in 455 patients with locally advanced or metastatic STS. Response rates (14 vs. 26%, $p<0.0006$) and median PFS (4.6 vs. 7.4 months, $p=0.003$) favored the combination arm. Median overall survival (12.8 vs. 14.3 months, $p=0.076$) failed to attain statistical significance. It is important to note that the sample size calculations were based on a 10% difference in 1-year survival (50% vs. 60%) and the results revealed a 9% difference (51% vs. 60%) in favor of the doublet, thus failing the statistical significance test [99]. This allows the clinician to personalize the dose-intensive regimen where tumor shrinkage may help control symptoms or facilitate rendering the patient free of gross disease. In the United States, the typical second-line regimen includes gemcitabine and taxotere with better activity in angiosarcomas and leiomyosarcomas of gynecologic origin. A randomized phase 2 study comparing gemcitabine to its combination with taxotere reported improved PFS and OS [100]. Dacarbazine is a weak agent with marginal activity as a single agent but has been compared to its combination with gemcitabine with the doublet showing improved response rates, PFS and OS, again with better activity in patient with leiomyosarcomas [101]. Trabectedin, an investigational agent in the United States, is approved by several regulatory agencies around the world for treatment of STS and appears to have activity in liposarcomas and leiomyosarcomas [102].

15.6.4.2 Adjuvant Chemotherapy

The Sarcoma Meta-Analysis Collaboration updated individual patient data from 14 trials of anthracycline-based adjuvant chemotherapy in adult-type STS conducted between 1973 and 1990 [103]. The primary objective of this analysis was to address the major problem common to all individual trials, namely, small sample size with inadequate power to detect a clinically meaningful difference in several important endpoints. The other issues related to heterogeneity of patients with different prognostic factors (grade, size, and location) and the use of non-ifosfamide-containing chemotherapy regimens obviously could not be corrected. Nevertheless, the published results of the meta-analysis in 1568 patients with a median follow-up of 9.4 years showed a statistically significant improvement in local and distant relapse-free intervals; however, the absolute improvement in overall survival of 4% failed to attain statistical significance. The clinically favorable subset of extremity STS comprised the majority (996 of 1568) of patients, and in that group, the survival benefit was 7% and did reach statistical significance. Pervaiz et al. expanded this group of patients to include four additional contemporary trials utilizing a combination of doxorubicin and ifosfamide as adjuvant therapy and showed that the overall survival improvement was 6% attaining statistical significance. These data also showed that the relative risks of recurrence and death were significantly improved (12% and 11% respectively) with doxorubicin and ifosfamide combination compared to doxorubicin alone (9% and 5% respectively) [104]. A study conducted by the Italian Sarcoma Group supports this proof of principle. These investigators enrolled the true high-risk population (AJCC stage 3 or locally recurrent extremity STS), used a dose-intensive anthracycline and ifosfamide combination with growth factor support as adjuvant chemotherapy, and reported a 19% improvement in overall survival at 5 years [105]. Unfortunately, with longer follow-up at 7 years, the distant metastases-free survival curves lost statistical significance. On the other hand, the EORTC reported the results of their adjuvant chemotherapy trial conducted between 1995 and 2003 in 351 patients showing no benefit in RFS or OS [106]. The chemotherapy regimen included a lower dose of ifosfamide (5 g/m^2) along with doxorubicin (75 mg/m^2), and the patient population included approximately 20% with non-extremity STS and 40% had grade 2 tumors. Several nonrandomized single and multi-institutional reports have shown similar divergent results, thus perpetuating the everlasting debate about the role of adjuvant chemotherapy in adult-type STS. In this era of personalized therapy, it

would make good clinical sense to personalize the multimodality treatment for a given patient based on tumor and host factors combined with individual risk tolerance. It is clear that the most effective chemotherapy to induce a response evaluation criteria in solid tumors (RECIST) response is a dose-intensive combination of anthracycline and ifosfamide. This also improves relapse-free interval in all patients and overall survival in true high-risk extremity STS.

15.6.4.3 Targeted Therapy

The identification of activating mutations in KIT and PDGFRA genes in the late 1990s redefined gastrointestinal leiomyosarcomas to GIST. A series of clinical trials tested imatinib in metastatic GIST and improved the historical median survival of 12–18 months to 4–5 years [107]. Imatinib has also been studied in the adjuvant setting and shown to improve RFS compared to placebo [108]. The SSG18 trial tested 3 years of imatinib compared to 1 year in patients at high risk for recurrence and reported improved RFS and OS in favor of the 3-year arm [109]. Results of a single-arm phase 2 trial investigating 5 years of adjuvant imatinib are pending analysis. Sunitinib and regorafenib are also approved for use in second- and third-line therapy respectively for patient with metastatic GIST resistant or intolerant to imatinib [110, 111, 133]. These exciting developments have inspired translational research in STS with sequencing of tumors to identify druggable targets. Dermatofibrosarcoma protuberans (DFSP) is a relatively rare subtype characterized by a t(17;22) resulting in upregulation of PDGFRB. In a small cohort study, all eight patients with recurrent/advanced DFSP responded with four achieving a CR, resulting in approval of imatinib for this indication [112]. Alveolar soft-part sarcoma is a chemoresistant histology where activity of sunitinib and cediranib has been reported. A randomized trial with crossover between these two agents is ongoing [113, 114]. Solitary fibrous tumor, previously classified as hemangiopericytoma, is another chemoresistant subset where activity of VEGFR inhibitors either alone or in combination with temozolomide has been reported [115, 116]. The mTOR signaling pathway is activated in PEComas (perivascular epithelioid cell tumors) with documentation of activity of sirolimus [117]. Similarly, for clear-cell sarcomas, also known as melanoma of soft parts, there is some early anecdotal activity of c-met inhibitors. Inflammatory myofibroblastic tumor typically shows ALK rearrangement and therefore the anecdotal activity of crizotinib [118]. The latest addition to the list of available and approved drugs for STS includes pazopanib, a broad spectrum inhibitor of VEGFR. A phase 3 trial compared pazopanib to placebo in patients with advanced/metastatic STS excluding liposarcomas based on the phase 2 data and showed improvement in median PFS (1.6 vs. 4.6 months) resulting in approval of the drug [119] (Table 15.5).

15.6.5 Gastrointestinal Stromal Tumors (GISTs)

GIST are presumed to arise from a precursor cell that gives rise to the interstitial cells of Cajal, which normally regulate gastrointestinal motility and autonomic nerve function. The median age of patients with GIST is around 60–65 years. Tumor sites are the stomach in most of cases, less frequently the small bowel (presenting with gastrointestinal bleeding, abdominal mass, or intestinal obstruction) [120].

The interest on this tumor entity has rapidly increased in the last years: with the elucidation of the peculiar molecular genetic characteristics – i.e., the oncogenic mutations of the receptor tyrosine kinases (RTK), genes KIT and PDGFRA (platelet-derived growth factor receptor alpha) – GIST has became the perfect model for targeted therapy, i.e., RTK inhibition by small molecules such as imatinib or sunitinib.

The clinical management of GIST is complex as necessarily multidisciplinary. The pathological diagnosis relies on morphology, immunohistochemistry (positive for CD117 and/or DOG1) [121], and mutational analysis (for KIT and PDGFRA genes). Mutational anal-

ysis has a predictive value for sensitivity to molecular-targeted therapy (e.g., tumors with exon 11 mutation fare better than those with exon 9 mutations), as well as a prognostic value [122], so that its inclusion in the diagnostic workup of all patients with GIST should be considered standard practice. Staging systems incorporate various prognostic factors, i.e., the mitotic rate, tumor size, and tumor site (gastric GISTs have a better prognosis than small bowel or rectal GIST). Tumor rupture is an additional adverse prognostic variable [123, 124].

Surgery is the mainstay of therapy for patients with GIST, which are localized and deemed to be resectable. Adjuvant treatment should be required according to the risk of relapse [125]. Adjuvant therapy with imatinib for 3 years may be considered the standard treatment for high-risk patients, since a placebo-controlled trial demonstrated that 1-year imatinib prolonged relapse-free survival

Table 15.5 Histology-driven systemic therapies for adult soft tissue sarcomas

Histotypes	Chemotherapy		Targeted therapy	
Adult soft tissue sarcomas	Doxorubicin + ifosfamide			
Non-adipocytic soft tissue sarcomas			Pazopanib (multitargeted receptor tyrosine kinase inhibitor)	
Synovial sarcoma	Ifosfamide	Trabectedin	Pazopanib	Bcl-2 antisense oligonucleotide; FZD10 monoclonal antibody; adoptive immunotherapy using tumor-infiltrating lymphocytes against NY-ESO-1 cancer/testis antigen
Leiomyosarcoma	Gemcitabine ± docetaxel	Dacarbazine, trabectedin	Vascular endothelial growth factor (VEGF) inhibitors	Mammalian targets of rapamycin (mTOR) inhibitors
Angiosarcoma	Paclitaxel	Gemcitabine	VEGF inhibitors (bevacizumab, sunitinib, sorafenib, pazopanib)	
Myxoid liposarcoma	Trabectedin			
Well-differentiated/ dedifferentiated liposarcoma			CDK, MDM2 inhibitors	
Dermatofibrosarcoma protuberans			Imatinib	
Alveolar soft-part sarcoma			VEGF inhibitors (sunitinib, cediranib)	
Clear-cell sarcoma			Sunitinib	mTOR inhibitors; mesenchymal-epithelial transition factor (MET) inhibitors
Desmoid-type fibromatosis			Imatinib	
Chordoma			Imatinib	
Pigmented villonodular synovitis			Imatinib	
Inflammatory myofibroblastic tumor			ALK inhibitors	
PEComas			mTOR inhibitors	
Solitary fibrous tumor	Temozolomide		Sunitinib	Bevacizumab

in macroscopically resected GIST larger than 3 cm [108], and a subsequent randomized trial showed the advantage in survival rates for 3 years of imatinib as compared to 1 year of therapy [109]. Adjuvant therapy should not be considered when the risk is low, while there may be a room for shared decision-making when the risk is intermediate [127]. The clinical decision about adjuvant therapy should take into account also the mutational status, e.g., PDGFRA D842V-mutated GIST should not be treated with any adjuvant therapy, given the lack of sensitivity both in vitro and in vivo.

Pretreatment with imatinib is indicated in those cases for which R0 surgery could be achieved through less mutilating/function sparing surgery in the case of cytoreduction (e.g., to avoid total gastrectomy) [128]. In locally advanced inoperable and metastatic patients, imatinib is the standard treatment [125, 129, 130], at the dose of 400 mg daily (800 mg for patients with KIT exon 9 mutations, that fare better on a higher dose level) [131]. The therapy should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumor progression [132]. In case of tumor progression, standard second-line treatment is sunitinib (another tyrosine kinase inhibitor) [110]. Regorafenib is currently considered the standard for the third-line targeted therapy (Demetri 2013).

15.6.5.1 Pediatric GIST

GIST is extremely rare in children and adolescents. The actual epidemiology of GIST in children and adolescents is not clear: an annual incidence of 0.02 per million in children <14 years of age has been estimated by the UK National Registry of Childhood Tumors [134]. A systematic review of the literature published in 2009 was able to identify 134 cases of GIST less than 21 years of age [134]. When occurring in pediatric age, GIST often has peculiar features, i.e., tumor occurs mainly in female (70 %) and arises most commonly in the stomach (80 %); it tends to be multifocal and slow growing, with a higher rate of lymph node metastases and frequent tumor recurrence; it is often wild type for KIT or PDGFRA genes, revealing gene mutations in only a minority of cases (16 % in the abovementioned review) [134–138] and high expression of IGF1R (insulin-like growth factor 1 receptor) without IGF1R genomic amplification [139]. Wild-type tumors are about 10 % of GIST cases. They can be associated to neurofibromatosis type 1 [140] or Carney triad/Carney-Stratakis syndromes, with paraganglioma, pulmonary chondroma, esophageal leiomyoma, and specific germline mutations of succinate dehydrogenase (SDH) subunits [141]. Many of the peculiar biological and clinical characteristics of pediatric GIST are shared with tumors of young adults and probably determine a different response to treatment: the proliferation of wild-type cells would be most effectively inhibited by second-generation RTK inhibitors such as sunitinib, nilotinib, dasatinib, and sorafenib than imatinib [109, 142, 144]. As a result of these unique features, management of GIST in adolescents and young adults still remains a challenge and may need to differ from management of GIST in adults. Young patients should be cared for in specialized centers, and efforts should be implanted to develop new research as well as prospective clinical trials tailored for them.

15.7 Summary and Conclusions

The term STS includes a highly heterogeneous group of different histotypes, which are generally characterized by local aggressiveness and propensity to metastasize. These tumors include entities that are not so rare in adolescents and young adults. The treatment of these patients appears particularly complex and necessarily multidisciplinary and requires adequate expertise. It is very important to emphasize that adolescents and young adults receive better treatments within selected and experienced institutions that enroll patients into clinical trials. Cooperation between pediatric oncologists and adult oncologists is of critical importance. Getting them to cooperate is still challenging, due to differences such as various potential cultural and logistic problems (methods of data collection or classifi-

cation systems), priorities and goals, but also a sort of reluctance to cooperate, that is a further obstacle that needs to be overcome. Treatment standardization is a main goal to define the treatment options for adolescents and young adult patients. In particular, histology as well as tumor biology and clinical characteristics appear to be more important than the patients' age. Although age per se may be considered a prognostic factor in STS (and recent biological hints may suggest molecular differences in some histological type according to age), it is likely that in many case a certain histotype would behave in a similar way when arising in children, adolescents, or adults. This leads to the consideration, for example, that RMS patients, regardless of their age, would receive the better treatment when following guidelines derived from the large pediatric experience, whereas the treatment of patients with adult-type sarcomas should acquire suggestions from the body of experience gained over the years by adult oncologists.

Cooperative studies are needed to investigate the role of new therapies that are specifically tailored for molecular targets, which might be the several specific chromosomal translocations identified in STS. Unfortunately, most of these new drugs are presently tested in adult population and only few data are available in underage patients. It is important that the oncology community may find a mechanism to facilitate the transfer of potentially effective new agents from the adult population to adolescents.

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Bone Sarcomas in the Adolescent and Young Adult Population

16

David M. Thomas and Jeremy Whelan

16.1 Introduction

Primary tumours of the bone comprise the most common malignancies affecting the skeleton in the adolescent and young adult population, although they comprise collectively less than 0.2 % of all neoplasms. The overall incidence of bone sarcomas is 1/100,000 population (SEER data, 2000–2011) [37]. The most common subtypes of primary sarcomas of the bone are osteosarcoma, Ewing sarcoma and chondrosarcomas. By contrast with older populations, bone sarcomas constitute the majority of sarcomas in adolescents and young adults. Osteosarcoma and Ewing sarcoma account for 39 and 29 % of all sarcomas of the bone in the 15–39-year-old group, while chondrosarcomas comprised over 21 % of sarcomas (Fig. 16.1). The incidence of chondrosarcoma rises progressively with age, while osteosarcomas demonstrate a bimodal distribution with peaks in both adolescence and older age. Ewing sarcoma is overwhelmingly a disease of adolescence (Fig. 16.2). The incidence is higher in males for all three sarcoma types.

The clinical significance of bone sarcomas in adolescents and young adult populations lies in four major aspects. First, the treatment of bone sarcomas is complex, multidisciplinary and intensive. While osteosarcoma and Ewing sarcoma are treated with surgery and chemotherapy, chondrosarcomas are generally regarded as refractory to chemotherapy and radiotherapy and are treated by surgery. Second, bone sarcomas contribute a disproportionate burden of morbidity and lethality attributable to cancers occurring in this group. Third, particularly for Ewing sarcoma, bone sarcomas are treated at both paediatric and adult institutions, and age-dependent differences in overall survival have been demonstrated. Finally, the morbidity and excess mortality associated with survivors of bone cancer in the AYA group are poorly understood, but likely highly significant contributors to the community burden of these diseases.

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16.2 Osteosarcoma

16.2.1 Epidemiology and Aetiology

Osteosarcoma arises as a consequence of the malignant transformation of cells of the osteoblast lineage. The age-adjusted incidence is

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0.33/100,000 population, and the peak incidence is in adolescence and young adulthood, although there is a second peak in old age. Males outnumber females in the AYA range by 1.4:1. The first peak coincides with the onset of peak bone growth and its aftermath, while the second peak occurs in association with environmental exposures like radiation or in association with increased states of bone turnover, like Paget's disease of the bone. These features suggest that osteoblast proliferation

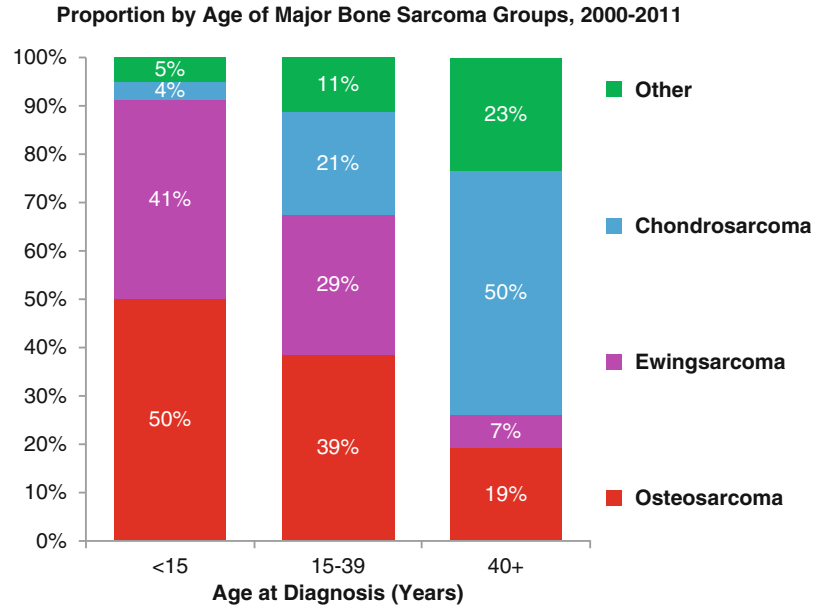

Fig. 16.1 Proportion of major bone sarcoma groups by age (SEER, 2000–2011)

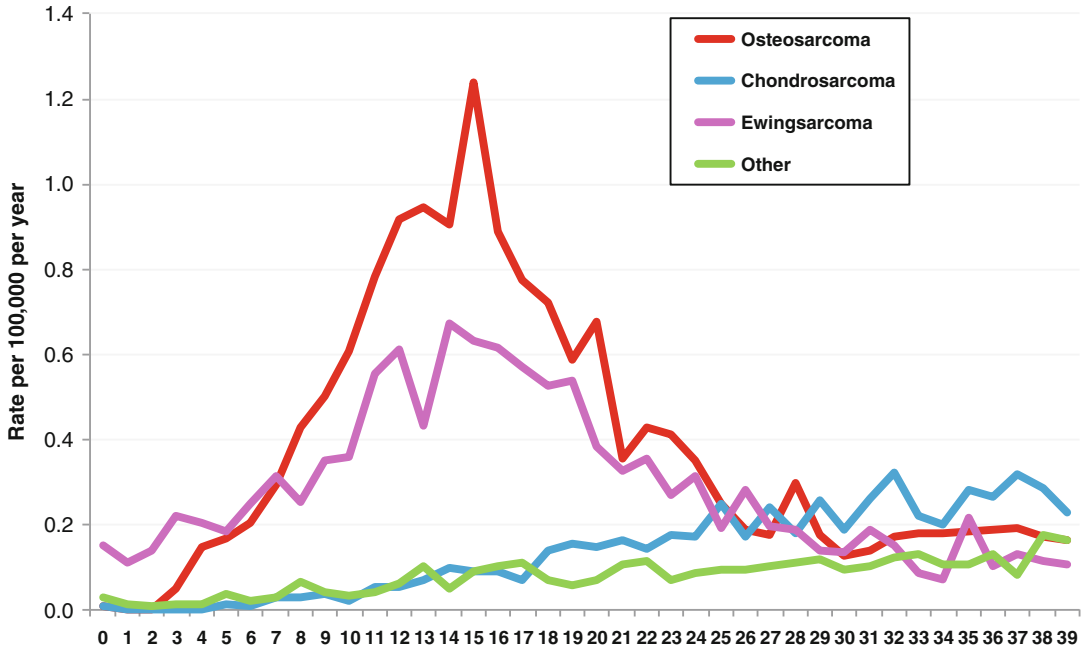

Fig. 16.2 Bone incidence by type and age from SEER (2000–2011)

is a factor in the development of osteosarcoma. Other benign predisposing lesions associated with osteosarcoma include fibrous dysplasia, bone infarction, chronic osteomyelitis, giant cell tumour of the bone and osteogenesis imperfecta [10]. The most common sites of disease are the long bones of the lower limb (68%), the upper limb (10%) and the skull (9%; Fig. 16.3).

There are both environmental and genetic risk factors for the development of osteosarcoma. The strongest known environmental risk factor is prior exposure to radiation, accounting for less than 5% of all cases, but particularly in older patients [4]. The risk of radiation-induced osteosarcoma is increased in the context of heritable syndromes associated with osteosarcoma. The best known of these is the retinoblastoma syndrome, in which the risk of osteosarcoma is greatly increased by exposure to ionising radiation [22]. Other heritable syndromes associated with osteosarcomas include the Li-Fraumeni syndrome, associated with germline mutations in *TP53*; and the helicase syndromes, which are associated with developmental features (Bloom syndrome, associated with mutations in *BLM*; Rothmund-Thomson syndrome, associated with mutations in *RECQL4*; and Werner syndrome, associated with mutations in *WRN*) [34]. Importantly, the likelihood of genetic factors contributing to cancer risk is greater in younger patients and may have clinical implications for choice of therapy. Taking a good family history is therefore important in the assessment of AYA with any sarcoma.

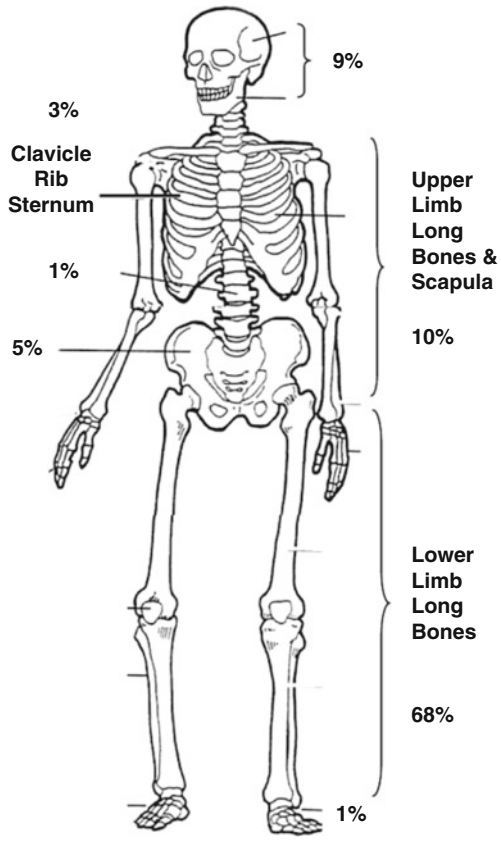

Fig. 16.3 Skeletal location of osteosarcoma primary tumours

16.2.2 Pathology and Biology

There are several well-described histologic varieties of osteosarcoma, but they are usefully divided into high-grade and low-grade tumours. The most common subtype is high-grade central osteosarcoma, which arises typically as a large, metaphyseal lesion of the long bones with intramedullary extension. Histologically, central high-grade osteosarcoma comprises malignant osteoblasts associated with neoplastic osteoid (disorganised in architecture). Further subcategorisation recognises osteoblastic, fibroblastic, chondroblastic and giant cell-rich variants, without clear clinical associations. High-grade central osteosarcoma is characterised by complex, unstable and aneuploid genotypes. Telangiectatic osteosarcoma is a high-grade tumour characterised by large, vascular and hemorrhagic spaces, typically arising within the metaphyses of the long bones. They account for less than 4% of all osteosarcomas. Small cell osteosarcoma account for less than 2% of all osteosarcomas and are characterised by small cells with lacelike malignant osteoid production. The main differential diagnosis for small cell osteosarcomas is Ewing sarcoma. Periosteal and high-grade surface osteosarcomas are tumours arising from the bone surface and comprise less than 5% of all osteosarcoma. All of these high-grade lesions are typically treated with chemotherapy as well as surgery.

Distinction between periosteal osteosarcoma, usefully regarded as of intermediate grade and with a lower metastatic potential, and high-grade surface osteosarcoma which behaves akin to high-grade central osteosarcoma is sometimes challenging. The value of chemotherapy for periosteal osteosarcoma is doubtful [15].

Low-grade central and parosteal types account for 1–2 % of all osteosarcoma and connote a good prognosis. They arise either as central or surface lesions and are characterised by relatively well-differentiated cells within osteoid that resembles fibrous dysplasia. Genetically, they differ from the high-grade bone tumours in being cytogenetically stable and relatively diploid and are typically associated with high-level amplification of MDM2 and CDK4 (2013b). The outcomes for this group of osteosarcomas are excellent, with 5-year survival rates in excess of 90 %. They are typically treated with surgery alone, unless there is evidence of de-differentiation.

16.2.3 Diagnosis and Staging

Clinically, osteosarcoma typically presents as unremitting pain that is worse at night and swelling and deformity. In some cases, patients present with pathologic fracture. The initial diagnosis is often made on plain radiology, which typically shows anatomic distortion and bony sclerosis or lucency, with or without evidence of fracture. As a general rule, if a diagnosis of osteosarcoma is suspected on plain radiology, the patient should be referred to an experienced orthopaedic oncologist working in a multidisciplinary team. This is an important point for adolescent and young adults, who—with in contrast with younger children—may be diagnosed outside specialised sarcoma centres. Histologic confirmation of the diagnosis is made either on open or core biopsy. It is important that the biopsy is performed with the awareness of the possible diagnosis, since the biopsy site and track can influence subsequent surgical planning.

Staging should involve comprehensive CT and MR imaging of the entire affected bone, since osteosarcoma is not infrequently associated with skip metastases. These are metastatic deposits that are located within the bone in which the osteosarcoma arises, but are not contiguous with the primary site. They connote an adverse outcome. In addition, a CT scan of the chest is also indicated, as the chest is the most common site of metastatic deposits. Most major referral centres may also perform a PET scan or technetium scintigraphy to identify occult bony metastases, since the second most common site of metastatic disease is to other bony sites. The outcomes for osteosarcoma that is metastatic at diagnosis are very poor.

16.2.4 Treatment

The introduction of adjuvant chemotherapy more than tripled survival for non-metastatic osteosarcoma [18]. Surgery remains critical to cure, and radiotherapy is infrequently used for local therapy, either alone or as an adjuvant. For non-metastatic, high-grade osteosarcoma, treatment most commonly involves preoperative chemotherapy with a backbone that involves doxorubicin, cisplatin and methotrexate (MAP). There has been debate as to the value of methotrexate, but it is included in most current regimens in young patients [6]. Regimens including this triad yield 5-year survival rates in excess of 70 % for patients with resectable disease. Recent clinical trials have tested the role of adjuvant mifamurtide (muramyl tripeptide), postsurgical response-adapted therapy in poor responders to neoadjuvant (MAP) and adjuvant interferon in good responders. Over 660 patients with localised osteosarcoma were treated preoperatively with MAP and then randomly assigned to receive ifosfamide and/or mifamurtide. The addition of mifamurtide without ifosfamide significantly improved 6-year OS from 70 to 78 % ($P = 0.03$) [27]. Unexpectedly, this effect was not observed in the arm containing ifosfamide, perhaps due to an unexplained drug interaction. Mifamurtide is currently only approved for use in the EU and other countries including Mexico, Libya,

Ukraine, Venezuela, Israel and South Korea but not in North America.

After metastasis at diagnosis, the most powerful known prognostic factor for overall survival in patients with osteosarcoma is response to neoadjuvant chemotherapy. The 5-year overall survival for good responders is over 80 % compared to 52 % for those with a poor response [6]. There appears to be a minor effect of age of onset on outcomes following treatment of resectable osteosarcoma. This is perhaps best illustrated in a study which pooled data on 4,838 patients from several study groups in which adolescents and adults appeared to have slightly worse outcomes than for children (hazard ratio 1.14, $P=0.03$; [6]. Interestingly, most of the difference appears linked to gender, with males having worse responses than for females (HR 0.85, $P=0.003$). A smaller analysis of COG trials reported a much stronger effect of age and weaker influence of gender but did not analyse gender, age and toxicity as in the Collins study [20]. It is perhaps worth noting that these are 'clinical trial' populations and in an unselected population registry-based studies the influence of increasing age is clearly apparent [8, 36]. The EURAMOS-1 trial, conducted as a transatlantic collaboration between the Northern American and European co-operative trial groups, randomised patients following neoadjuvant MAP and surgery to either a good response arm or a poor response arm. The good response arm demonstrated more than 90 % necrosis of tumour cells in the postoperative specimen, where the poor response arm demonstrated less than 90 % necrosis. In the EURAMOS-1 trial, good responders were randomised to receive a year of adjuvant pegylated interferon-alpha or to continue with MAP. Recently published results suggest no benefit for the interferon arm [2]. Those in the poor response arm were randomised to receive a regimen containing ifosfamide and etoposide or further MAP. The initial results have been reported in abstract form to show no benefit and increased toxicity for the arm containing ifosfamide and etoposide [25]. This unexpected and important result suggests that, although response to preoperative chemotherapy is a powerful prognostic indicator, adaptation of postoperative chemotherapy as tested in EURAMOS-1 does not alter outcomes.

Outcomes for metastatic osteosarcoma at diagnosis, or following early relapse, remain poor (5-year overall survival for those with metastases at diagnosis 26 % compared to 63 % for those without metastases, $P<0.001$; [6]). However, it is important to note that oligometastatic disease to the lungs that occurs more than 12 months following definitive therapy can be managed using metastasectomy with curative intent [13, 26].

16.2.5 Late Effects

An institutional cohort of 883 evaluable patients with non-metastatic osteosarcoma, with a median age at diagnosis of 15 years, was followed for a median of over 10 years, with 310 deaths [24]. The major causes of death were recurrent osteosarcoma (22 % of deaths from recurrent osteosarcoma occurred after 10 years of follow-up), second malignant neoplasms (5 %) and cardiac impairment (2 %). Overall, 36 survivors (6 %) developed a second neoplasm, after a median interval of 8 years. For a median of 9.5 years from diagnosis, fertility was impaired in 47/54 evaluated male patients (31/44 post-pubertal patients azoospermic) and was probably increased by cumulative ifosfamide doses. It is likely that these patients were selected on the basis of clinical infertility and do not represent the rates amongst all male survivors. Amongst female survivors, 6/207 (2.8 %) experienced permanent amenorrhoea, most of whom were over 35 years of age at diagnosis. Since this survivorship cohort had a median age in their twenties, long-term late effects will undoubtedly continue to accumulate, probably varying on the basis of treatment regimen and patient factors including genetic predisposition to cancer. The consequences of surgery are likely significant, and rehabilitation programmes are an important part of management of this disease.

16.3 Ewing Sarcoma

16.3.1 Epidemiology and Aetiology

Ewing sarcoma is a small round cell sarcoma of uncertain histogenesis, but probably arising in a mesenchymal stem cell [35]. Ewing sarcoma (ES) typically arises in the bone, but may arise within any tissue. Most ES are characterised by recurrent translocations involving *EWSR1* and a number of partner genes. The age-adjusted incidence of Ewing sarcoma is 0.2/100,000 of the population, and 80 % of cases arise under 20 years of age [37]. Ewing sarcoma does occur in individuals over 30 years of age, but this is rare. There is a slight male-female preponderance (1.4:1). There are no known environmental associations. Although neither familial clustering nor a genetic basis for ES has been identified, EW is more common in Caucasian than African Americans [40], and atypical inheritance patterns have been observed that depart from Mendelian models [31].

ES is a cancer in which there is a strong age-dependent effect on survival [14, 21]. Children have a markedly better survival from ES than adolescents and young adults. This effect is at least partly independent of patterns of care, since on the same randomised trial, the event-free survival for those over 17 years of age was 44 % compared to 70 % for those under 10 years of age (relative risk 2.5, $P=0.001$) [14]. Gender may also play a role in determining outcomes for older patients, with males having worse survival than females [21].

16.3.2 Pathology and Biology

ES typically occurs in the diaphyseal regions of the long bones, pelvis or ribs, but may occur at almost any anatomical site. The site of disease is important prognostically, since outcomes are worse for axial compared to appendicular tumours [14]. Most cases comprise homogenous, small, round cells with scant cytoplasm and usually little matrix (2013b). They are typically CD99 (MIC2) positive immunohistochemically, although this marker is neither always present nor specific for ES. The diagnosis is typically made on detection by fluorescence in situ hybridisation or PCR of rearrangements involving *EWSR1* that result in fusion genes. The most common partner is the transcription factor *FLI1* (85 %), but Ets family members including *ERG*, *ETV1*, *FEV* and others have been described. ES bears a low burden of mutations, including in the canonical cancer genes, and evidence is gathering that the fusion gene may function epigenetically [36]. A recent finding of interest has been the exquisite sensitivity of ES cell lines to poly ADP-ribose phosphate inhibitors [12], although the basis for this is not understood (Fig. 16.4).

16.3.3 Diagnosis and Staging

ES typically presents with persistent pain, often worse at night, with or without a mass or deformity. In addition, systemic features are also observed, including fever and weight loss.

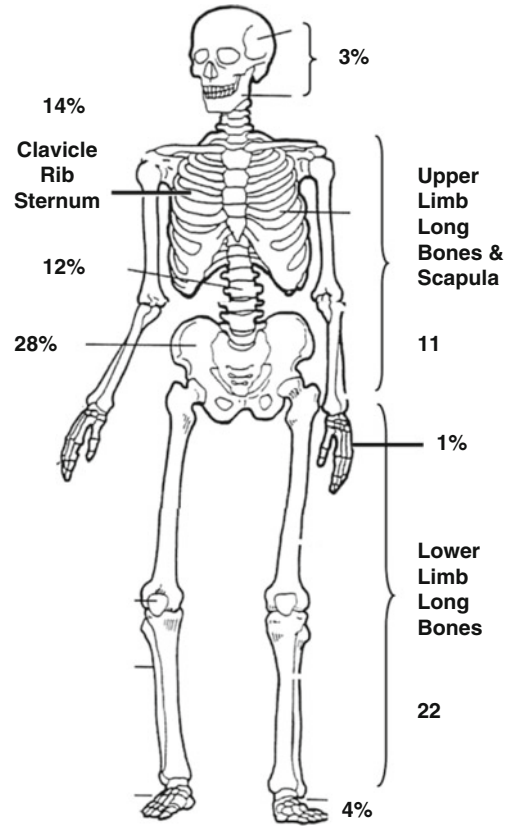

Fig. 16.4 Skeletal location of Ewing sarcoma primary tumours

Pathological fractures are not common [9]. Plain radiology and CT scanning usually show a mixed lytic/sclerotic lesion with a permeative pattern of bone destruction. Pathologic confirmation of the diagnosis may be made by core or excisional biopsy. Staging typically involves CT and MRI of the affected part, including draining regional nodes as this sarcoma may sometimes spread via the lymphatic route. Lung metastases comprise 35 % of metastatic sites, while 13 % had bone metastases, and 7 % had marrow infiltration. CT scanning of the chest, bone scan or PET scan for occult bony sites of disease and bone marrow biopsy are recommended. Patients with metastatic disease have a markedly worse survival than those without (22 % 5-year event-free survival compared to 69 % for patients with non-metastatic disease [14]). Molecular detection of ES in bone marrow aspirates was associated with a 53 % disease-free survival compared to 80 % in those patients who were clear of disease [32].

16.3.4 Treatment

The 5-year survival following local therapy for ES (with either surgery or radiotherapy) was 22 % [30]. The nature and consequences of surgery are under-explored in the AYA population and depend on the site and scale of the operation required for complete resection with adequate margins. It is worth noting the major nature of pelvic and other axial tumour surgeries. Current results for neoadjuvant chemotherapy with local control exceed 70 % for children with non-metastatic disease [14, 23, 38]. In addition, response to preoperative chemotherapy correlates with overall outcomes, reinforcing the importance of chemotherapy to overall outcomes for ES [7]. The backbone for most regimens includes doxorubicin or actinomycin D, vincristine and cyclophosphamide, alternating with ifosfamide and etoposide (VDC/IE) [14]. The addition of ifosfamide and etoposide improved survival for patients with non-metastatic disease, but not for patients with metastatic disease at diagnosis. An alternative regimen utilises vincristine, ifosfamide, doxorubicin and etoposide (VIDE) as induction prior to local therapy and a postoperative regimen of vincristine, actinomycin D and ifosfamide or cyclophosphamide (VAC/VAI) [23]. The relative merits of ifosfamide versus cyclophosphamide remain unclear.

More recently, the compression of the VDC/IE schedule from every 3 weeks to every 2 weeks was shown to be tolerable and more effective [39]. The 5-year event-free and overall survival for the interval compression schedule was 73 % and 83 %, respectively, compared to 65 % and 77 % for the standard arm. There are two important caveats to this study. The first was that the study was only able to achieve marginal statistical significance for event-free survival ($P=0.048$), while the overall survival did not reach formal thresholds for significance ($P=0.056$). The second more important issue for AYA is that ES trials are overwhelmingly dominated by paediatric or adolescent cases: 88 % younger than 18 years in one case [39] and 87 % in another [14]. Given the worse outcomes overall for older patients in both of these studies, and the lack of numbers to enable subset analysis for the reasons behind this effect, it is unclear whether it is reasonable to extrapolate findings from the cohort as a whole to the older age group. Nonetheless, in the absence of better data on the older population, it is reasonable to use treatment recommendations based on these trials.

For relapsed patients, regimens involving irinotecan and temozolomide [5] or cyclophosphamide and topotecan [16] have yielded response rates between 30 and 60 %. Despite activity, response duration is typically short. There is no conclusive evidence to support high-dose therapy either in relapse or in high-risk disease at diagnosis. Recent studies suggest substantial activity of agents that target the insulin-like growth factor pathway in a modest subset of patients with relapsed disease [28, 29]. Further development of these compounds has been challenging because it has not been possible to predict responders and nonresponders. The role of the PARP inhibitors is currently a matter for clinical trials.

16.3.5 Late Effects

As a general rule, there is substantial overlap between the late effects seen in ES and osteosar-

coma survivors. In a cohort of 543 ES survivors followed up for a median of over 7 years, 220 had died [24]. Of these, 212 (96 %) died from disease, 5 (2 %) from second neoplasms and 3 from complications of therapy. It is important to note that the relapse rates from ES have different kinetics from osteosarcoma, with a higher proportion of relapse continuing after 10 years of follow-up. Overall, 15 patients developed a second neoplasm with a median interval of 7 years. While no patient in this study died of cardiomyopathy, 1.3 % demonstrated a reduction in cardiac function, and half of these cases required therapy. Infertility was tested in 23 male patients in this cohort, with impaired fertility in 91 % of this highly selected population. Of 99 female survivors, 25 had permanent amenorrhea, which may reflect high-dose therapy or the use of pelvic radiotherapy, since the pelvis is not an uncommon site of disease. As with osteosarcoma, the long-term sequelae of local therapies on the limb and overall function are likely to be significant, and rehabilitation should form a component of early follow-up.

16.4 Chondrosarcoma

16.4.1 Epidemiology and Aetiology

Chondrosarcomas are malignant neoplasms derived from chondrocytes. The overall incidence of chondrosarcoma is 0.2/100,000 of the US population. Amongst the AYA population, their incidence rises with progressive age, such that more than 50 % occur between 30 and 39 years of age. The majority of chondrosarcomas occur in older patients. Males are more commonly affected than females in the AYA group. Most (85 %) of chondrosarcomas arise in the absence of pre-existing lesions and are called primary chondrosarcomas. Secondary forms of chondrosarcoma arise in enchondromas or osteochondromas, which may be solitary or part of a recognised syndrome (Maffucci syndrome and Ollier's disease) [1]. These syndromes are congenital but not hereditary. Secondary chondrosarcomas tend to arise earlier in younger patients and may therefore be expected to be more frequent in the AYA population. Chondrosarcomas represent a spectrum of malignancy and are generally resistant to both chemotherapy and radiotherapy. A rare subtype, mesenchymal chondrosarcoma, is more common before the age of 40 years and may have differing biological characteristics [11, 38].

16.4.2 Pathology and Biology

Chondrosarcomas are formed by malignant transformation of cells of the chondrocyte lineage and produce variable amounts of cartilaginous matrix. They arise at any skeletal site, but most commonly in the pelvis, femur and shoulder girdle. Chondrosarcomas may be divided into low- (61 %), intermediate- (36 %) or high-grade (3 %) lesions or a de-differentiated form [3]. These categories correspond to clinical behaviour, with low-grade lesions having a very high cure rate and rarely metastasising, while de-differentiated chondrosarcomas have a poor prognosis and frequently metastasise. There is a tendency for untreated lesions to progressively de-differentiate over time. Within the bone, chondrosarcomas may arise at the endosteal surface (central chondrosarcomas) or from the surface of the bone (peripheral or periosteal chondrosarcomas). Recently central chondrosarcomas were found to harbour mutations in the *IDH1* and *IDH2* genes in more than 50 % of cases, including primary and secondary types [1]. In addition, a modest frequency of potentially actionable mutations has been identified in hedgehog pathway genes [33].

16.4.3 Diagnosis and Staging

As with other bone tumours, patients with chondrosarcoma present with pain, swelling or deformity. Patients with low-grade lesions may present with a long history of deformity at peripheral sites, unless complicated by fracture. Radiologic features include cortical erosion,

medullary sclerosis and evidence of pre-existing enchondroma or osteochondroma. A core or excisional biopsy is required to confirm the diagnosis, which may be suspected on radiology. A notable point is the difficulty in distinguishing low-grade tumours from benign lesions. The distinction in some cases requires comparison with the radiologic findings, since the morphology of benign enchondroma and low-grade chondrosarcoma may be identical. In this setting, the diagnosis of low-grade chondrosarcoma depends on radiologic evidence of destruction of the bone cortex or the size of the cartilage cap in the case of osteochondroma. Intermediate- or high-grade chondrosarcoma is confirmed by the histologic findings of increasing cellular atypia and cellularity. De-differentiated chondrosarcoma histologically may resemble undifferentiated pleomorphic sarcoma, with little evidence of matrix production.

Staging procedures should include CT and MRI of the affected part. While metastasis from low-grade lesions is almost never seen, for larger intermediate-grade, high-grade and de-differentiated chondrosarcoma, CT scan of the chest is important to exclude systemic metastasis.

16.4.4 Treatment

In all non-metastatic cases, treatment is based on surgical resection of the disease. There is no evidence for benefit from adjuvant therapy with radiotherapy or chemotherapy. For individuals who have metastatic disease at diagnosis, radiotherapy may offer palliation, along with surgical management of symptomatic or dominant metastatic sites. There is no evidence for activity of chemotherapy in this setting, and novel therapies are urgently needed. Recent trials of hedgehog pathway inhibitors were disappointing [17]. The early clinical development of IDH1 and IDH2 inhibitors holds theoretical promise for these diseases. Patients with metastatic disease should be offered clinical trials.

By contrast, the rarer mesenchymal subtype may be more sensitive to chemotherapy [11].

16.4.5 Late Effects

The major problem with low- and intermediate-grade chondrosarcoma is inadequate local excision and recurrence, so close monitoring of cases is required. In cases of secondary chondrosarcoma, monitoring may include regular surveillance of other sites of disease, clinically and radiologically. The long-term physical and psychological consequences for survivors relate to the morbidity of surgery required for cure. The nature and significance of long-term surgical sequelae are not well described and in particular the role of early and aggressive rehabilitation in modifying outcomes.

16.5 Summary

Bone tumours are a major cause of mortality in the AYA population and a source of lifelong morbidity amongst survivors. Treatment for all bone tumours in this age group depends on effective local therapy, which for the most part involves surgery with or without radiotherapy. In this chapter, we have focused on the details of often intensive systemic therapies, but it is important to note the lifelong consequences of surgery, both functionally and psychologically. Collaboration on protocols that are appropriate for all young AYA affected by these diseases has been a hallmark of bone sarcoma clinical trials in recent decades. Unfortunately, there is some evidence for worse outcomes for AYA than for children. There is evidence for a strong genetic basis for young-onset sarcomas and a high rate of second malignant neoplasms in this group. The rates of cardiac dysfunction appear low (<5 %) amongst those who receive chemotherapy, but it is important to note that we do not have good long-term data on cardiac sequelae, which may be expected to increase as survivors reach ages at which cardiovascular diseases become more common. In addition, the effects of radiotherapy and chemotherapy on fertility are probably more significant amongst women between 30 and 39 years of age, for whom early menopause may be limiting for family planning.

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Cancer of the Kidney, Bladder, and Prostate

17

Michael Leahy, Filippo Spreafico, and Archie Bleyer

Abstract

In the AYA population, kidney and bladder cancer account for 5 % and 2 % of all invasive cancers in male and female AYAs, respectively, and in the United States, prostate cancer has emerged as a contributor to the AYA cancer scene in older AYAs. The incidence of both kidney and prostate cancer had had a distinct increase during the last two decades. Whereas the increase in kidney cancer is at least partially due to overdiagnosis, the reason for the increase in prostate cancer is not known. Men diagnosed with prostate cancer before 40 years of age are nearly three times more likely to have metastatic disease at the time of diagnosis than in those diagnosed between the ages of 40 and 80, whereas at all ages, renal cell carcinoma and bladder cancer are predominantly nonmetastatic at diagnosis. The survival rate in men with prostate cancer has not improved in 15- to 29-year-olds to the extent that it has in men over 30 years of age. Both renal cell carcinoma and prostate cancer have a worse survival in younger AYAs than those toward the upper end of the AYA age range, overall and stage for stage. Bladder cancer has a better prognosis in AYA females than in older women. To what extent the biology of these cancers is different in AYAs than in older adults remains to be determined.

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17.1 Kidney Cancer

17.1.1 Biology, Pathology, Etiology

Renal tumors in adolescents and young adults aged 15–39 years include several different histotypes, but registration in the SEER database does not distinguish between them. However, taken as a single cohort, renal cell carcinoma (RCC) predominates and is the main contributor to the epidemiologic statistics quoted. However, within this age range, there is a significant change of the proportion of cases attributed to each histotype with RCC being extremely uncommon in the under 20s with a rising incidence to become the most common type overall. In comparison, Wilms' tumor (WT), which is predominantly seen in childhood, has a decreasing incidence through the age range.

For completeness, malignant neoplasms of the kidney in this age range include renal cell carcinoma (RCC), papillary renal carcinoma, chromophobe carcinoma, collecting duct carcinoma, transitional cell carcinoma (TCC) of the renal pelvis, and Wilms' tumor (nephroblastoma). In addition, lymphomas and sarcomas of various sorts can arise in the kidney. The histopathologic diagnosis of a renal tumor in an adolescent or young adult can be challenging, not only for general pathologists who are usually not familiar with the histopathologic features and variants of these tumors, but also for pediatric pathologists. It is therefore essential to apply appropriate immunohistochemical and molecular biology studies in order to clearly identify the histotype which may very significantly affect the choice of treatment and the predicted outcome.

A detailed family history should be taken to identify families with inherited syndromes associated with an increased risk of renal malignancy such as von Hippel-Lindau syndrome and RCC.

17.1.2 Translocation RCC

The term "translocation RCC" is now used to describe a pathological entity defined by the presence of a pathognomonic chromosomal translocation. Although translocation RCCs were initially described as typically adolescent tumors, it transpires that adult translocation RCCs may overall vastly outnumber pediatric cases because of the much higher incidence of RCC in the adult population. A key question is whether translocation RCC represents the same disease across age groups. If this is the case, adult trials on new drugs – where increased resources have been allocated to characterize these tumors – might open to AYA patients as well.

Translocation RCC is characterized by translocations involving Xp11.2 chromosome or, less frequently, 6p21, likely comprise the majority of RCCs in adolescents [1–4]. On the basis of clinical, morphological, immunohistochemical, and genetic similarities, the 2013 International Society of Urologic Pathology Vancouver classification of renal neoplasia grouped these tumors together under the heading of "MiT family translocation RCC" [5]. The MiT subfamily of transcription factors includes TFE3, TFEB, TFC, and MiTF.

Diagnostic challenges with TFE immunohistochemical staining, lack of consistency in translocation RCC morphology, and infrequent use of specific FISH assays likely explain the fluctuating proportion of cases within the different reports. It is realistic to assume that many adolescent RCCs reported as papillary or clear cell types in previous series would, if reexamined today, turn out to be unrecognized translocation RCCs.

Different gene fusions are possible, which might partially explain slight differences in clinical signs and the tumor's morphologic appearance. The proportionally much smaller group of translocation RCCs in adults (accounting for less than 5 % of renal tumors) probably display a different clinical behavior from younger patients, with aggressive advanced-stage disease and widespread systemic metastases at diagnosis [4, 6]. Translocation RCCs in adolescents have been described in some reports as being indolent, even when the lymph nodes were involved [2, 3, 7], but some authors have warned that their clinical course may be aggressive

[8]. It should be remembered that, as these tumors have only been recently recognized, their natural history is still poorly defined and extended follow-up is recommended because, regardless of the age of the patient, translocation RCCs seem to have the potential to metastasize also after many years.

17.1.3 Epidemiology

17.1.3.1 Incidence

Recent analysis of the US SEER data [51] for this publication shows that the incidence of renal cell carcinoma (ICD-O-3 8310/3-8319/3) in AYAs increases exponentially with age in males and until age 35 in females (Fig. 17.1, left panel inset). Above age 35, renal cell carcinoma predominates in men, but in AYAs, it has a higher incidence in females (Fig. 17.1, left panel). At all ages, localized disease is the predominant stage at diagnosis (Fig. 17.1, right panel), with more than 80 % of AYAs presenting with localized disease and 8 % each with regional and distant metastatic disease at diagnosis (Fig. 17.1, right panel inset). Whereas in older adults the incidence of renal cell carcinoma is greatest in Hispanics and blacks, in AYAs, it is greatest in non-Hispanic whites and native North Americans (Fig. 17.2). At all ages, the incidence is lowest in Asians/Pacific Islanders (Fig. 17.2).

17.1.3.2 Incidence Trends

In older adults, there has been a steady increase in incidence since at least 1975 (Fig. 17.3, right panel). In AYAs, the incidence remained the same until 1992 (Fig. 17.3, left panel), when a marked increase in incidence began to be seen. Since 1992, the rate of increase in incidence has been much greater in AYAs than in older adults (Fig. 17.4, upper panel), especially in females and particularly in females 15 to 25 years of age (Fig. 17.4, lower panel). The root cause of these changes is unknown, but this pattern would be seen if there had been a recent increase of exposure of the population to an environmental agent which increased risk.

17.1.4 Clinical Presentation and Diagnosis

The diagnosis of renal tumors in AYAs is challenging. The classic triad of local symptoms of the primary malignant renal tumor (hematuria, flank mass, and abdominal pain) may be absent or appear late. Metastatic disease may present with local symptoms from metastatic sites or with generalized symptoms, like weight loss, cachexia, fevers, and sweats. Symptoms are thus nonspecific and clinical examination is relatively insensitive at detecting a small tumor. The differential diagnosis is likely to be dominated by nonmalignant conditions, first of all urinary tract infections. Inevitably this contributes to a delay in diagnosis for many patients. For example, hematuria in this age group is usually due to urinary tract infection. In older patients, in whom malignant disease is more likely, hematuria is routinely a trigger for full investigation to exclude malignant disease by imaging, cytology, and endoscopy. However, in the younger patient, empiric treatment with a suitable antibiotic is reasonable for the first episode, although assessment should include microbiological examination of the urine. Patients with recurrent or persistent hematuria, especially when no infective agent is identified, should be referred for further investigation including a pelvic examination, renal tract ultrasound, urine cytology, and eventually cystoscopy.

If a renal tumor is suspected, diagnostic imaging studies play a central role in the evaluation of initial extent of disease and for planning surgery or monitoring the response to therapy, in cases in which a systemic preoperative treatment is indicated. Parameters that should be carefully evaluated are the extent of the tumor within and behind the kidney, involvement of the contralateral kidney, the presence of intravascular tumor thrombosis (renal and cava veins), and the presence of retroperitoneal lymph node involvement.

The initial radiographic study is usually an abdominal ultrasound examination. Cross-sectional imaging, either contrast-enhanced computed tomography or magnetic resonance imaging of the abdomen, is then recommended to further evaluate the nature and the extent of the renal mass. Despite thorough clinical and radiographic evaluation,

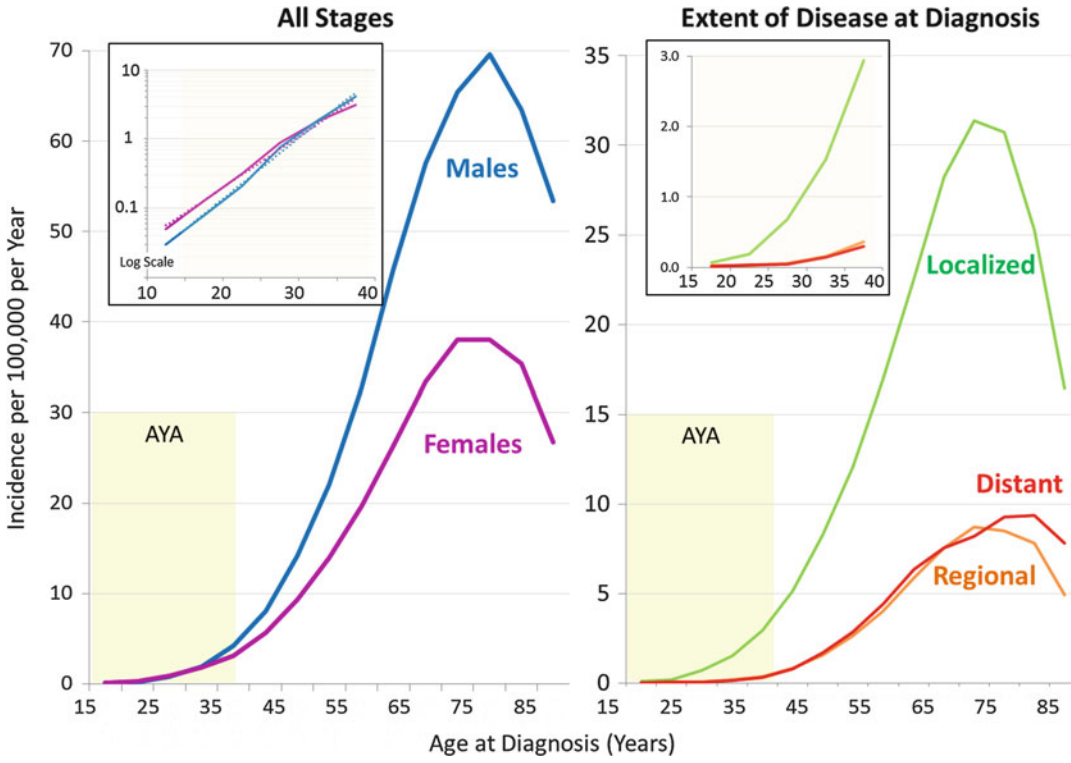

Fig. 17.1 Incidence of renal cell carcinoma by age, sex (*left panel*), and extent of disease (*right panel*) at diagnosis, 2000–2011, SEER18. The *left panel* inset has a log scale for the y-axis and exponential regressions (*dotted lines*)

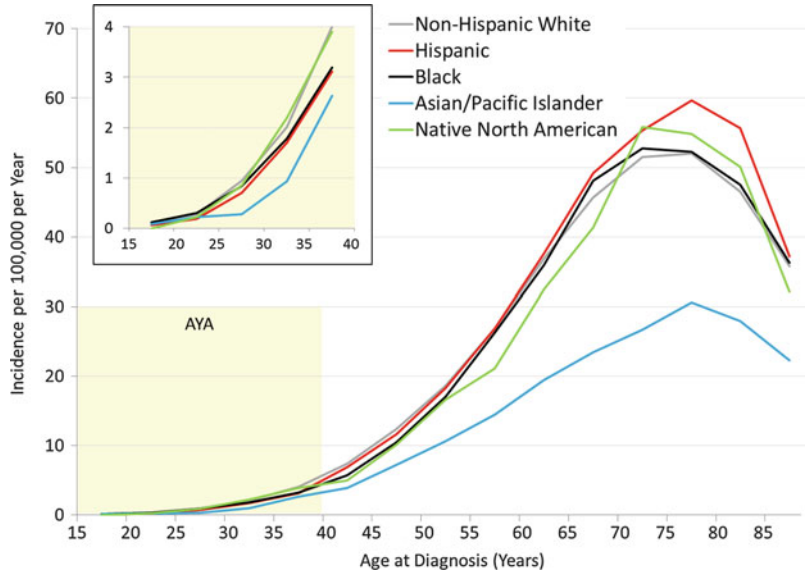

Fig. 17.2 Incidence of renal cell carcinoma by age and race/ethnicity, 2000–2011, SEER18

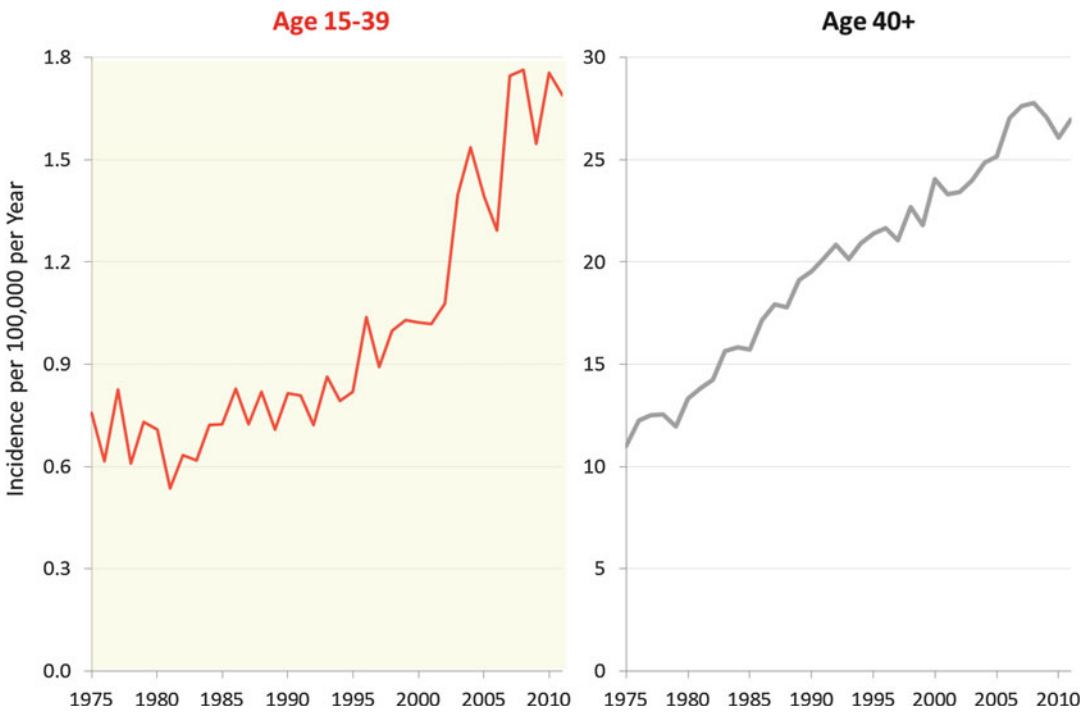

Fig. 17.3 Annual incidence of renal cell carcinoma by age, 1975–2011, SEER9

some renal masses will remain indeterminate, and their management is subject to individual clinical opinions. Careful correlation of clinical and imaging findings may facilitate the preoperative diagnosis of renal lesions; however, a percutaneous needle biopsy might be indicated to correctly plan the following steps toward diagnosis and treatment, especially in this age group when tumors different from Wilms' tumor are more frequently seen.

17.1.5 Treatment

Apart from Wilms' tumor, which is usually highly chemosensitive, surgery remains the mainstay of curative therapy for patients with renal tumors in this age group. Complete surgical removal at the earliest possible occasion remains the approach most likely to lead to a full recovery.

17.1.5.1 Wilms' Tumor (WT)

The literature suggests that outcome for AYAs with WT is worse than that for pediatric patients [9]. There are various possible explanations for this observation. In the UKW3 trial for patients with WT, increasing age was an independent poor prognostic factor (although the age categories studied were less than 2 years, 2–4 years, and greater than 4 years, respectively, and very few patients were older than 15 years) [10]. Since WT is very sensitive to chemotherapy, children presenting with advanced-stage or metastatic disease are curable, with long-term survival over 70 % [11]. The possibility that chemosensitivity may reduce with age is supported by case reports of older patients who failed to respond to treatment [12, 13], but the consensus remains that pediatric chemotherapy protocols should still be followed where possible and can be successful in some cases [12, 14]. In the largest series in the literature of adult WT, the overall survival of 17 patients was 67 % [15]. Of note, a significant proportion of AYAs diagnosed with WT are delayed in starting postoperative chemotherapy for various reasons, and this seems to represent a negative prognostic factor [9]. In addition, AYA series on WT report a higher incidence of advanced-stage disease (stage III or IV) than that noted in

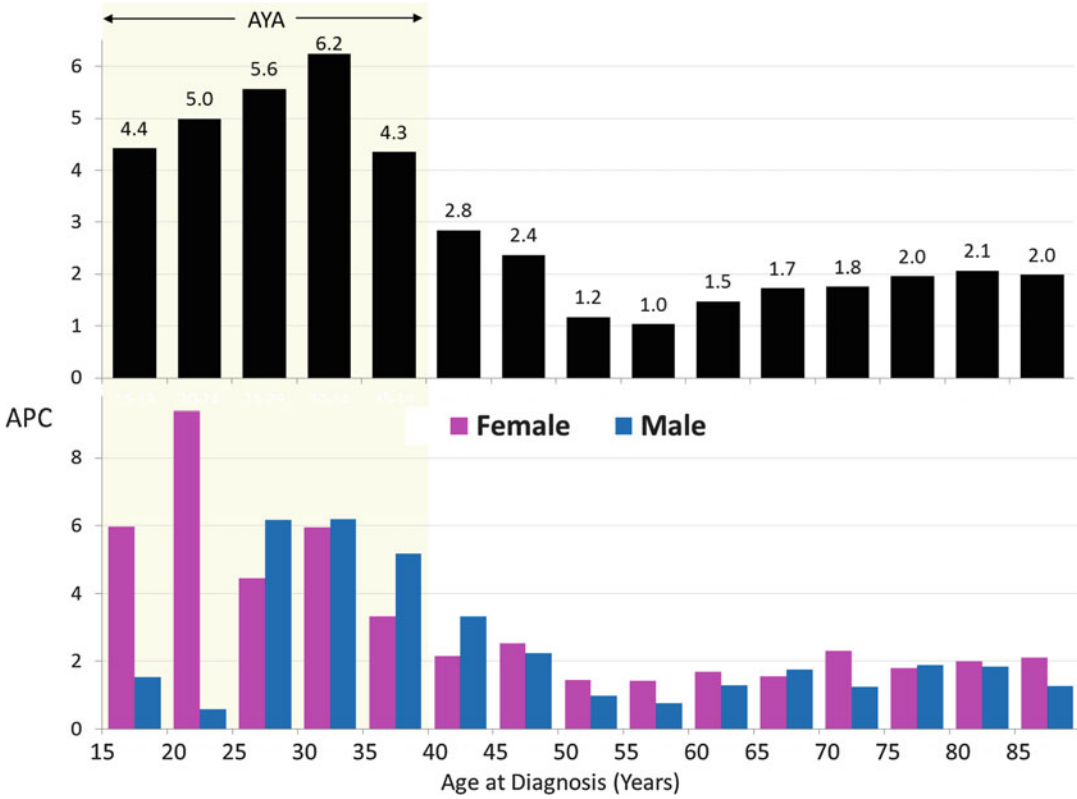

Fig. 17.4 Annual Percent Change (APC) in incidence of renal cell carcinoma by age and sex, 1992-2011, SEER13

pediatric series. Cytogenetic studies of a single case suggest that there may be different molecular lesions in adult cases [16] and this may also explain different response to systemic therapy. However, the consensus remains that AYA patients should be treated according to (pediatric) protocols developed by the International Society of Pediatric Oncology (SIOP) or the Children's Oncology Group (COG).

17.1.5.2 Renal Cell Carcinoma

Though rare in adolescents, there are important questions regarding the best treatment approach and accurate pathologic classification. There is increasing evidence to suggest that RCC arising in adolescents differs from adult cases [1, 17, 18] (reviewed in [19]). Importantly, age-related differences may mean a significantly dissimilar response to therapies between different age groups.

Surgical treatment aiming for complete tumor resection remains the mainstay of therapy, radical nephrectomy being the gold standard. Since the incidence of RCC is an increasing AYAs (Fig. 17.3, right panel), primary radical nephrectomy should be regarded as the initial treatment in this age group or biopsy considered in cases of doubtful diagnosis. While elective partial nephrectomy is being used in adults based on clearly defined criteria, caution is needed in transferring this approach directly to adolescents because of the potentially different intrarenal behavior of translocation RCC. However, since surgical approaches that preserve a healthy renal parenchyma are advocated for adults with small-volume tumors and have demonstrated a good long-term oncological outcome, it is reasonable to assume that they should be studied in adolescents as well. The question of the most adequate extension of retroperitoneal lymph node dissection remains controversial, especially in cases without clinical evidence of lymph node spread. It is noteworthy that, while lymphatic spread by

RCC certainly makes the outcome worse in adults, the same is probably not true for younger patients. The therapeutic value of complete retroperitoneal lymph node dissection is still controversial, especially in patients without suspected nodal involvement, be they adults or adolescents [20]. However, given that current adjuvant therapies are not curative, it might be worth emphasizing whether a more aggressive approach to radical lymphadenectomy should be advocated to achieve surgically complete disease resection in these patients. Since the incidence of RCC increases with age throughout childhood and equals or exceeds that of WT during the second decade of life, a pragmatic recommendation might be to discuss the indication for lymph node dissection with the surgeon instead of sampling, in adolescents.

The landscape of systemic therapies in RCC has recently been changed by the introduction of drugs targeting tumor-related angiogenesis and signal transduction [21–23]. These are the multitargeted receptor tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib), the inhibitors of the mammalian target of rapamycin (mTOR) pathway (temsirolimus, everolimus) and the antiangiogenic monoclonal antibody bevacizumab.

In previous years, research focused largely on biological therapies, with tantalizing results in small series that suggested that the disease is amenable to manipulations of the immune system with cytokines. Both interleukin-2 and interferon have previously shown a small benefit on progression-free interval, yet are now limited to very selected groups of adult patients. In the adult, treatment of metastatic RCC using conventional cytotoxic chemotherapy has not been associated with clear evidence of significant benefit on outcome.

Data on the use of antiangiogenic agents in RCC is largely confined to the older adult population, and studies on adolescents are largely limited to retrospective case reports or series collected at only one or a handful of institutions [7, 17]. It is worth noting that the largest clinical efficacy trials on targeted molecules have been conducted on clear cell subtype of RCC. Importantly, von Hippel-Lindau gene inactivation has been identified as a main driver in clear cell RCC, with somatic mutations or hypermethylation being present in over 90 % of cases, enabling the rationale for therapies contrasting tumor angiogenesis in the clear cell subtype of tumors. But while targeted drugs have become the standard of care for adult metastatic RCC, there are currently few data on their effectiveness in pediatric translocation RCC, and their use should be considered for patients with unresectable metastatic or advanced-stage disease [24].

The standard of first-line care for adult metastatic RCC is based on administering tyrosine kinase inhibitors targeting the VEGF receptor, while mTOR inhibitors are generally used as a second-line treatment when tyrosine kinase inhibitors fail or as first-line therapy for poor-risk patients [25–27]. On the other hand, the utility of these therapies in the adjuvant setting remains to be seen. This uncertain benefit, together with their toxicity and the relatively better outlook for adolescents with completely resected involved lymph nodes, supports the decision not to use adjuvant therapies in younger patients. What might be recommended for adolescents with metastatic RCCs is sequential treatment with VEGF pathway-targeted therapies, optimizing the results in terms of efficacy and safety. In the final decision as to the best approach to RCC, it should be emphasized that, despite transient responses to targeted therapies, no durable complete remissions have been obtained without chronic, often multiline treatments in most patients. Initial nephrectomy may also be useful even in the face of metastatic disease, and selected patients may benefit from metastasectomy of the lung and even the brain.

17.1.6 Outcomes

17.1.6.1 Survival

Previously published data suggest that the overall survival rate for adolescents with RCC (irrespective of stage) is around 50–60 %, with outcomes worsening with older ages [17, 28–30]. Patients with tumors localized in the kidney, with or without regional lymph node spread, have a good

prognosis, while the outcome remains poor for patients with distant hematogenous metastases.

Geller et al. recently reported on 120 consecutive young patients with RCC (median age was almost 13 years), prospectively registered on the Children's Oncology Group study AREN03B2, forming a large prospective series of well-characterized pediatric tumors for the first time [18]. The authors can confirm that RCC in adolescents typically presents at advanced stage, with Xp11.2 translocation type being the most common (47 %), that lymph node involvement is frequent (48 %) – even among patients with small associated primary tumors – and imaging sensitivity for the detection of lymph node metastases remains poor. Noteworthy, as these tumors have only been recently recognized, their natural history is poorly defined, and extended follow-up is recommended because, regardless of the age of the patient, translocation RCCs seem to have the potential to metastasize also after many years.

Updated analysis of SEER data for this report shows that during 2000–2011, the 5-year RCC-specific survival rate was inversely proportional to age at diagnosis above age 30 (Fig. 17.5) [52]. Below age 30, however, the reverse was true, and for 20- to 25-year-olds, the 5-year rate was lower than in middle-aged adults (Fig. 17.5). Renal cell carcinoma that presents with localized disease has a >90 % 5-year cancer-specific survival at all ages up to 75 years (Fig. 17.6). Among AYAs, it is >95 % (Fig. 17.6). AYAs with metastatic disease at diagnosis have a significantly better 5-year RCC-specific survival than older patients (Fig. 17.6). The reverse appears to be true for regional disease at diagnosis (Fig. 17.6). Blacks have the lowest 5-year renal cell carcinoma-specific survival among the major races/ethnicities in the United States, especially among AYA patients (Fig. 17.7).

17.1.6.2 Survival Trends

Both male and female AYAs have had an improvement in their RCC survival rate similar to that in older adults, and both have a 5-year cancer-specific survival rate that is about 15 % greater than in corresponding older adults (Fig. 17.8).

17.1.7 Summary

There are significant challenges in managing adolescent or young adult patients with renal malignancies. Diagnosis is difficult and may be delayed, but as soon as a malignant diagnosis is confirmed, the patient and their family should be referred without delay to an institution that can

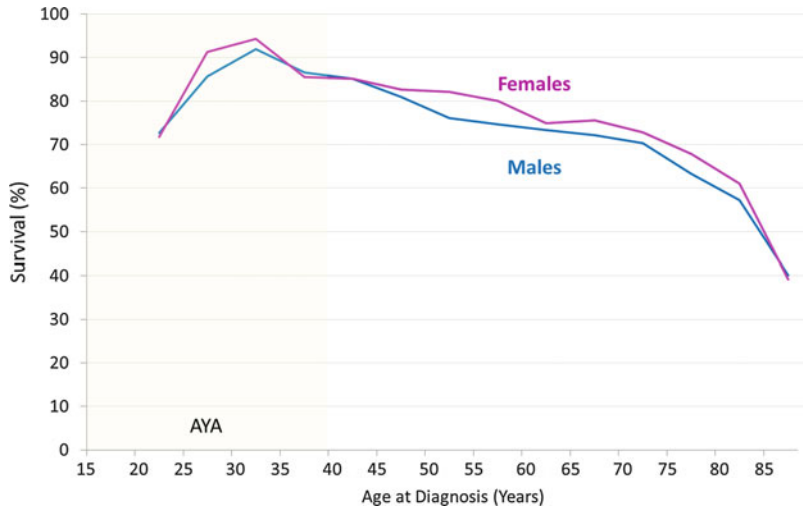

Fig. 17.5 A 5-year RCC-specific survival by age (15+ years) and sex, 2000–2011, SEER. Age subgroups with <25 patients are not included (age <20)

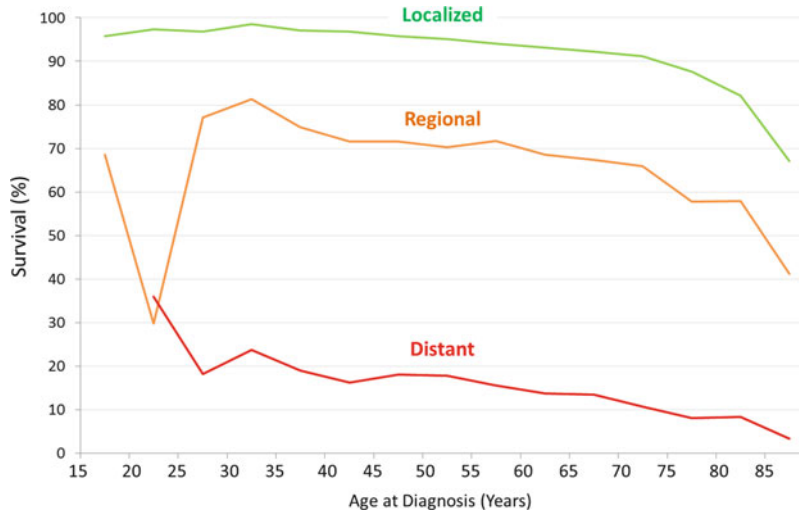

Fig. 17.6 A 5-year renal cell carcinoma-specific survival by stage and age, 2000–2011, SEER. Age subgroups with <11 patients are not included (age <20)

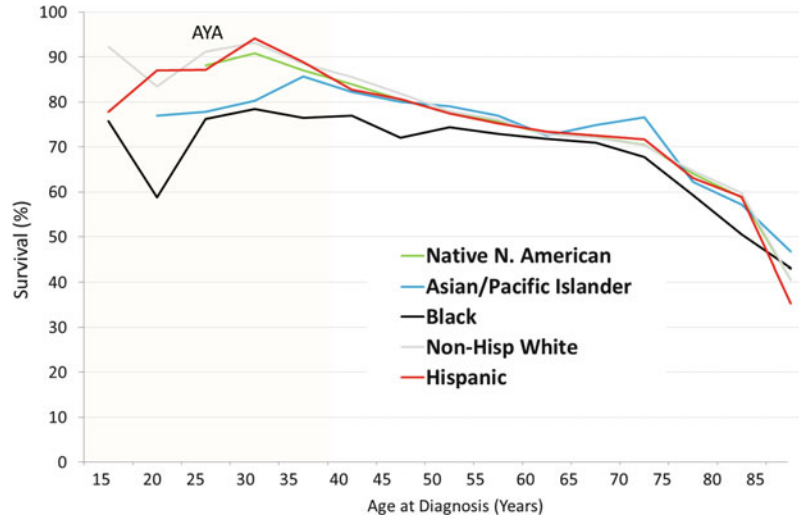

Fig. 17.7 A 5-year head/neck cancer-specific survival by age (>15 years) and race/ethnicity, 2000–2011, SEER. Age subgroups with <9 patients are not included

provide both the highly specialized tumor-specific multidisciplinary team to deliver treatment and, ideally, one where age-specific support services are available.

Confirmation of the diagnosis is the first crucial step. Expert histopathologic review should be performed on all tumors, since the chance of an unusual histology in this age group is high. Treatment planning should involve surgical, radiation oncology, and medical oncology input.

The overall survival rate for AYAs with RCC is around 50–60 %, with outcome worsening with older patients [17, 28–30]. Patients with tumors localized in the kidney, with or without regional lymph node spread, have a good prognosis, while the outcome remains dismal for patients with distant hematogenous metastases.

Treatment guidelines developed for the management of adult patients should be assessed carefully before extrapolating them to a different

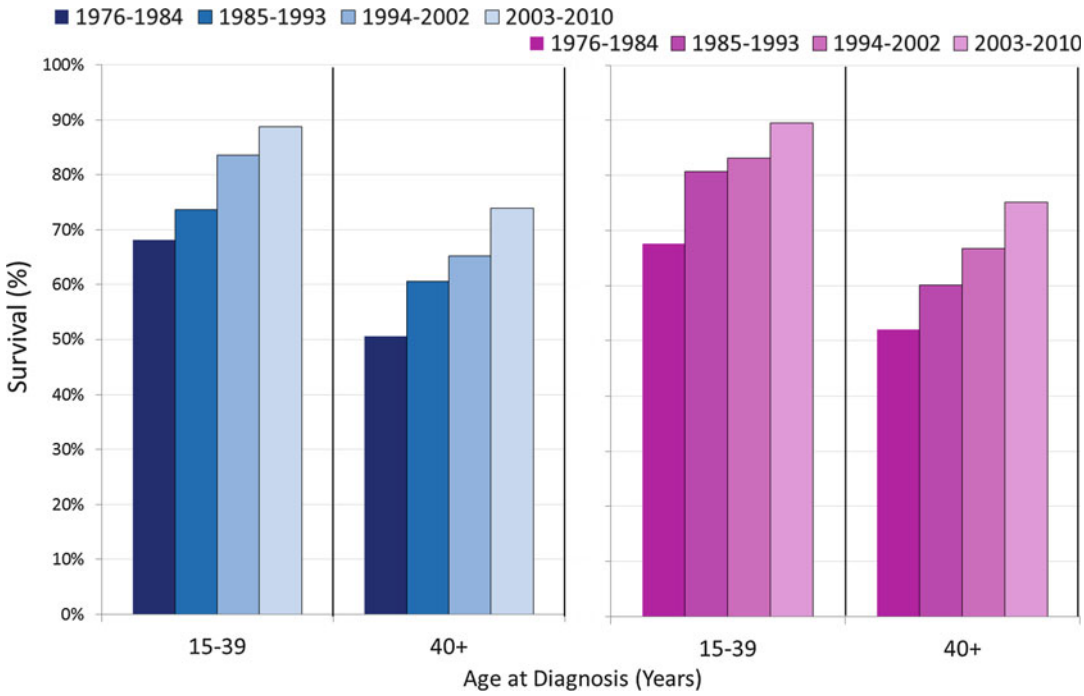

Fig. 17.8 A 5-year renal cell carcinoma cancer-specific survival by age and era, 1976–2010, SEER9

age group, but in the absence of good data to support different approaches, these are still the best recommendations for care in many cases. More research is required into the etiology (in which genetic susceptibility may play a greater part), natural history, and response to therapy in the unusually young patient with these forms of cancer.

17.2 Bladder Cancer

17.2.1 Biology, Pathology, Etiology

In the adult population, the commonest cancer of the bladder is transitional cell carcinoma (TCC) of the urothelium, which may also present in the urothelium of the renal pelvis and ureter. Clearly, this reflects the fact that this tissue is exposed to carcinogens in the urine. Polymorphism with regard to key protective pathways may account for increased risk [31] and may be implicated in patients with a very young age at diagnosis. Normal urinary physiology is also protective, and young patients who require bladder augmentation due to neurological disorders are at a higher risk of developing TCC [32]. Excess incidence of urinary cancer, including very young patients, has been detected in studies of areas affected by heavy pollution [33]. In addition to TCC, rare histological variants are also found, and one might expect these tumors to account for a higher proportion of cases in the much younger patient population [34].

In one of the few published series of adolescent patients diagnosed with bladder cancer, all of the patients had well-differentiated and low-stage tumors [35]. This may be due to "lead-time effect" where early diagnosis of a tumor whose natural history is to progress from low grade to high grade and from localized to metastatic will lead to an association between young age at diagnosis and low grade and lower stage. This hypothesis is also supported by a very large epidemiological study from the National Cancer Database, which demonstrated an association

between young age and low stage [36]. In a more recent series, younger age (<40 years) was confirmed to be associated with good overall survival due to a higher proportion of low-stage, low-grade tumors. However, in those patients with high grade, there was a higher risk of recurrence [37].

17.2.2 Epidemiology

17.2.2.1 Incidence

In the updated SEER analysis covering 2000–2011, the incidence of bladder cancer had a distinct sigmoid relationship with age (Fig. 17.9) [51]. Males had a greater incidence than females, but this difference was most marked after the age of 30 (Fig. 17.10). The vast majority of bladder cancers in AYAs were localized at diagnosis, and the remainder were regional with very few cases of AYAs presenting with distant metastases (Fig. 17.11). In addition to an association with gender, a significant association was seen with ethnicity: non-Hispanic white people being at significantly more risk than others (Fig. 17.12).

17.2.2.2 Incidence Trends

In older adults, the incidence of bladder cancer rose slightly between 1975 and 2005 but recently began to reduce slowly (Fig. 17.13). In AYAs, there has been a more noticeable fall in the incidence that began in 1980 (Fig. 17.13). The cause of these changes remains unknown.

17.2.3 Clinical Presentation and Diagnosis

Bladder tumors are usually diagnosed as a result of investigation of hematuria. Diagnostic workup should then include endoscopic biopsy of the tumor itself and mapping biopsies of the rest of the bladder to look for carcinoma in situ. Bimanual examination under anesthesia remains a critical part of assessing tumor stage.

Patients with invasive tumors should have staging cross-sectional imaging of the chest, abdomen, and pelvis and imaging of the upper urinary tracts. Bone scanning is advised increasingly in view of the high incidence of asymptomatic bone metastases. Other investigations will be determined by the patient's clinical symptoms and signs.

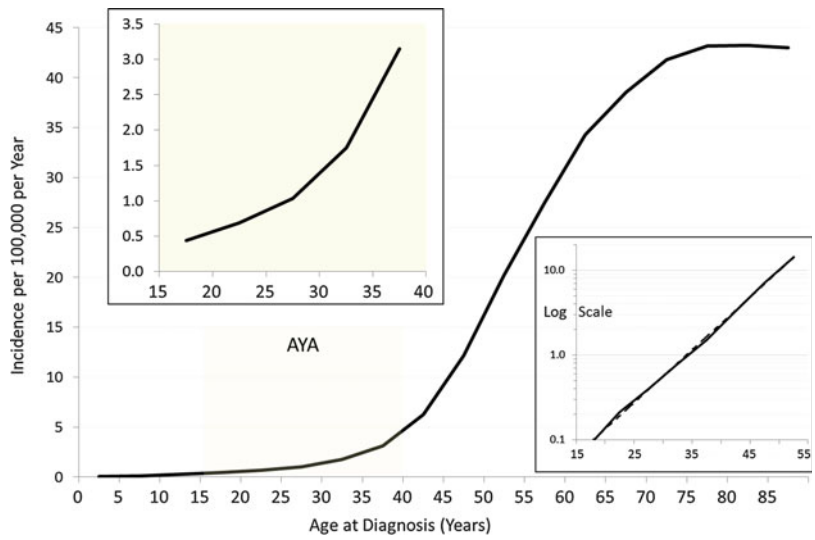

Fig. 17.9 Incidence of bladder cancer by age, 2000–2012, SEER18. *Left inset* enlarges the AYA age range, and *right inset* has a log y-axis and exponential regression (*dashed line*)

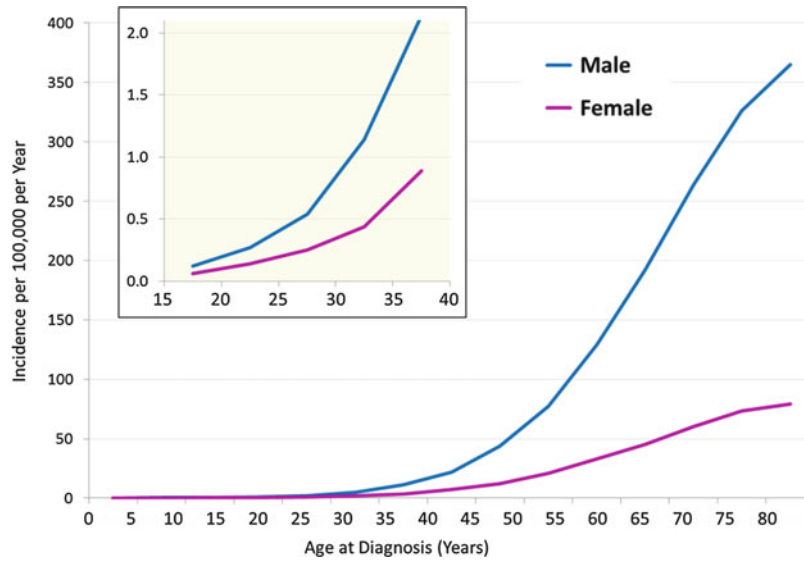

Fig. 17.10 Incidence of bladder cancer by age and sex, 2000–2012, SEER18. The inset enlarges the AYA age range

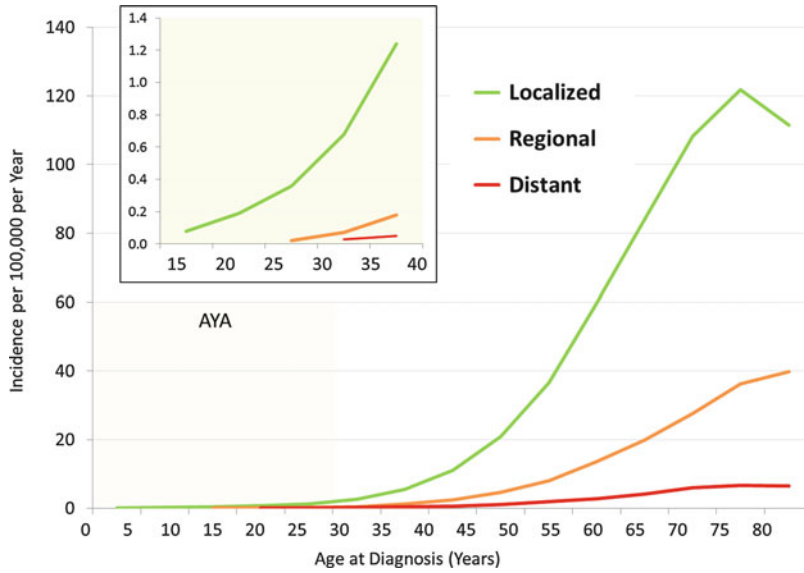

Fig. 17.11 Incidence of bladder cancer by age and stage (extent of disease) at diagnosis, 2000–2012, SEER18. The inset enlarges the AYA age range

17.2.4 Treatment

Tumors of pTa and pT1 are usually managed by endoscopic extirpation with a single postresection instillation of epirubicin, mitomycin-C, or BCG (Bacillus Calmette-Guerin) into the bladder. Surveillance for local relapse is mandatory and can be performed by flexible cystoscopy. Urine cytology is of potential benefit in follow-up.

Invasive tumors (pT2–pT3) are usually managed by radical cystectomy (or nephroureterectomy in the case of upper tract tumors) with lymph node dissection. Recent data, from reanalysis of a systematic meta-analysis of randomized clinical trials of neoadjuvant chemotherapy with

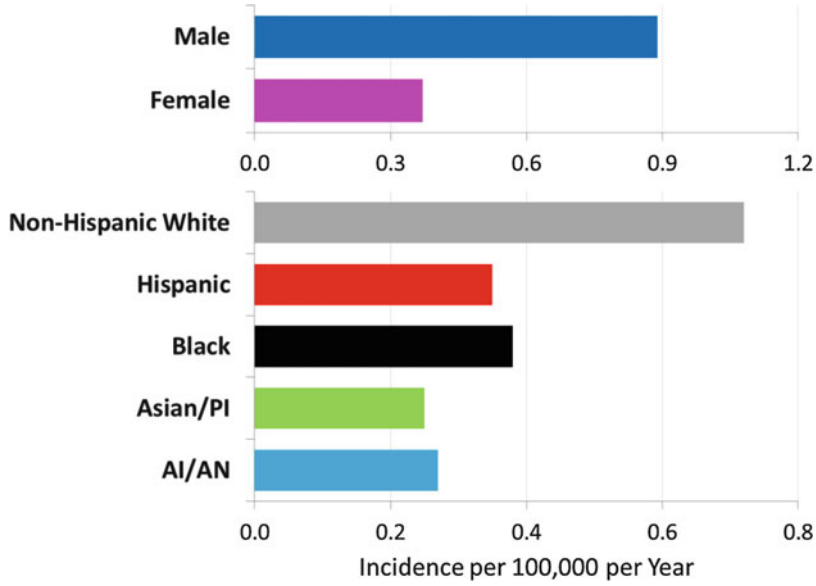

Fig. 17.12 Incidence of bladder cancer in AYAs 15 to 39 years of age by sex and race/ethnicity, 2000–2012, SEER18

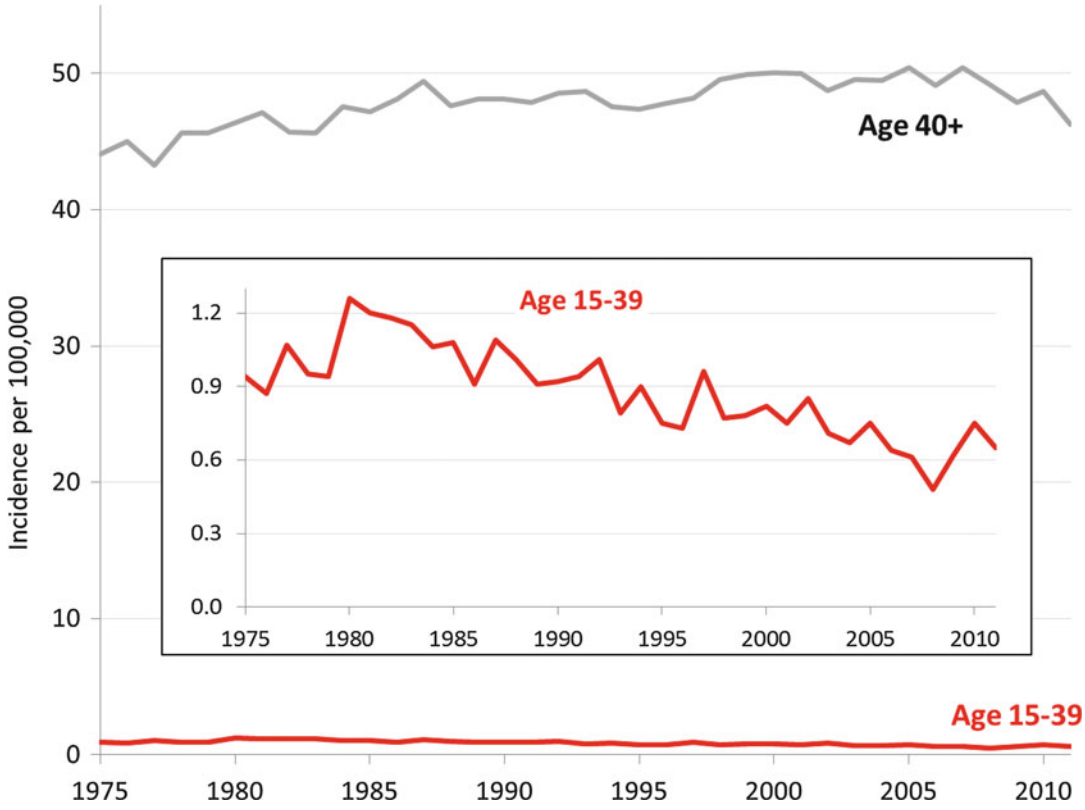

Fig. 17.13 Annual incidence of bladder cancer by age, 1975–2012, SEER9. The inset enlarges the AYA age group

platinum-containing combination regimens such as MVAC (methotrexate, vinblastine, Adriamycin, and cisplatin), suggests a small improvement in overall survival of approximately 6 % at 5 years [38]. Patients who are unfit for radical surgery (common in the usual elderly adult population but unlikely in the teenager or young adult presenting with this disease) may be managed with radical radiotherapy, although this would only really be appropriate in the young patient for those who are clearly beyond treatment of curative intent.

Metastatic TCC of the urothelium is sensitive to both radiotherapy and cytotoxic chemotherapy, and patients with metastatic or inoperable local disease should be managed with a multimodal treatment plan to optimize their survival and quality of life. This will result in a small number of long-term survivors among selected patients who have received aggressive combination chemotherapy based on cisplatin, had good performance status at the start of treatment, and have metastases restricted to lymph node sites [39]. In the adult, cisplatin is the drug associated with the highest single-agent activity, and randomized controlled trials have shown that combination therapy is superior to single-agent treatment. Doxorubicin, methotrexate, vinblastine, gemcitabine, and the taxanes all have demonstrable activity. Several well-tested combinations exist: MVAC, CMV (cisplatin, methotrexate, and vinblastine), and GC (gemcitabine and cisplatin), and many new doublets and triplets have been tested in small series.

17.2.5 Outcomes

17.2.5.1 Survival

AYAs with localized disease at diagnosis had the best survival rate of all ages, over 97 % at 5 years (Fig. 17.6) [52]. At all ages above 25, the 5-year bladder-cancer-specific survival rate was strongly and directly dependent on stage at diagnosis. Among AYAs, the 5-year bladder-cancer-specific survival rate of those with distant disease at diagnosis was 10–20 %, whereas those with localized disease had a >95 % 5-year survival (Fig. 17.14). Among AYAs with regional disease at diagnosis, the 5-year bladder-cancer-specific survival rate declined precipitously with increasing age from 90 % to 50 % (Fig. 17.14).

17.2.5.2 Survival Trends

There was no change in their overall 5-year cancer-specific survival rate since 1976 among AYAs with bladder cancer despite some improvement in the rate among those 40 years of age and older (Fig. 17.15).

17.2.5.3 Mortality

In the United States, nearly twice as many AYA males died of bladder cancer than AYA females (Fig. 17.8). Among AYAs with bladder cancer, native North Americans and Asians/Pacific Islanders had the greatest death rate, followed by blacks, and, with the lowest rate, whites (Fig. 17.16).

17.3 Prostate Cancer

17.3.1 Introduction

Prostate cancer in teenagers is so rare that almost no epidemiological data have been published and the literature is confined to case reports [40]. Studies of “early-onset” prostate cancer (albeit defined as diagnosed under the age of 55 years) generally only contain cases aged down to the mid-30s and reveal associations with inherited polymorphisms of critical genes [41–44].

17.3.2 Epidemiology

17.3.2.1 Incidence

According to SEER data for 2000-2011, the incidence of prostate cancer rises rapidly in AYAs over 30 years of age (Fig. 17.17, left panel) [52]. Ten percent of men diagnosed with prostate cancer before 40 years of age have distant disease at the time of diagnosis, in comparison to 4 %

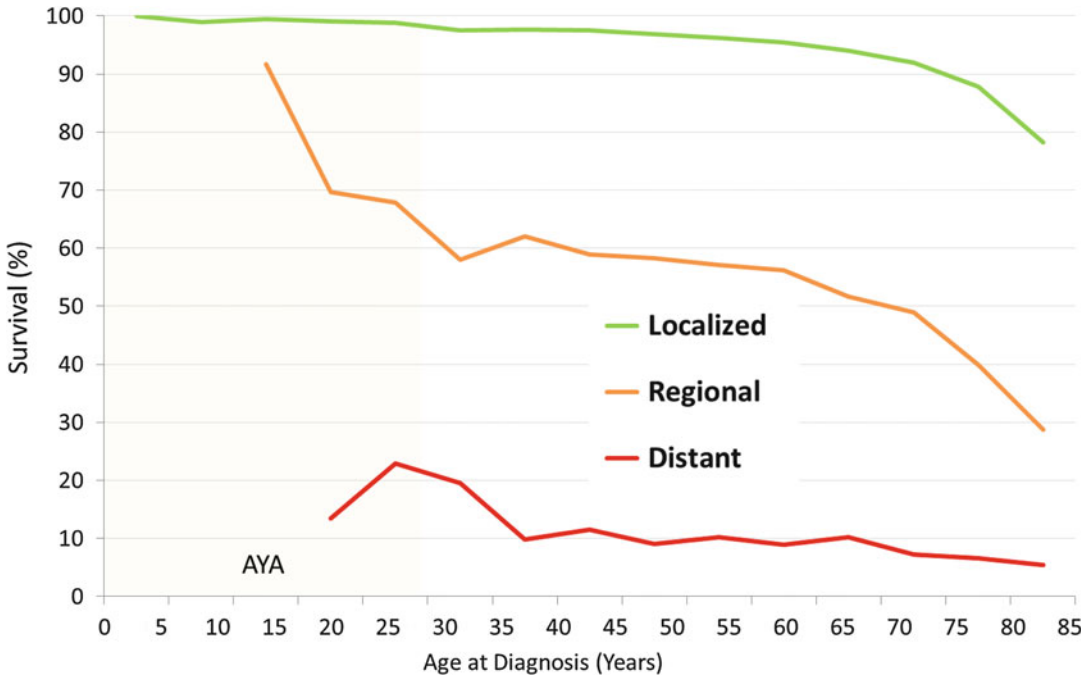

Fig. 17.14 A 5-year bladder-cancer-specific survival by stage (extent of disease at diagnosis) and age (15+ years), 2000–2011. Only age groups with at least ten patients are shown

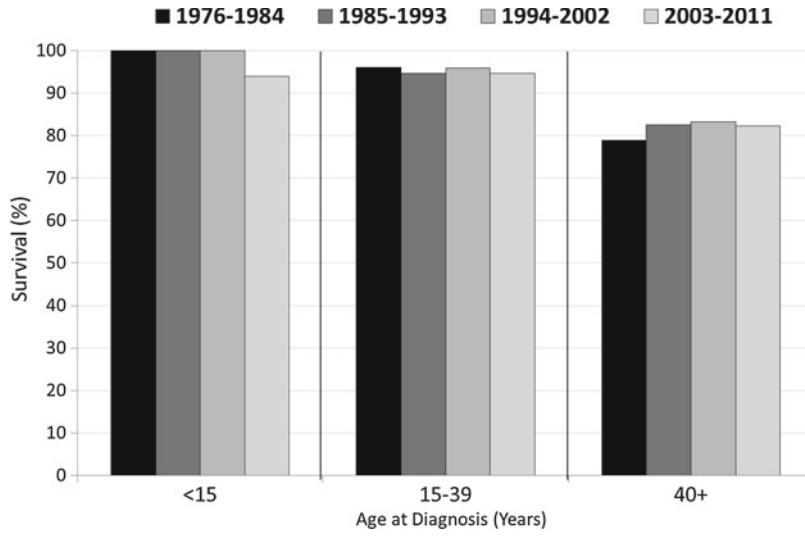

Fig. 17.15 A 5-year bladder-cancer-specific survival trends by age, 1976–2011

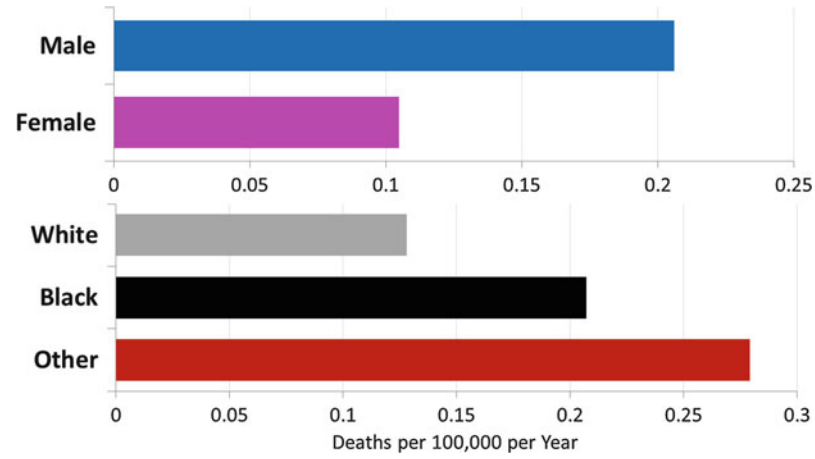

Fig. 17.16 Death rate by sex and race, age 15–39, 2000–2011

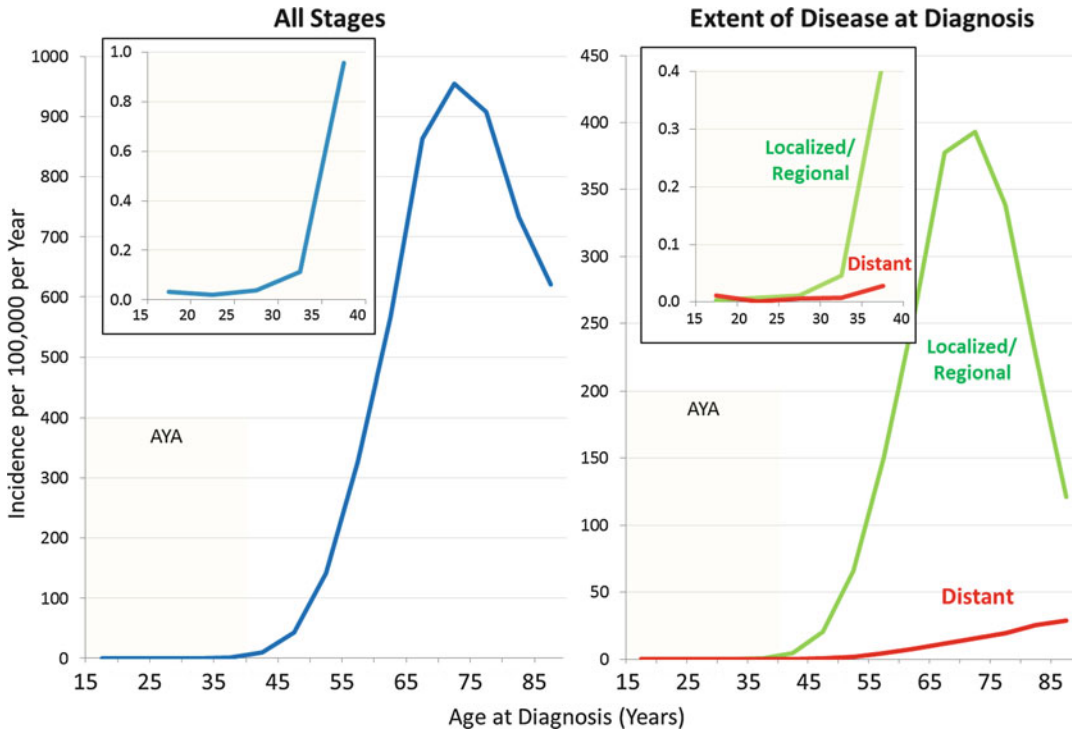

Fig. 17.17 Incidence of prostate cancer by age (15+ years) (*left panel*) and stage (*right panel*), males, 2000–2011. The insets enlarge the AYA age range

between the ages of 40 and 80 (Fig. 17.17, right panel).

In AYA and older men, prostate cancer was most common in blacks (Fig. 17.18). In AYA men, it was least common in Hispanics, whereas in older men, it was more frequent than Asian/Pacific Islanders and native North Americans (Fig. 17.18).

17.3.2.2 Incidence Trends

Between 1976 and 2011, there has been a dramatic increase in the United States in the incidence of diagnosis of prostate cancer in 25- to 49-year-old men, which is greater than any other cancer that has had an increase in incidence in the age group (Fig. 17.19). Between 1992 and 2011, the increase in incidence averaged 6.3 % per year

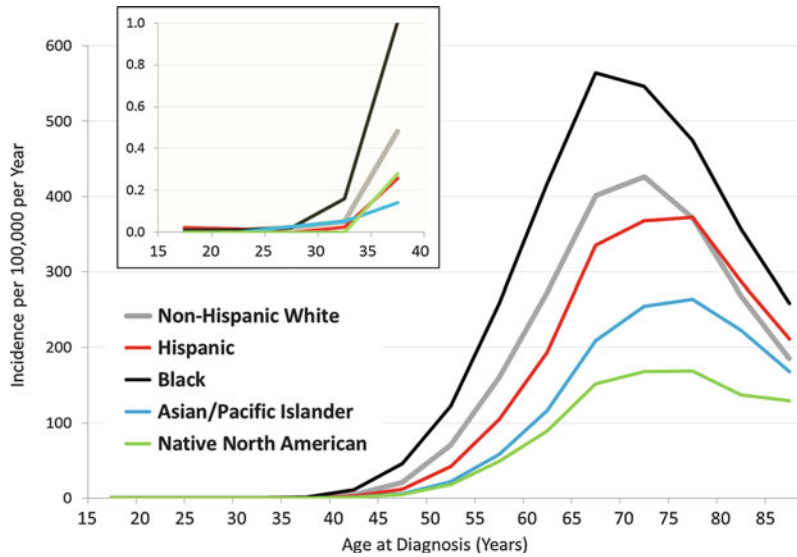

Fig. 17.18 Incidence of prostate cancer by age (15+ years) and race/ethnicity males, 2000–2011. The inset enlarges the AYA age range

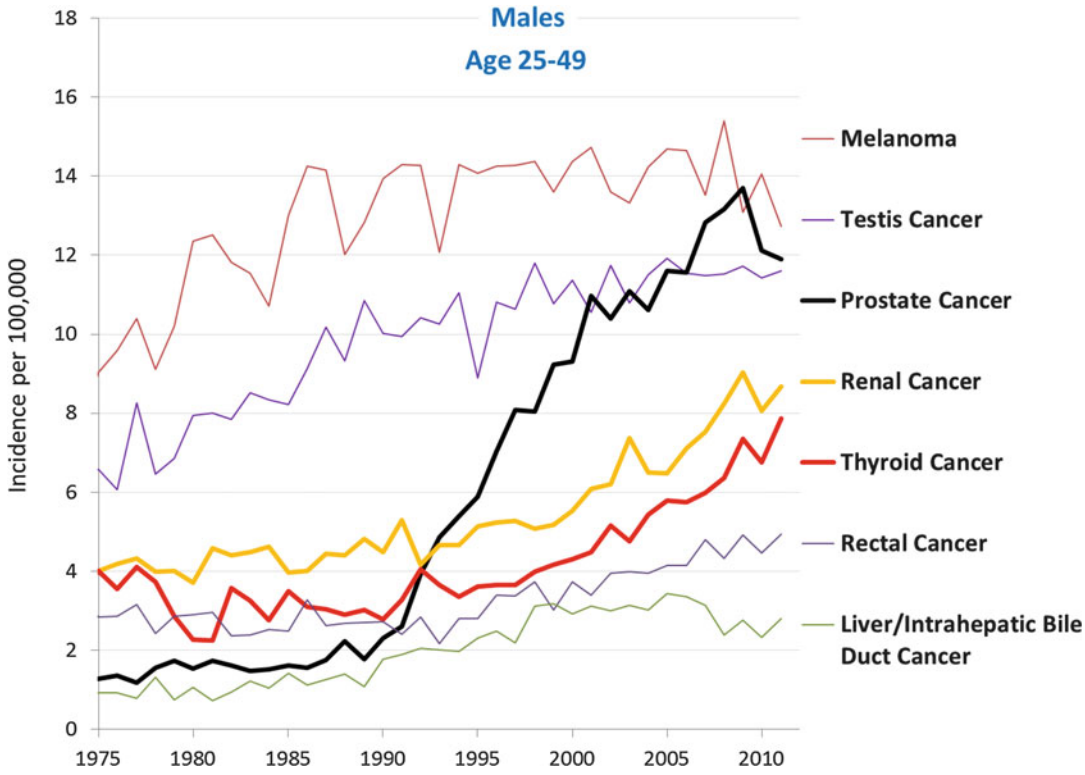

Fig. 17.19 Annual incidence of invasive cancers in males of age 25–49 years with increasing incidence trends, 1975–2011, SEER9

and was inversely proportion to age within the group (Fig. 17.20). During the same interval, a reciprocal and symmetrical decrease in incidence occurred in older age cohorts (Fig. 17.20). Among 35- to 39-year-olds, the increase during 1992–2011 averaged 7.1 % per year (Fig. 17.20) such that during 2006–2010, prostate cancer accounted for 1.4 % of the all invasive cancer in men this age (SEER18) and averaged 105 men per year in the United States. Reasons for these trends have not been ascertained. The introduction of screening for elevated serum levels of prostate-specific antigen (PSA) is known to have had a significant effect on the diagnosis of prostate cancer in older men, but PSA screening is not approved for men in their 30s or 40s, and no definite correlation has been established between the date of introduction of screening and the changes in the incidence of AYA with prostate cancer.

17.3.3 Biology

Ethnic, familial, and genetic factors are thought to play a role in early onset of prostate cancer, but the biology of prostate cancers detected at young age is not well understood. A genomic analysis of 11 early-onset prostate cancer cases by Weischenfeldt et al. revealed a key role of the androgen-androgen receptor axis [45]. The authors suggested a specific pathogenesis for young-age prostate cancers, distinct from the classical elderly-onset prostate cancers. It is noteworthy that young-age prostate cancer is associated with a considerably increased risk of prostate cancer in family members. Recently, a number of susceptibility genes such as *BRCA2* and *HOXB13* were reported (reviewed in [46]).

17.3.4 Clinical Presentation and Diagnosis

In the very rare situation of a patient under the age of 25 years diagnosed with a prostate tumor, the impression gained from the few case reports is of tumors that are different biologically to those seen in the normal age range of elderly men. The tumors are usually undifferentiated, metastasize early, have lytic rather than sclerotic bone metastases, and respond poorly to hormonal therapies [40]. Although few studies have shown an association of very young age and high-stage disease, it is unclear whether early age at diagnosis adversely influences the outcome in young patients with prostate cancer. Furthermore, it is likely that more aggressive early-onset prostate cancer is seen more frequently in African-American young men than in Caucasian men.

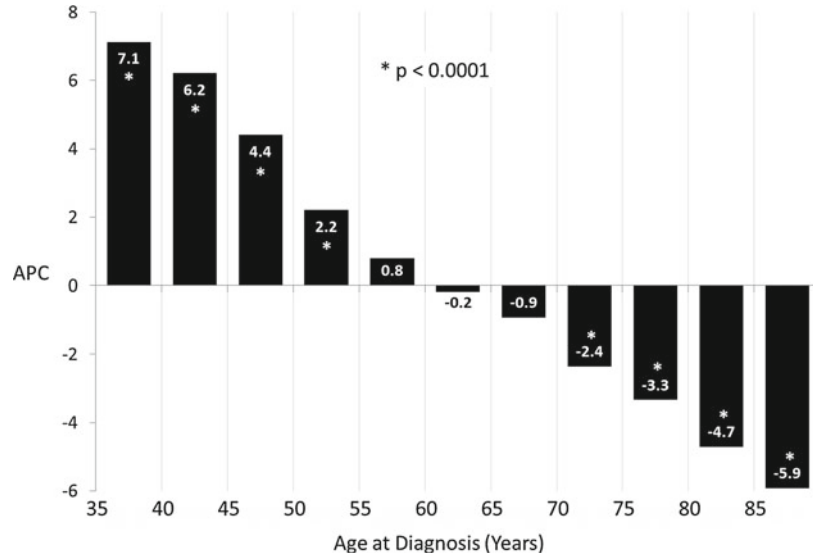

Fig. 17.20 Annual Percent Change (APC) in the incidence of prostate cancer, 1992–2011, SEER13, by age (35+ years)

In the 30–39-year age group, patients appeared less likely to have a high-grade tumor. And while most men diagnosed with prostate cancer before 40 years of age had localized disease at diagnosis, the younger age cohort, despite having a lower proportion of high-grade tumors, paradoxically appeared more likely than older men to be diagnosed with metastatic disease [47, 51].

Patients may present with pelvic pain, dysuria, poor urinary stream, and possibly hematuria. Digital rectal examination may reveal clues to the diagnosis, but is relatively insensitive. Pelvic imaging by MRI, CT scan, or transrectal ultrasound may also sometimes miss a diffuse tumor of the prostate, and biopsy procedures (transrectal ultrasound-guided tru-cut biopsy procedures) are therefore often performed to a template to ensure coverage of the gland.

Staging should include screening for bone metastases by whole-body radionucleotide bone scintigraphy as well as cross-sectional imaging to exclude soft tissue and visceral metastases. Various serum markers are used routinely in the adult population, particularly prostate-specific antigen, and this can be a very useful marker to follow disease activity and response to treatment.

17.3.5 Treatment and Outcomes

A diagnosis of a prostate malignancy at young age raises a number of important questions both about their biology and their management. While a 60-year-old man with a low-risk prostate cancer is a suitable candidate for active surveillance, a similar scenario in a young man might prompt immediate intervention, taking into account his longer life expectancy and the suspicion that prostate cancer detected at young age might behave more aggressively.

In the rare patient with clinically organ-confined disease, radical prostatectomy is offered increasingly over the alternatives based on radiotherapy (radical external beam radiotherapy and brachytherapy). In view of the comments above, surgery may be preferred to radiotherapy in the very young patient being treated with curative intent. Nerve-sparing techniques to preserve continence and sexual function are possible without sacrificing outcome if the tumor is very small. Neoadjuvant treatment with hormonal therapy is of unproven benefit and is not advised outside the context of a clinical trial. Postoperative hormonal treatment may have a small impact in patients with node-positive disease.

In the adult, metastatic adenocarcinoma of the prostate is sensitive to a variety of hormone manipulations. First-line therapy is usually with gonadotrophin-releasing hormone analogues such as goserelin or leuprolide, to suppress androgen production by the testis. Second-line therapy typically involves attempting to ensure that even peripheral and hepatic testosterone production is blocked; this is achieved by adding an antiandrogen to the luteinizing hormone-releasing hormone analogue. Stilboestrol fell out of favor in view of an excess of thromboembolic events, but may still have a role in third-line therapy in selected patients. Young age has been reported to be a negative prognostic factor in series of patients treated by androgen deprivation therapy, although in most series the definition of young age is usually <=55 years [48].

Hormone therapy has dominated the management of the elderly adult with prostate carcinoma, and cytotoxic therapies are reserved for the final hormone-refractory phase in selected patients. However, recent evidence showing a small survival advantage with docetaxel-based therapy has demonstrated that cytotoxic chemotherapy may have an important role to play in the treatment of prostate carcinoma [49]. Given the suggestion that hormonal therapies are ineffective in the very young patient with prostate cancer, and that some success in partial response and palliation may be obtained with cytotoxic chemotherapy, it would be reasonable to select younger patients for this modality of therapy early in their treatment. Bisphosphonate treatment has also been shown to be of some benefit in maintaining quality of life in the adult population by reducing the risk of skeletal events.

17.3.5.1 Survival

Between 2000 and 2011, male AYAs had a worse 5-year prostate-cancer-specific survival (Fig. 17.21) [52]. The 5-year survival rate for

patients aged 15–39 years was 80–90 % compared to 95 % in patients aged 40–70 years. The youngest patients seem to fare worst, with the 5-year cancer-specific survival rate 65 % in 20- to 24-year-old men, 70 % in 25- to 29-year-olds, 75 % in 30- to 34-year-olds, and >90 % in 35- to 39-year-olds. The only race/ethnicity with a sufficient number of patients in the youngest age levels to allow an assessment of the 5-year prostate-cancer-specific mortality rate in AYAs is the non-Hispanic white population, in whom survival was directly proportional to age from age 20 to 40 (Fig. 17.21, gray triangles and curve).

17.3.5.2 Survival Trends

In terms of survival trends, the lower 5-year cancer-specific survival rate in AYA men in the 1970s and 1980s caught up with older men in 30- to 39-year-olds but not in 15- to 29-year-olds (Fig. 17.22). The death rate from prostate cancer paralleled the incidence as function of age until 65 years (Fig. 17.23). The proportion of deaths relative to new cases was higher, up to 40 %, than any age between 40 and 80 (Fig. 17.23). The fewest deaths relative to new cases occurred in 40–70-year-old men (Fig. 17.23).

17.4 Summary

There appears to be a significant change in the epidemiological profile of prostate cancer emerging with early-onset prostate cancer increasing in incidence and associated with a different natural history [50]. This suggests a different underlying biology with a greater component of risk due to genetic factors. This change, while mostly affecting patients usually considered older than the AYA range, is of importance to services providing care to AYA patients too and may demand changes to the clinical management protocols for screening and treatment of patients with this condition.

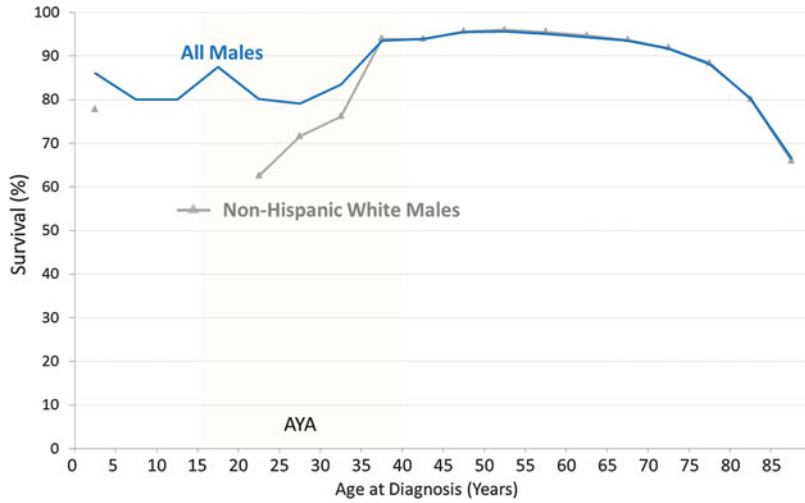

Fig. 17.21 A 5-year prostate-cancer-specific survival by age, all males and non-Hispanic males, 2000–2011, SEER18

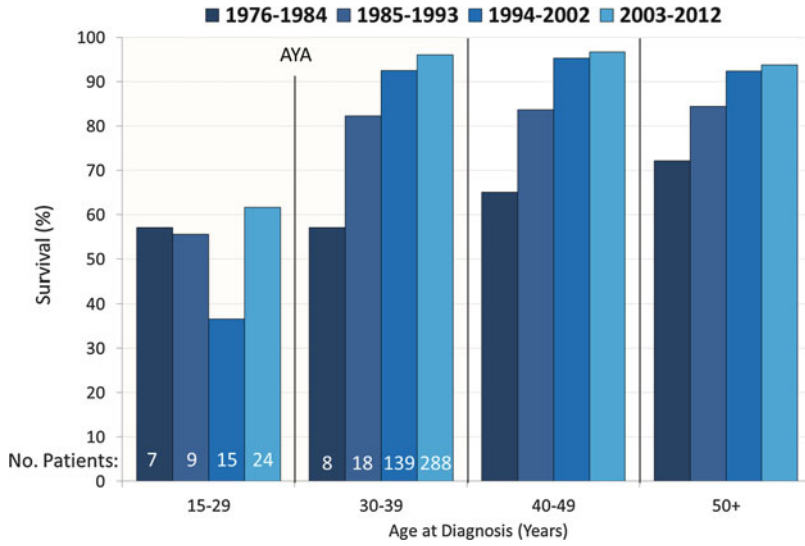

Fig. 17.22 A 5-year prostate cancer-specific survival by era and age, 1976–2012, SEER9

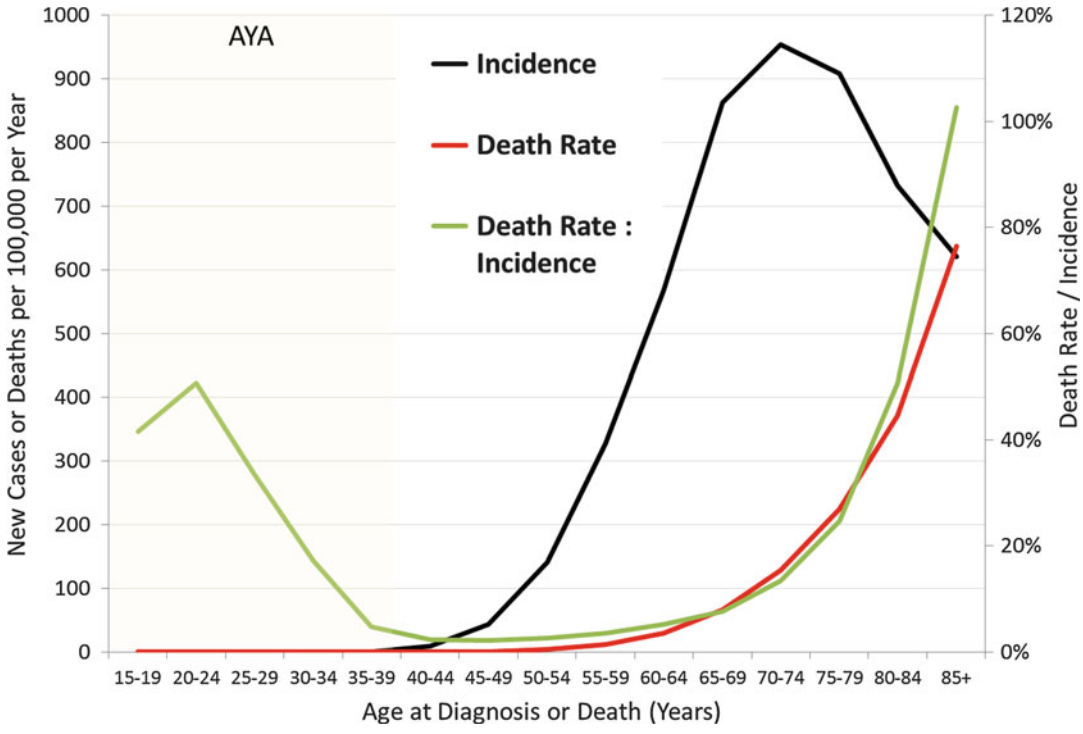

Fig. 17.23 Incidence, mortality, and ratio of deaths: incidence by age, 2000–2011

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Liver Tumors

18

Marcio H. Malogolowkin, Arun Rangaswami, Allison O'Neill, Jack Plaschkes, and Arthur Zimmermann

Abstract

Primary neoplasms of the liver are rare in adolescents and young adults (AYAs), ages 15–39 years, accounting for only 1% of all neoplasms. Hepatocellular carcinomas (HCCs) are the most common liver tumor seen in AYAs as well as in older adults. Available SEER data have shown a steady increase in the incidence of liver and intrahepatic bile duct tumors between 1976 and 2011 for all age groups and for both sexes. Despite the improvement in diagnosis and treatment, survival of patients with HCCs continues to be dismal. In contrast to older adults in whom almost all cases of HCCs are cirrhosis related, secondary to viral infection or alcohol consumption, less than a third of the AYA patients diagnosed with HCCs have an identifying cause such as hepatitis or other inflammatory liver diseases, and therefore the treatment strategies differ significantly.

Children and adolescents with HCC have been treated according to clinical trials designed for the treatment of childhood hepatoblastoma that includes chemotherapy and surgical resection or liver transplant when feasible. On the other hand, treatment for adults with HCC has been based on the extent of disease and liver function. Treatment strategies can be divided in three groups: (1) patients with localized disease (early stage);

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(2) patients with advanced disease as determined by the extensive hepatic involvement, vascular invasion, or presence of extrahepatic disease; and (3) patients with significant liver dysfunction. Since these strategies are so different, they are discussed separately in this chapter.

Given the rarity of malignant liver tumors in the AYA population, national and international collaboration will be essential to evaluate novel therapeutic approaches, to establish the role of liver transplantation for these patients, and to continue to improve our understanding of the biology of HCCs in this population.

18.1 Introduction

Primary neoplasms of the liver are rare in adolescents and young adults, ages 15–39 years, accounting for only 1 % of all neoplasms. This is similar to the 1.1 % incidence seen in individuals 0–14 years of age. Hepatoblastomas comprise over two-thirds of the malignant liver tumors in children, while hepatocellular carcinomas are the most common liver tumor seen in adolescents and young adults as well as in older adults. Very little evidence-based information about the biology, epidemiology, treatment, and outcome is available for liver tumors in adolescent and young adults.

This chapter will briefly review the available data regarding the incidence, etiology, pathology, biology, treatment, and outcomes of liver tumors in adolescents and young adults. We will focus on hepatocellular carcinoma and highlight the similarities and differences between these tumors in adolescents, young adults, and older adults.

18.2 Epidemiology

18.2.1 Incidence

The estimated incidence of liver and intrahepatic bile duct tumors increases with age from 2.0 per million in individuals 15–19 years of age to 14.6 per million for those 25–29 years of age (Table 18.1). According to the Surveillance, Epidemiology, and End Results (SEER) data, 404 adolescents and young adults in the USA were diagnosed with these tumors in the year 2000 [1].

The incidence of liver cancer is relatively constant between 5 and 35 years of age, but then it steadily increases with age (Fig. 18.1). Available SEER data collected between 1975 and 2011 have shown a steady increase in the incidence of liver and intrahepatic bile duct tumors between 1976 and 2011 for all age groups and for both sexes (Figure Incidence Trend). The distribution of different histologic types varies with age. While hepatoblastoma accounts for 90 % of liver tumors in children less than 5 years of age and less than 5 % for those older than 15 years of age, hepatocellular carcinoma presents two peaks of incidence: the first during the early AYA years (age 15–29) accounting for 80 % of the liver tumors in this age group and the other in the middle-aged population. Hepatic sarcomas are a rare type of liver tumors that occur primarily before 15 years of age, while adenocarcinoma of the liver, cholangiocarcinoma, and other intrahepatic bile duct tumors peak during the AYA age range (Figs. 18.2 and 18.3 Biopathology

Table 18.1 Incidence, incidence trends, and number of new diagnoses of liver cancer, US SEER

Age at diagnosis (years)	15–19	20–24	25–29
US population (in millions), year 2000 census	19.90	18.70	17.63
Average incidence, 1975–2000, per million	2.0	5.6	14.6
Average annual increase, 1975–2000, SEER	0	1.8	2.6
Estimated incidence, year 2000, per million	2.0	5.6	14.6
No. of persons diagnosed with liver and intrahepatic bile duct cancer, year 2000, USA	41	105	258

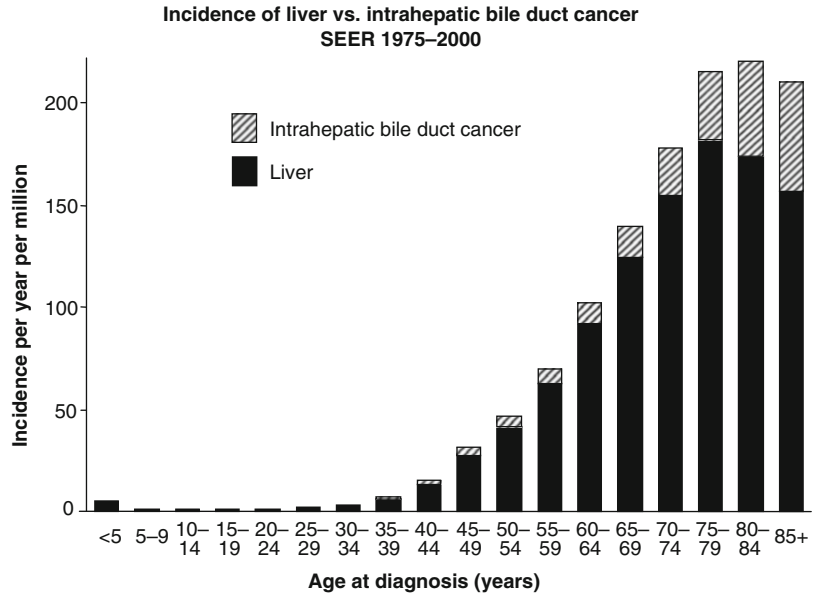

Fig. 18.1 Relative incidence during 1975–2000 of liver and intrahepatic bile duct cancer in US patients by age at diagnosis (Data from the US SEER Program (Bleyer et al. [1]))

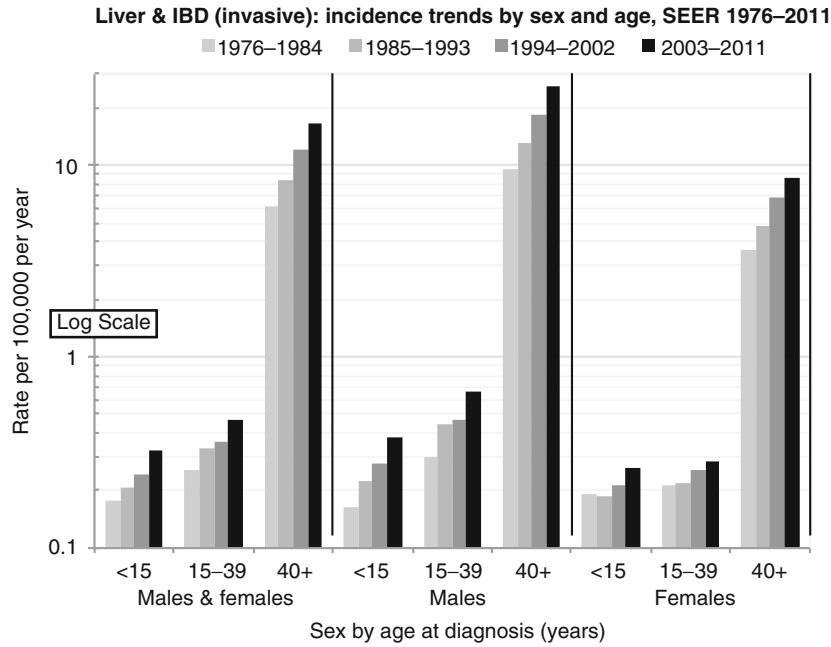

Fig. 18.2 Incidence of liver and intrahepatic bile duct cancer in the USA by sex and age. *IBD* intrahepatic bile duct (Data from the US SEER Program Bleyer WA; Source: SEER 9 Areas, NCI)

by Age). Eleven percent of the liver tumors in the AYA population originate from the intrahepatic bile duct.

The incidence of liver cancer is greater in males than females in all age groups (Fig. 18.4 Incidence). Liver tumors are more prevalent in Asians/Pacific Islanders in AYA and older persons (Figs. 18.4, 18.5, 18.6, and 18.7 Incidence).

Bosch et al., utilizing population-based cancer registries and the World Health Organization (WHO) mortality data bank, reported the incidence and mortality of liver cancers worldwide

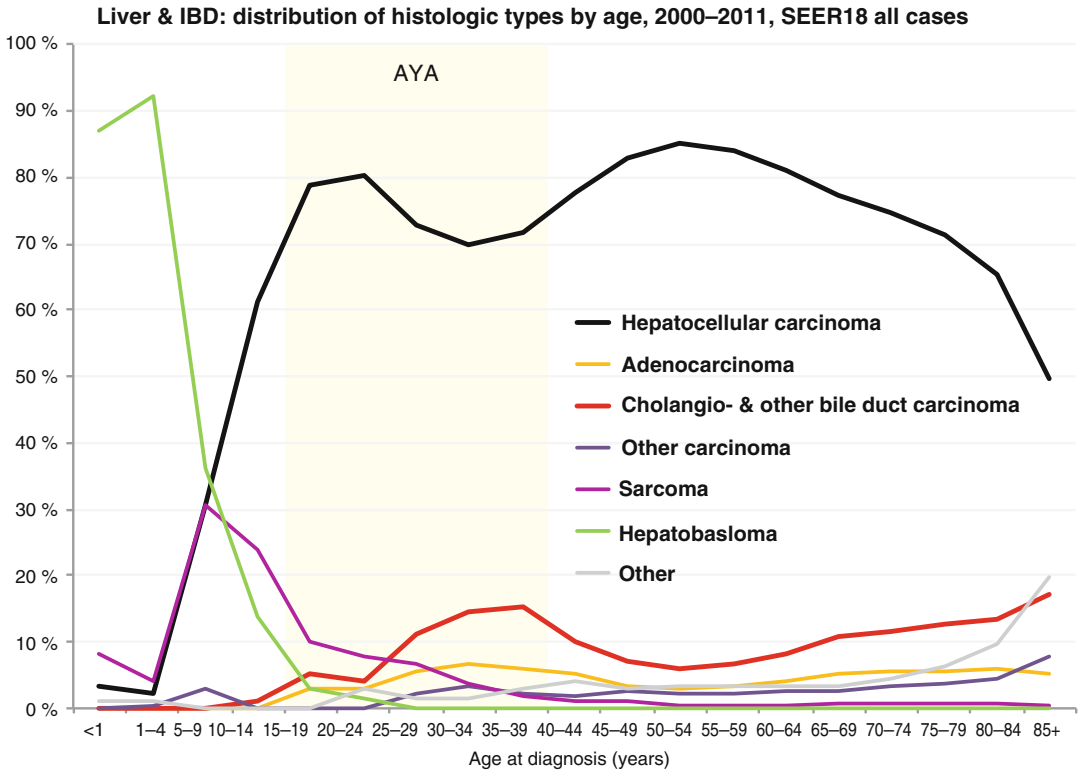

Fig. 18.3 Histologic types of liver and intrahepatic bile duct cancer by age. *IBD* intrahepatic bile duct (Data from the US SEER Program Bleyer WA; Source: SEER 18 Areas, NCI)

[2]. With an estimated 437,000 new cases in 1990, liver cancers ranks fifth in frequency in the world, accounting for 5.4 % of all human cancer cases. Liver cancer corresponds to 7.4 % of all cancer cases among men and 3.2 % of all cancers among women. The largest estimated concentration of liver cancer cases are located in East Asia (China, Hong Kong, Korea, Mongolia, and Japan), in Middle Africa (Cameroon, Chad, Congo, and Equatorial Guinea), and in some Western African countries (Gambia, Guinea, Mali, and Senegal [3]). The lowest concentration of liver cancer is seen in Northern Europe, in Australia, in New Zealand, and in the Caucasian populations in North and Latin America [3].

Liver cancer-specific survival rate decreases steadily with age. Survival in AYA is one-half that seen in young persons, and for persons 25 years or older, it is similar to those of middle-aged adults (Fig. 18.6 Survival). For all ages, disease presentation with regional or distant extension is associated with worse outcomes. While the 5-year liver cancer-specific survival rate for AYAs with localized disease at diagnosis was approximately 50 %, those with regional or distant involvement continue to have a dismal outcome with survival rates less than 20 % (Fig. 18.7 Survival). The overall death rate from liver and intrahepatic bile duct cancer has steadily increased since the early 1980s. The death rate for AYAs has been relatively constant to slightly improve since the early 1980s; however, that due to intrahepatic bile duct cancers has dramatically increased over the years (Fig. 18.8 Death Rates).

18.3 Risk Factors and Etiology

Hepatocellular carcinomas appear to result from complication of previous hepatic damage due to metabolic or inflammatory disorders. Chronic infection with hepatitis B virus is the leading

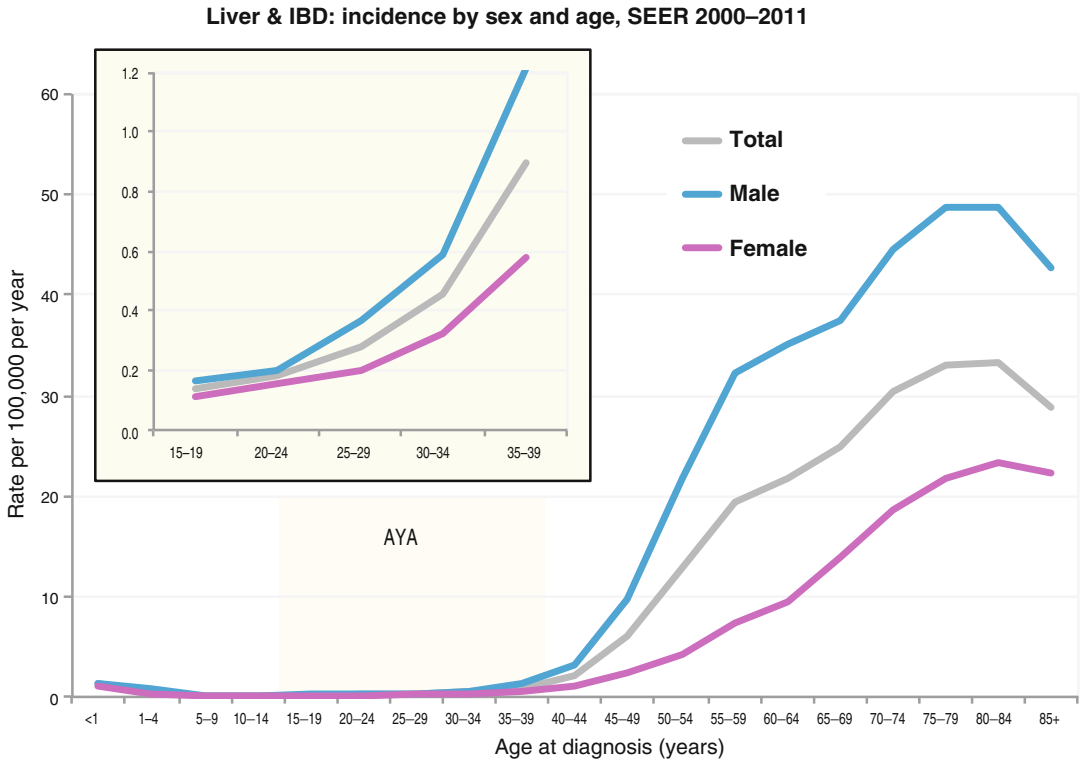

Fig. 18.4 Incidence of liver and intrahepatic bile duct cancer in the USA by sex and age, 2000–2011. *IBD* intrahepatic bile duct (Data from the US SEER Program Bleyer WA; Source: SEER 18 Areas, NCI)

cause of HCC in children, adolescents, and young adults in Asia and Africa. However, in the Western countries, less than a third of the adolescent or young adult patients diagnosed with HCC have an identifying cause such as hepatitis or other inflammatory liver diseases [4, 5]. This is in marked contrast to older adults in which almost 90 % of the cases are cirrhosis related, secondary to viral infection or alcohol consumption [6]. The prevention of a carrier state in children by a universal program of hepatitis B immunization has shown a dramatic decrease in the chronic hepatitis B virus prevalence and a decline in the rates of HCC in Taiwan among children less than 15 years of age [7].

Less frequently HCC is associated with congenital diseases such as hereditary tyrosinemia, biliary cirrhosis, glycogen storage disease, and alpha-1 antitrypsin deficiency [8–11]. Prolonged exposure to anabolic steroids, toxin-contaminated foods (aflatoxin), and potential hepatic carcinogens (pesticides, vinyl chloride, thorotrast) have also been associated with the development of HCC [12–14].

18.4 Pathology and Biology

18.4.1 Hepatocellular Carcinoma (Adult Type)

The pathologic features of hepatocellular carcinoma (HCC) of the adult type (ordinary HCC) are well established (Figs. 18.9). Adult-type HCC also develops in children, adolescents, and young adults. Similar to cancers occurring in the older age group, HCCs in younger individuals display distinct macroscopic growth patterns, including expanding, invasive, pedunculated, multinodular, and diffuse lesions. The main clinical and biological features have been reviewed [15–17]. To date, no differences have been recognized among children, adolescents, and adults

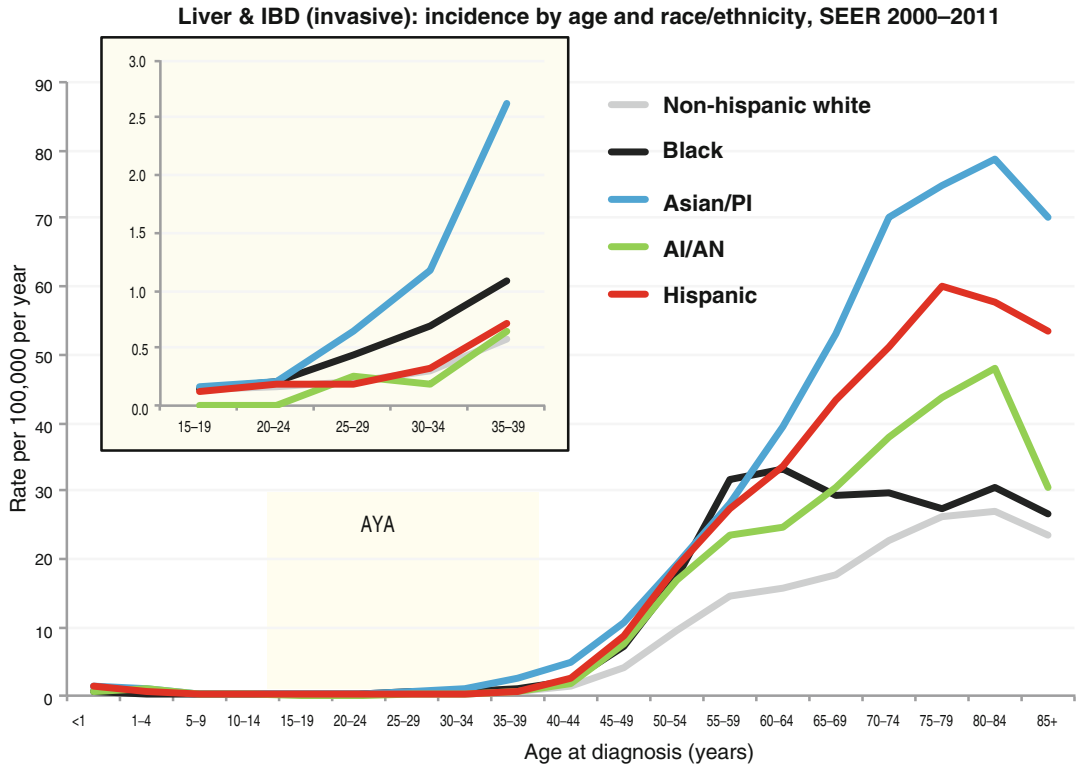

Fig. 18.5 Incidence of liver and intrahepatic bile duct cancer in the USA by age and race/ethnicity, 2000–2011. *IBD* intrahepatic bile duct (Data from the US SEER Program Bleyer WA; Source: SEER 18 Areas, NCI). Note: Hispanic may overlap with black, Asian/PI (Asian/Pacific Islander), and AI/AN (American Indian/Alaska Native)

in the biology and pathology of typical, ordinary HCC. A systematic analysis of the significance of histopathologic risk factors identified in patients with adult-type HCC [18] has yet to be performed in adolescents and young adults.

18.4.2 Fibrolamellar Hepatocellular Carcinoma

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a primary liver cancer characterized by a single expanding mass with typical histologic features consisting of large eosinophilic cells embedded in an abundant collagen-rich stroma, the latter forming "fibrolamellae" between the cancer cells (Fig. 18.10). This tumor occurs most often in young individuals. It accounts for about 30% of HCC in patients younger than 20 years of age. Typically, FL-HCC develops in the absence of underlying cirrhosis, hepatitis viral infection, or metabolic disorders, and serum AFP is not elevated. FL-HCC may be associated with high serum vitamin B12-binding capacity, express a neuroendocrine signature [20], and exhibit aromatase activity causing gynecomastia [21]. A clear cell variant of FL-HCC exists [22]. The neoplasm has distinct immunohistochemical features [23], including reactivity for cytokeratin 7 [24]. FL-HCC markedly differs from ordinary HCC with respect to karyotypic and genomic abnormalities. Recently, a recurrent and highly characteristic chimeric transcript located to chromosome 19 has been identified in FL-HCC. The transcript encodes a protein containing the amino-terminal domain of DNAJB1, a homolog of the molecular chaperone DNAJ, fused in frame with PRKACA, the catalytic domain of protein kinase A (DNAJB1-PRKACA fusion) [25]. The fusion results in increased cAMP-dependent protein kinase A activity, and

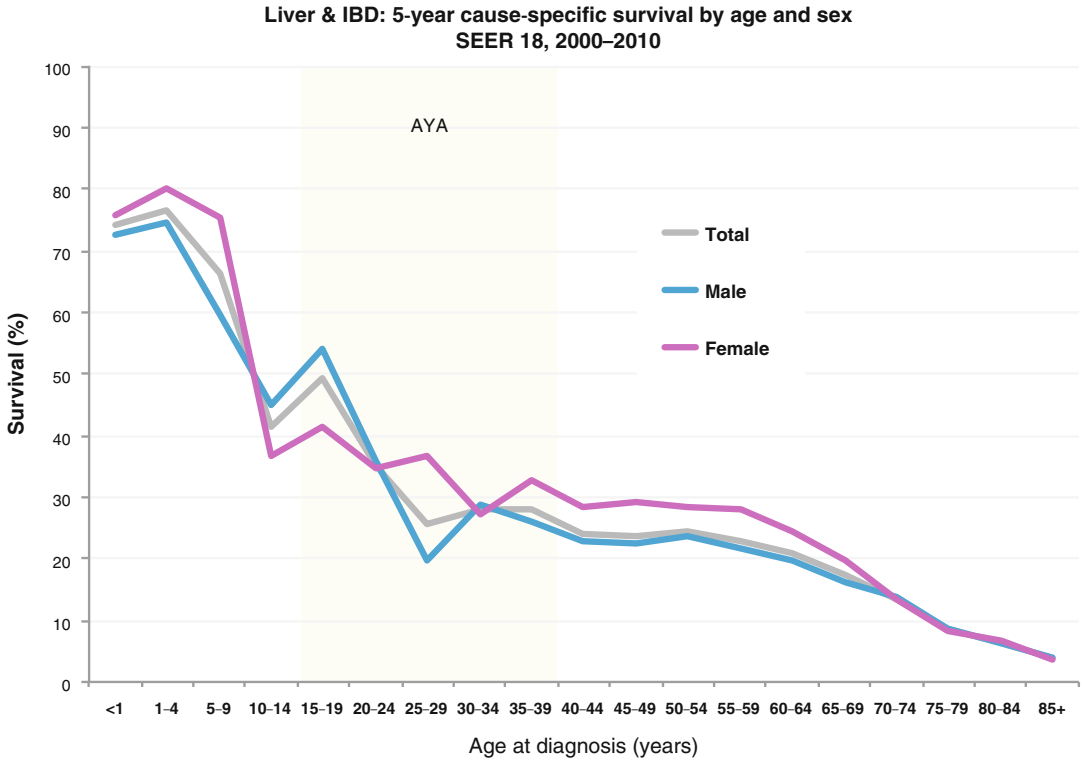

Fig. 18.6 5-year survival of patients in the USA with liver and intrahepatic bile duct cancer by age and sex, 2000–2011. Abbreviations: *IBD* intrahepatic bile duct (Data from the US SEER Program Bleyer WA; Source: National Cancer Institute: SEER18 Areas)

the fusion protein is oncogenic in HCC cells. Later studies confirmed the association of this chimeric transcript with FL-HCC, suggesting that this alteration is a highly characteristic molecular signature for FL-HCC [26–29]. A second gene fusion event found in FL-HCC is a translocation between CLPTM1 and GLIS3 genes, generating a transcript that promotes malignant transformation in cell lines [29].

18.4.3 Hepatoblastoma

Hepatoblastoma (HB) is rare in adolescence and adulthood [30]. In fact, the large majority of HB is diagnosed in infants and children less than 5 years old. There is evidence that HB is the most prominent member of a HB family of tumors, which share distinct molecular features, including abnormalities of the Wnt/beta-catenin signaling pathway (see below). Conventionally, HBs were divided into epithelial HB and mixed epithelial-mesenchymal HB, the latter subclassified into those with or without teratoid features [31–33] (Figs. 18.11). A novel classification was worked out in the frame of an International Pathology Symposium in March 2011 in Los Angeles. Twenty-two expert pathologists of COG, SIOPEL, GPOH, and JPLT as well as pediatric oncologists and surgeons formulated a consensus classification published in 2014 [34] (Table 18.2).

HB can develop in young adults and older patients [35]. The pathology of HB is the same in young and older subjects, and the criteria for histological diagnosis have been reviewed recently [32, 36]. However, molecular signatures will be required to test whether adult HBs are the same or different entities in comparison with HB of young age. There are intriguing situations whereby HCC

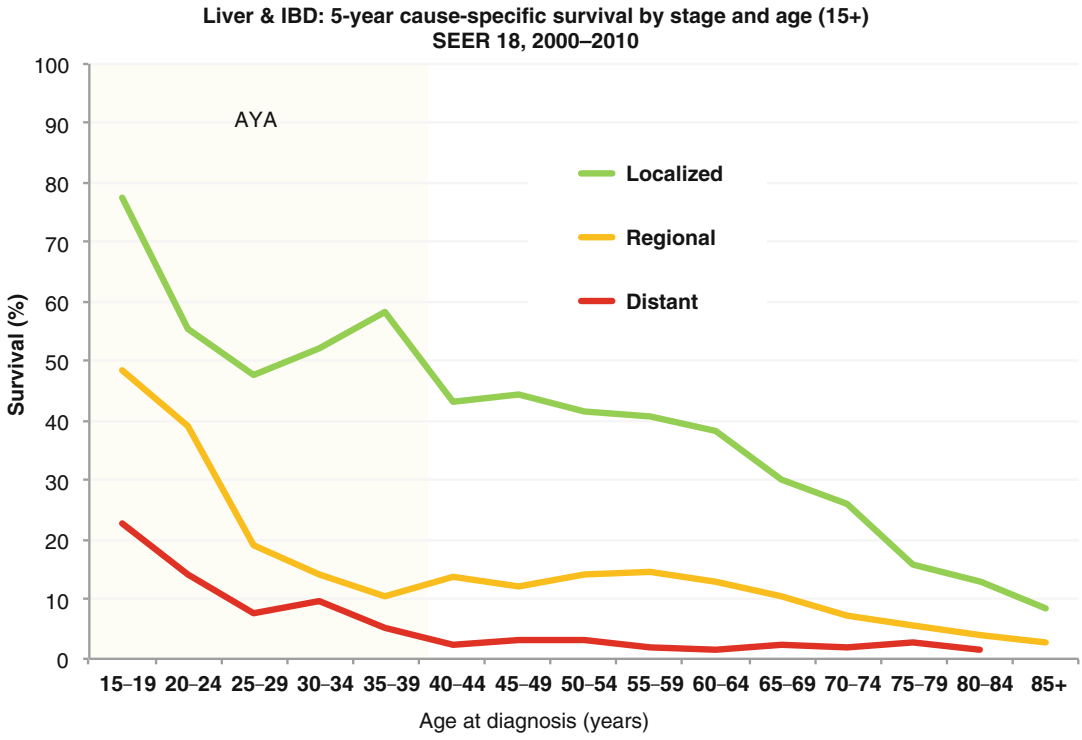

Fig. 18.7 5-year survival of patients in the USA with liver and intrahepatic bile duct cancer by stage and age, 2000–2011. Abbreviations: *IBD* intrahepatic bile duct (Data from the US SEER Program Bleyer WA; Source: National Cancer Institute: SEER18 Areas). Excludes unstaged – too few cases

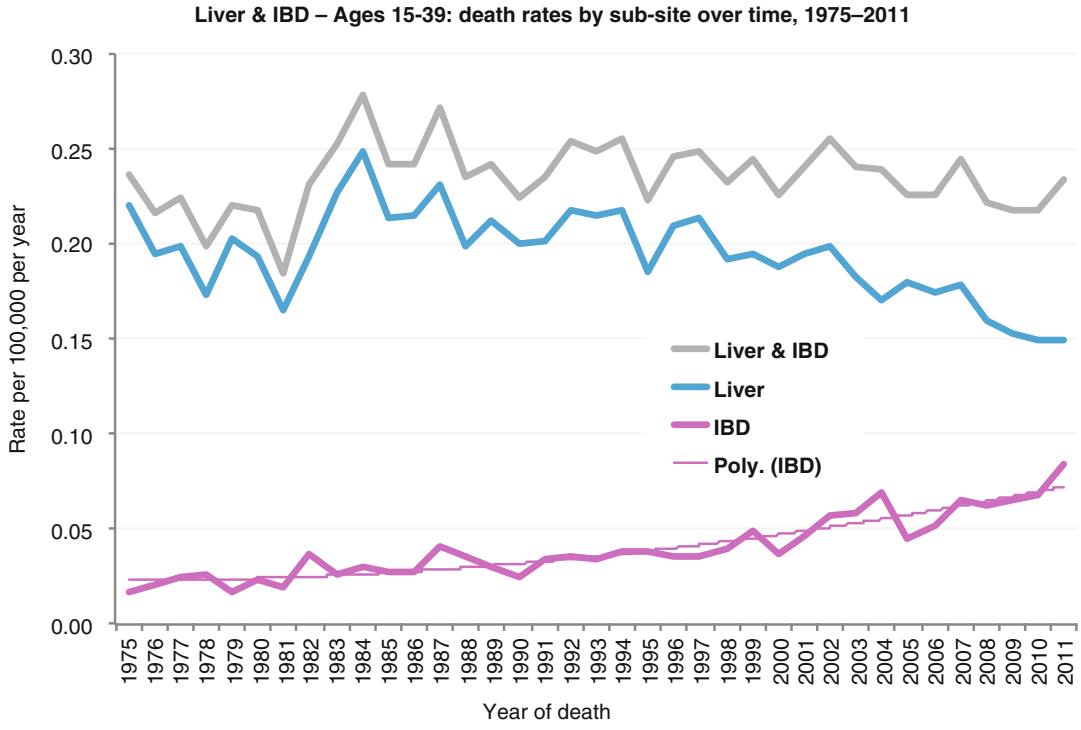

Fig. 18.8 Death rate of patients in the USA with liver and intrahepatic bile duct cancer (ages 15–39) by tumor site, 1975–2011 (Data from the US SEER Program Bleyer WA; Source: NCHS Mortality, Total U.S.)

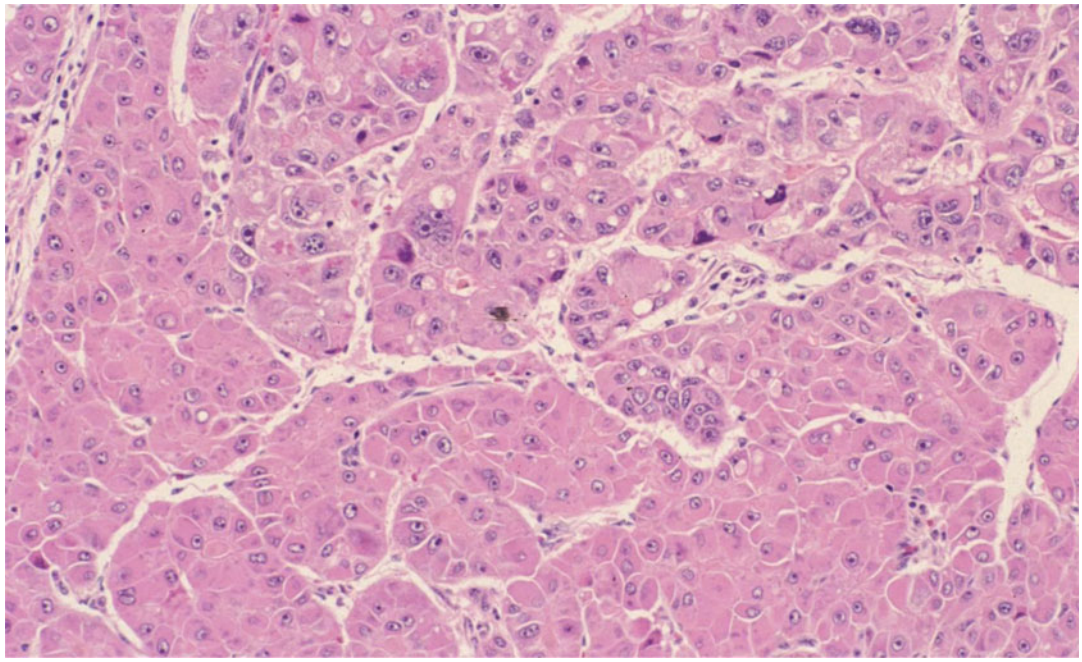

Fig. 18.9 Hepatocellular carcinoma, trabecular type: thick plates without typical intervening sinusoids

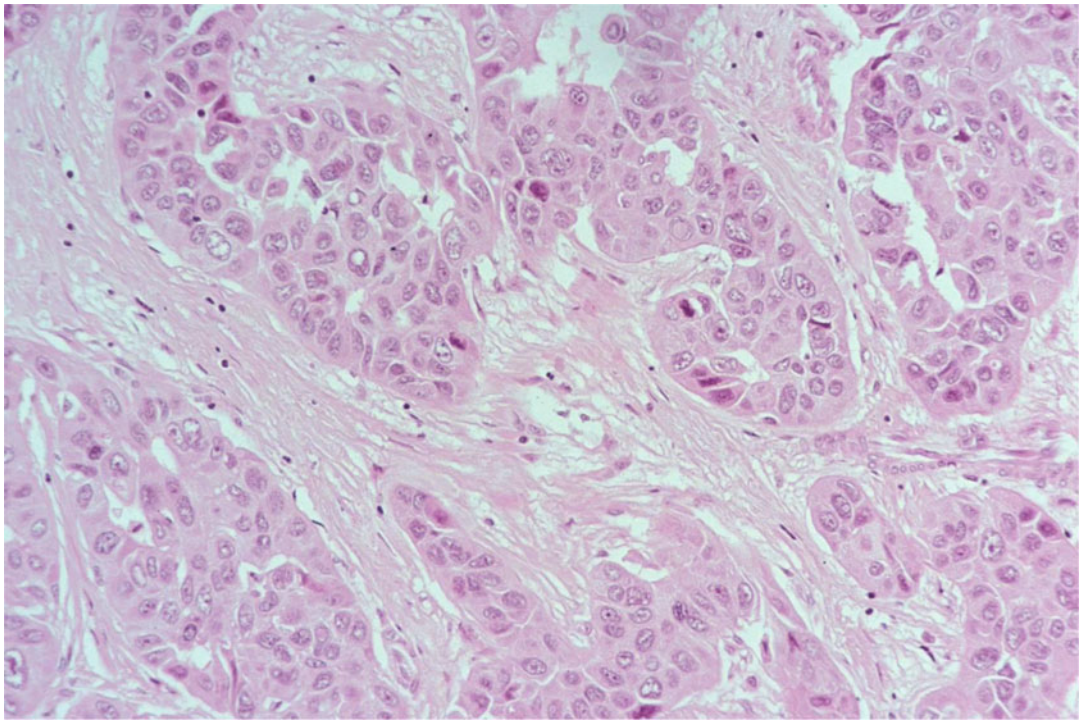

Fig. 18.10 Fibrolamellar carcinoma: solid nests of large and eosinophilic cells are embedded in a collagen-rich stroma forming fibrolamellar structures

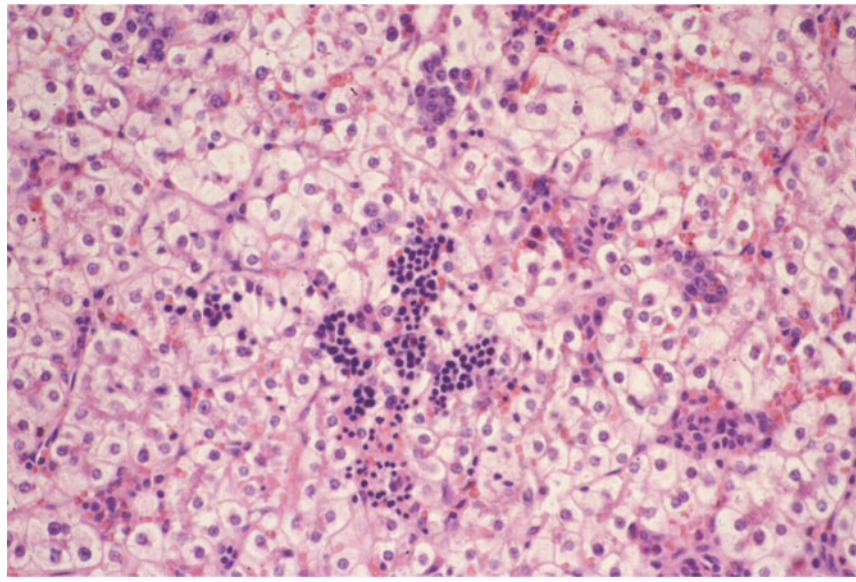

Fig. 18.11 Hepatoblastoma fetal morphology type: most of the tumor cells exhibit a clear cytoplasm. Extramedullary hemopoiesis is present

occurs in combination with HB [37] or HCC recurring as HB [38], suggesting a possible filiation of these neoplasms. Part of hepatic tumors in older children and adolescents contain HCC-like components and exhibit signs of cholangiocyte differentiation. Such highly aggressive lesions have been termed "transitional liver cell tumor" [39] and may be related to pleomorphic or anaplastic variants of HB. Similar to infants and children, adolescents and young adults may also develop unusual HB family tumors that have recently been identified, including small cell HB with "rhabdoid features" (tumors that do not immunohistochemically express the chromatin-remodeling protein INI1/hSNF5/SMARCB1) [40], and cholangioblastic HB.

The oncogenic pathways of HCC and HB differ in many respects. HCCs show multiple chromosomal aberrations (mainly losses), whereas HBs exhibit a lower number of chromosomal changes [30, 41]. In contrast to HCC, p53 gene (and related genes) mutations are almost lacking in HB, and p53 protein overexpression is seen infrequently [15, 42–44]. HB can develop in the setting of imprinting disorders, including Beckwith-Wiedemann syndrome (BWS) involving the loss of imprinting of IGF2 [45]. In BWS, HB was only detected in patients with chromosome 11p15 paternal uniparental disomy (UPD) [46]. HB can also complicate paternal uniparental disomy 14 and epimutations and microdeletions that affect the maternally derived 14q32.2 imprinted region, a constellation found in Kagami-Ogata syndrome [47].

In cancerogenic pathways leading to HB, abnormalities of the Wnt/beta-catenin signaling pathway play a central role [41, 48]. This signaling cascade is critically involved in cancer stemness and malignant behavior [49]. Beta-catenin gene mutations in HB involve the degradation targeting box [50], and the activation of beta-catenin involves both epithelial and mesenchymal HBs [51]. Mutations of beta-catenin gene in HB are associated with overexpression of proliferation factors, including cyclin D1 [52]. Based on its role on priming and expansion of stem and progenitor cells, beta-catenin activation may affect hepatic stem cells, including DLK1-positive oval cells present in HB [53]. Beta-catenin activation in a distinct progenitor cell type is sufficient to cause HB and HCC [54]. Beta-catenin can activate different transcriptional programs in subsets of HB, associated with distinct expression of hepatic stem-cell markers in

Table 18.2 Los Angeles hepatoblastoma classification

Epithelial hepatoblastomas
Fetal HB:
Well differentiated: uniform (10–20 μm), round nuclei, cords with minimal mitotic activity (<2 mitotic figures per 10/400× microscopic fields); extramedullary hematopoiesis present
"Crowded" or mitotically active: more than two mitotic figures per 10/400× microscopic fields; conspicuous nucleoli, usually less glycogen
"Pleomorphic or poorly differentiated": moderate anisonucleosis, high nucleus/cytoplasmic ratio, and prominent nucleoli
"Anaplastic": marked nuclear enlargement and pleomorphism, nuclear hyperchromasia, and abnormal mitotic figures
Embryonal HB:
Tumor cells 10–15 μm in diameter, high nucleus/cytoplasmic ratio, angulated nuclei, primitive tubular structures, and extramedullary hepatopoiesis usually absent
Macrotrabecular:
Epithelial HB (fetal or embryonal) growing in trabeculae of more than five cells thick (between the sinusoids)
Small cell undifferentiated:
Tumor cells 5–10 μm in diameter, no distinct architectural pattern, minimal pale amphophilic cytoplasm, round to oval nuclei with fine chromatin structure and inconspicuous nucleoli, and mitotic figures present; part of tumors lack nuclear INI1 expression
Cholangioblastic HB:
Bile duct-like profiles are present, usually at the periphery of epithelial HB islands; this pattern may predominate
Mixed epithelial-mesenchymal hepatoblastomas
HB with stromal derivatives:
Presence of spindle cells ("blastema"), osteoid, skeletal muscle, and cartilage
Teratoid HB:
Mixed HB plus primitive endodermal components, neural derivatives, melanocytes, and glandular elements

Lopez-Terrada et al. [34]; modified

immature tumors [55]. Alterations of other components of the Wnt signaling pathway have been found in HB, including mutations of the adenomatous polyposis coli (APC) and AXIN genes.

A further hepatic tumor showing abnormal Wnt/beta-catenin signaling is nested stromal-epithelial tumor (NSET; ossifying stromal-epithelial tumor) [56, 57]. This neoplasm occurs in both the pediatric age group and in adolescents and rarely in adults and is characterized by multiple clustered nests of immature epithelial cells embedded in a spindle-cell stroma with osteoid foci, surrounded by a sheath of myofibroblasts. NSET may be associated with Cushing's syndrome due to ectopic ACTH production [58] and usually shows a benign course, although recurrent and metastatic disease occurs. Marked nuclear reactivity of nested cells for beta-catenin is a consistent finding [31]. A later study uncovered mutations of the beta-catenin gene in NSET, characterized by large deletions in exon 3, suggesting that this neoplasm is related to HB with defective mesenchymal-epithelial transition [59]. This relation is supported by the association of NSET with Beckwith-Wiedemann syndrome [60]. Beta-catenin mutations occur in a subset of hepatocellular adenoma. Beta-catenin-activated hepatocellular adenoma can give rise to malignant hepatic tumors, including well-differentiated atypical HCC [61].

Recently, gene mutations affecting cellular functions other than those linked to Wnt signaling were detected in HB, including the ubiquitin ligase complex [62] and the transcriptional coactivator, Yap1 [63]. A subset of HB exhibits mutations of the transcription factor NFE2L2, involving residues that are recognized by the KEAP/CUL3 complex for proteasomal degradation [64]. Aggressive subsets of HB with HCC-like properties showed loss of genomic stability

and promoter mutations of telomerase reverse transcriptase (TERT) [64].

18.5 Clinical Presentation and Diagnosis

Since HCC in adults most often presents on a background of chronic liver disease, the symptoms are frequently masked by those associated with the underlying disease and are frequently found during routine screening exams in at-risk individuals. In children and adolescents with no underlying liver disease, the symptoms are usually of short duration, and most often patients present with an enlargement of the abdomen and an associated palpable right upper quadrant mass. Anorexia, weight loss, and abdominal pain are frequently seen in association with advanced disease. Rarely, it may present as an acute abdominal crisis secondary to tumor rupture. Jaundice, vomiting, fever, and pallor are rare. On physical examination hepatomegaly is common, and a palpable hard mass is frequently found. If the tumor is associated with preexisting inflammatory or metabolic diseases of the liver, signs associated with cirrhosis of the liver can be found, including splenomegaly and spider angiomata. Most frequently there is extensive involvement of the liver by the tumor, and often the tumor is multifocal in origin. The presence of ascites may suggest intra-abdominal extension, and at least one-thirds of the patients present with metastatic involvement, with the lungs being the most common site of disease.

Mild normochromic-normocytic anemia can be seen, as well as thrombocytosis and occasionally polycythemia secondary to extrarenal secretion of erythropoietin. Hepatic enzymes can be elevated; however, elevation of bilirubin is infrequent, unless it is associated with cirrhosis of the liver.

Alpha-fetoprotein (AFP) is the most valuable laboratory test for diagnosis and monitoring of hepatic tumors. Alpha-fetoprotein is a normal globulin present during fetal life, synthesized in the liver and fetal yolk sac. Elevated levels of AFP are seen during the newborn period, and adult levels are reached by about 1 year of age. The biologic half-life of AFP is 5–7 days. The level of AFP at diagnosis has been shown to be of prognostic value, and it can be utilized to monitor response to therapy and disease recurrence in hepatoblastomas [65]. Alpha-fetoprotein levels, however, can be normal in at least 30–50 % of the patients with HCC. Levels of carcinoembryonic antigen (CEA) and ferritin can also be increased in hepatocellular carcinoma [66]. The fibrolamellar variant of hepatocellular carcinoma can be associated with an abnormality of the vitamin B12-binding protein, which can occasionally be used to monitor disease status and response to therapy [67]. Screening for viral hepatitis (B and C) should be performed in all patients.

Plain radiographs of the abdomen frequently demonstrate the presence of a right upper quadrant mass, and calcifications may be noted in approximately 6 % of the malignant tumors [68]. Ultrasonography is a reliable and noninvasive imaging technique in establishing the presence of an intrahepatic mass and when used in conjunction with AFP measurements is a sensitive tool for screening of patients at high risk of developing HCC. It aids in differentiating solid from cystic masses and in determining the presence and extension of vascular extension [69, 70]. HCC are highly vascular tumors that preferentially supplied by hepatic artery branches rather than the portal venous system [71]; therefore, when triple-phase imaging techniques are used, these tumors typically demonstrate contrast enhancement in the arterial phase and washout of contrast media in the portal venous phase. In the USA, computed tomography (CT) or magnetic resonance imaging (MRI) is currently the preferred modalities for imaging these tumors [72]. Despite the tremendous advancement in radiographic imaging, including [^{18}F] fluorodeoxyglucose-positron emission tomography (FDG-PET) and diffusion MRI [73], changes in unidimensional tumor size, as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) system, continue to be the most widely used method to assess treatment response [74]. There

are numerous limitations in using the RECIST system for the evaluation of response, including the lack of reproducibility and the fact that size alone does not capture the biologic effects of targeted treatment.

18.5.1 Differential Diagnosis

Some other liver tumors (non-HB and non-HCC) which can occur in this age group should be considered in the differential diagnosis are discussed below.

18.5.1.1 Embryonal (Undifferentiated) Sarcoma of the Liver

It is a specific well-described but rare tumor not to be confused with rhabdomyosarcoma but generally responding to some similar type of chemotherapy used in the treatment of rhabdomyosarcoma [75].

It occurs mostly in older children and adolescents. Twenty-five percent occur between the age of 11 and 20 and 6 % between 16 and 20 years.

The tumor mainly presents as a large solitary mass often proceeded by rather unspecific abdominal symptoms. Liver function is usually not compromised.

The imaging can be confusing in that on ultrasound it appears solid but on CT and MRI may show cystic elements even so far as to be misinterpreted as a solitary cyst [76]. Therefore histological diagnosis is essential and can show some specific cells, i.e., "polygonal" cells.

There is no standard treatment protocol, and initially this tumor was considered highly malignant with a poor prognosis. This opinion has of late needed revising especially since the advent of preoperative chemotherapy [77]. Most tumors respond very well to rhabdomyosarcoma-like therapy, i.e., VAC regimen with vincristine, actinomycin, and cyclophosphamide, and to agents like doxorubicin and cisplatin. When these tumors are completely resected, the prognosis is relatively good [77].

With this approach and some personal experience, even some ruptured tumors are curable [78].

18.5.1.2 Adenocarcinoma, Cholangiocarcinoma, and Other Bile Duct Carcinomas

Since the incidence of adenocarcinoma, cholangiocarcinoma and other intrahepatic bile duct cancers peak in the AYA years they should be considered as part of the differential diagnosis.

18.5.1.3 Benign Tumors

Focal Nodular Hyperplasia (FNH) and Liver Cell Adenoma

These are essentially tumors of adults most commonly found in women taking contraceptives but occasionally also occur in the age group under consideration here, but with no know hormonal etiology. In the AFIP (Armed Forces Institute of Pathology Monograph (1977–1999)), 20 % of the total of the benign liver tumors seen between the age of 11 and 15 years were FNH.

Focal Nodular Hyperplasia

It often presents as an asymptomatic mass in the liver, which can mimic well-differentiated carcinoma. However there is usually a very specific scar-like lesion in the center, which differentiates it on imaging from this and from liver cell adenoma and the other benign lesions [79]. In children it has been associated with other diseases such a sickle cell disease, vascular malformations, and limb hyperplasia [80]. Also it has been described in children who have undergone treatment for solid tumors [81].

Liver Cell Adenoma

Liver adenomas have a bimodal distribution, occurring within the first year of life and then again over the age of 5. Liver adenomas can be quite large and present with abdominal symptoms, like distension and pain, and their growth is unpredictable.

Obviously, for benign lesions the only possible treatment apart from the "watch, wait, and see" approach, is surgical excision. There are no hard and fast rules about which is best, and the various guidelines are very flexible and the results of both approaches acceptable [82]. Basically symptomatic lesions should be excised if feasible without too great a risk.

Neither lesions pose a realistic risk of malignancy so that the "watch, wait, and see" approach with regular imaging and follow-up is quite appropriate.

18.5.2 Tumor Staging

Tumor staging is used to determine prognosis and planning therapy and provides a common language to compare results of clinical trials. Since children and adolescents with HCC have been treated according to therapeutic trials for hepatoblastoma, the staging classifications used by the pediatric groups are very different than those used by the adult oncology groups. In North America the most widely used staging system is based on the extent of tumor and surgical resectability [83–85], while the International Society of Pediatric Oncology (SIOP) uses a preoperative staging system (Pretreatment Extent of Disease System – PRETEXT) (Fig. 18.12). PRETEXT relies on radiological staging using the main veins and bile ducts to identify the number of liver sectors involved by the tumor [86, 87]. Since more than 70 % of HCC in adults develop in cirrhotic livers, the conventional pretreatment TNM staging system is clinically inadequate because it does not take in consideration parameters of hepatic function. Instead, current staging

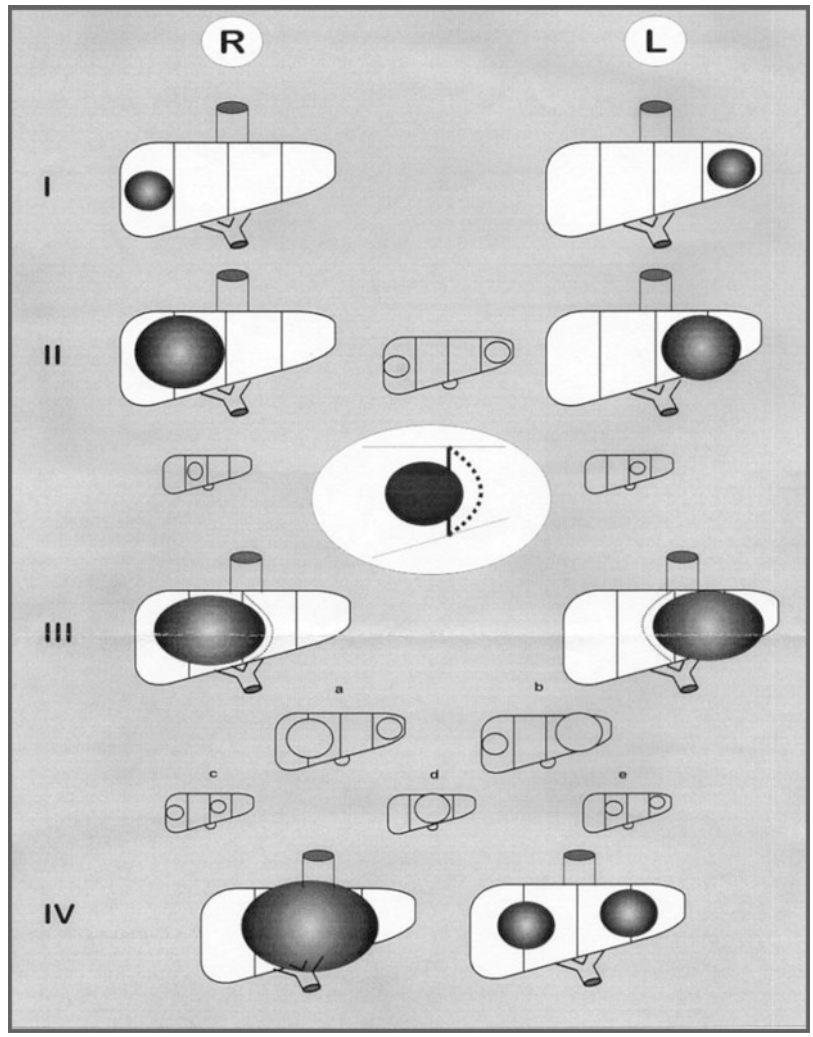

Fig. 18.12 Pretreatment Extent of Disease System (PRETEXT) of the International Society of Pediatric Oncology (SIOP)

systems used in adult liver cancer trials, such as the CLIP (Cancer of the Liver Italian Program) [88], the BCLC (Barcelona Cancer of the Liver Committee) [89], the CUPI (Chinese University Prognostic Index score) [90], and the Japanese Okemah system [91], incorporate the extent of disease and liver function according to the Child-Pugh (CP) system [92], to determine risk groups and for treatment planning. The CP system was first developed in the 1960s as a tool to access the prognosis of surgery for variceal bleeding in patients with cirrhosis and portal hypertension, and it is based on a score derived from five variables including conventional liver function tests (albumin, bilirubin, INR), extent of ascites, and degree of hepatic encephalopathy. Some of the variables considered in the CP grading system are interrelated (e.g., ascites and albumin levels), and the grading of ascites and encephalopathy relies on arbitrarily defined and highly subjective cutoff points. Recently, Johnson et al. reported on the results of a new evidence-based approach, the ALBI grade model (albumin and bilirubin) to evaluate liver dysfunction that eliminates the need for subjective variables such as ascites and encephalopathy [93]. The study included greater than 6,000 patients from four different global regions (Japan, Europe, China, and the USA) and with disparate etiologies. They concluded that the ALBI model stratified patients in three liver function categories that compared favorably with the CP score for impact on survival, but that is simpler to ascertain, objective, and discriminatory.

In contrast to adults and since adolescents and young adults frequently develop hepatocellular carcinoma without preexisting cirrhosis, it would seem appropriate to use a system least dependent on the functional state of the liver, such as the TNM or PRETEXT system.

18.6 Treatment and Outcomes

Since the treatment strategies and outcomes for children and adolescents with hepatocellular carcinoma are so different than those for adults, they will be discussed separately in this chapter.

18.6.1 Adults with Hepatocellular Carcinoma

HCC is the fifth most common solid tumor worldwide and is the third leading cause of cancer-related death. Despite the many advances in treatment discussed below, greater than 70 % of the patients present with advanced disease and will not benefit significantly from these treatment modalities.

Since the main risk factor for HCC is liver cirrhosis caused by alcohol consumption and/or chronic infection by hepatitis B or C, primary prevention through vaccination (hepatitis B) and implementation of adequate health standards and antiviral treatment to prevent progression to cirrhosis (hepatitis C) may be the only effective ways to change this outcome. As previously discussed, a universal program of hepatitis B immunization has resulted in a decrease in HBV-related hepatocellular carcinoma [7, 94] However, no therapy has demonstrated to be efficacious once cirrhosis develops. Therefore, surveillance aimed at early detection of tumor and implementation of effective therapy is the only option to diminish tumor-related mortality. The European Association for the Study of the Liver recommends that patients with cirrhosis who could undergo potentially curative treatment for HCC should have surveillance ultrasonography and serum AFP every 6 months [95].

Because more than 90 % of HCC in adults arise in patients with underlying cirrhosis and hepatic dysfunction, the treatment of HCC requires management of both the malignancy as well as the liver disease.

The standard management for early-stage disease consists of tumor resection or liver transplantation that currently is the only curative option. Less than a third of these patients are eligible for surgery. Hepatic resection is the best surgical option for patients without cirrhosis, and for those with cirrhosis, limited surgical resection, liver transplantation, or tumor ablation is an available management option. The selection of patients for resection includes tumor size, degree of hepatic dysfunction, and anticipated future liver remnant since surgery in patients with cir-

rhosis can be associated with significant morbidity and mortality [96]. The 5-year survival rate for surgical resection of early stage is 45–50 % compared to 65–70 % for transplantation (97 liver transplant is regarded as the ideal therapy because it theoretically cures both the tumor as well as the underlying liver disease [97–100]). Patients that fit the Milan criteria (single nodule <5 cm or *≤3 nodules each ≤3 cm) have a 4-year disease survival greater than 80 %* [101]. However this treatment is not readily available worldwide, and in some countries the shortage of cadaveric donors impacts negatively in the usefulness of transplantation [97, 102]. The lack of sufficient cadaveric donors has prompted the use of living donor liver transplantation as a feasible alternative [103–105], and preliminary results demonstrate similar outcomes. While adjuvant therapies have been used to prevent tumor progression while patients are on the waiting list, the benefit of these therapies has yet to be confirmed by randomized studies.

For patients with HCC confined to the liver whose disease is not amenable to resection or transplantation, locoregional therapies, including tumor ablation, can be considered. These include percutaneous intratumoral injection of chemical substances (ethanol, acetic acid, hot saline) or by modifying the temperature of tumor cells (radio frequency, microwave, laser, and cryoablation) [106–112], stereotactic radiation therapy, transarterial embolization, radioembolization, or chemoembolization. Although these therapies are not curative, these approaches produce tumor destruction while preserving the uninvolved liver parenchyma, and at times it may be used as a bridge for more definitive therapy, such as liver transplantation. To date, the use of adjuvant therapy to prevent recurrence after curative treatment, including the use of daily sorafenib for up to 4 years, has shown no benefit [113, 114].

Systemic chemotherapy is the only therapeutic option for patients with extrahepatic disease, portal venous system involvement, or metastatic disease. However, one needs to be careful in evaluating the reported results of this approach since the patients for whom systemic chemotherapy has been routinely offered are those with advanced disease and with compromised liver function. Poor liver function may lead to increase morbidity and mortality. The discouraging results obtained with past studies may in part reflect the need for adjusting the doses of the therapeutic agents to the degree of liver dysfunction. Hepatocellular carcinomas are considered widely chemotherapy resistant. Response rates from 15 to 35 % have been reported with single agents, but durable remission is uncommon. The high incidence of overexpression of the multidrug resistance gene (MDR-1) and the gene product P-glycoprotein may in part explain some of this chemotherapeutic resistance of HCC [115–117]. Doxorubicin used as a single agent or in combination showed no clear evidence of survival benefit [117–122]. Other chemotherapeutic agents of the older generation that have been studied as single agents for the treatment of HCC include 5-fluorouracil [123–125], cisplatin [126, 127], and etoposide [128, 129]. The newer generation chemotherapeutic agents, like capecitabine [130], gemcitabine [131, 132], paclitaxel [133], and irinotecan [134] as single agents, have not shown any better response and at times even shown lesser activity.

The promising cisplatin, recombinant interferon-α2b, doxorubicin, and 5-fluorouracil (PIAF) regimen failed to show a significant survival difference when compared in a randomized trial single-agent doxorubicin [135]. Despite advancements in the use of systemic chemotherapy, its use in adults is not generally recommended.

Advancement in systemic therapies will come from the use of newer targeted therapies. Numerous signaling pathways, such as epidermal growth factor, VEGF, Ras/Raf/Map kinase, Wnt/beta-catenin, Akt/mammalian target of rapamycin (mTOR), have been implicated in the pathogenesis of HCC and have been targeted with novel therapeutic agents 136]. Sorafenib, an oral multikinase inhibitor with antiangiogenic and antiproliferative actions, was the first targeted therapy proven to provide survival benefit over placebo in patients with advanced HCC and Child-Pugh class A, treated on two phase III randomized studies [137, 138]. Despite the sig-

nificant adverse effects (diarrhea, weight loss, and hand-foot skin reaction) and the failure of these studies to demonstrate symptomatic improvement or improved quality of life, sorafenib was approved in 2007 for the treatment of HCC patients in the USA and Europe and become the standard of care and benchmark to surpass for newer and future targeted therapies.

Finally, there is no proven effective therapeutic option for patients with significant liver dysfunction, or decompensated cirrhosis therapy should focus on symptomatic relive to avoid unnecessary suffering.

A recent review of adult patients with fibrolamellar HCC documented that those patients had an overall statistically significant increase in the 5-year survival when compared to those with conventional HCC. However, further subgroup analysis demonstrated that the 5-year survival was no different among non-cirrhotic patients or for patients undergoing liver transplantation [139].

18.6.2 Children and Adolescents with Hepatocellular Carcinoma

Despite the fact that HCC is biologically different than hepatoblastoma, children and adolescents with HCC have historically been treated similarly. And most often they have been treated according to international cooperative studies conducted by the four major pediatric liver tumor study groups (the Children's Oncology Group (COG), International Childhood Liver Tumor Strategy Group (SIOPEL), German Society for Pediatric Oncology and Hematology (GPOH), and Japanese Study Group for Pediatric Liver Tumor Group (JPLT)).

Complete tumor resection has been the cornerstone of therapy for liver tumors in pediatrics and offers the only realistic chance of long-term disease-free survival [4, 5, 85, 140]. New surgical techniques and careful patient management during and after surgery have minimized the risks associated with liver resection and improved resection rates. In general the type of surgery is dependent on the extent of liver involvement, as defined by the PRETEXT classification, and is resected according to the segmental scheme of Couinaud (segmentectomy, hemihepatectomy, or extended hepatectomy).

Tumors with invasion of all major hepatic veins or portal veins, extensive multifocality, or extensive liver involvement (PRETEXT IV) should be considered for liver transplantation [5, 141]. The results for liver transplantation in pediatric HCC have significantly improved, and it may offer an important chance of cure for patients with tumors confined to the liver [141–145].

Systemic chemotherapy with cisplatin and doxorubicin with or without other agents has become an important part of the therapy for children with HCC, and it has been used as adjuvant therapy for patients who undergo complete tumor resection at the time of diagnosis, to induce tumor shrinkage preoperatively in those tumors considered unresectable, or for tumor control, while patients are waiting for liver transplantation.

A number of guiding principles should be taken into account when considering transplantation for HCC in children [146]. HCC tumor progression while on chemotherapy is a relative contraindication, since occult extrahepatic micrometastatic disease is increasingly possible in this situation. PRETEXT III or IV pediatric "de novo" tumors in the absence of underlying cirrhotic liver disease and in the absence of extrahepatic disease are generally considered candidates for transplant, regardless of their Milan criteria. The problem with Milan criteria in children is that most children present with large tumors in otherwise healthy livers, whereas the Milan criteria were developed in adults with small multifocal tumors and underlying cirrhotic liver disease. Two recent series questioned the relevance of Milan criteria to pediatric HCC [147, 148]. In view of the lack of improvement in results of conventional treatment of pediatric HCC over the past two decades, most clinicians treating pediatric HCC do not recommend adherence to Milan criteria in children who present with large de novo tumors and no evidence of extrahepatic disease [23, 146–148].

According to a review of the published literature and data presented by members of pediatric liver tumor study groups during international meetings, a total of 243 patients were enrolled and treated on these international cooperative studies. When feasible, patients were submitted to an up-front resection of their tumors. Unresectable tumors were biopsied followed by neoadjuvant chemotherapy (consisting of a platinum agent in combination with one or more drugs) in an attempt to shrink the tumor and facilitate resection while waiting for liver transplantation. The majority of the patients (60 %) were older than 10 years of age. Advance and metastatic disease were seen at diagnosis in 58 % and 30 % of the patients, respectively. Up-front complete tumor resection was successfully performed in 19 % of the patients. Of the 162 patients evaluable for tumor response to chemotherapy, 2 (1 %) had complete response and 66 (41 %) a partial response. Resection post-chemotherapy was attempted in 134 patients. Of these patients, complete tumor resection was achieved in 46 (34 %); partial resection in 29 (22 %) and 14 (10 %) underwent liver transplantation. Overall 91 (37 %) of 243 patients had complete resection of the tumor at some point during therapy. Despite this significant response rate to chemotherapy and resectability of the tumor, the event-free and overall survival remained dismal [149, 150].

The above data as reported by these international trials support the fact that HCC in children and adolescents may indeed be a distinct entity. A distinct pathogenic pathway may explain why children and adolescents with HCC can tolerate and respond to chemotherapy better than their adult counterparts. It may also justify the use of a more aggressive approach for the treatment of these children and adolescents.

The combined data from these international studies allows us to better anticipate the characteristics of these tumors and potential response to treatment. An aggressive up-front surgical approach to the treatment of children with localized unifocal tumors is warranted and supported by an overall survival greater than 80 % for those who had a complete tumor resection at diagnosis. Response to chemotherapy in this group of patients was almost 40 %. This chemotherapy response rate is much higher rate than reported in adult studies (10–20 %) but less worse than that seen in children with hepatoblastoma [149, 150]. As a result of this response, more than two-thirds of the patients who received preoperative chemotherapy went on to have an attempt at surgical resection of the tumor, and complete resection was accomplished in one-third of them, a remarkable rate considering the known relative resistance of these tumors to chemotherapy. Lastly, this data does not allow for comments in regard to the efficacy of liver transplantation for this disease. However, the fact that only 10 % of the patients were submitted to a liver transplant may be an indication that the strict transplantation criteria used in adults may be too restrictive for the pediatric population.

Differently than what has been reported for adults, patients with FL-HCC do not have a favorable prognosis and do not respond differently to current therapeutic regimens than patients with conventional HCC [151, 152]. This result is different than those published in a recent report by Allan et al. In this report, 218 patients between ages 0 and 19 with HCC reported to SEER between 1973 and 2009 were identified, and although the overall outcomes for these patients were not different than for those enrolled on international cooperative studies, patients with FL-HCC exhibited greater survival compared to those with conventional HCC [153].

As for adults, locoregional therapies, including tumor ablation, transarterial embolization, radioembolization, or chemoembolization, can be used as a bridge to liver transplantation, to improve resection, and/or for palliation and symptom control.

Due to the small numbers of children and adolescents with recurrent or progressive liver tumors enrolled on phase I studies, patients with HCC have not yet benefited from the explosion of available targeted agents like adult patients. Currently most available data come from limited phase I/II studies of these agents or single-institution reports. Sorafenib is the only agent used regularly alone or in combination with conventional chemotherapy for the treatment of

pediatric HCC. A recent report from the GPOH group demonstrated that the use of sorafenib in combination with cisplatin and doxorubicin was feasible and associated with partial response or stable disease in six out of seven patients with unresectable disease [154].

18.7 Future Perspectives

The overall survival for children and adults with hepatocellular carcinoma, with the exception of highly selected patients for whom complete tumor resection is feasible, continues to be dismal.

In the Western countries, hepatocellular carcinoma in older adults is secondary to liver cirrhosis caused by alcohol consumption and/or chronic infection by hepatitis B or C; primary prevention through vaccination (hepatitis B) and implementation of adequate health standards and antiviral treatment to prevent progression to cirrhosis (hepatitis C) may be the only effective ways to change this outcome. In Asia and African countries, hepatocellular carcinoma is related to chronic infection with hepatitis B virus acquired at birth or at an early age. Universal hepatitis B immunization programs will continue to dramatically reduce the incidence of HCC in these countries.

Since no therapy has demonstrated to be efficacious once cirrhosis develops, surveillance aimed at early detection of tumor and implementation of effective therapy is the only option to diminish tumor-related mortality.

In contrast to the older adults in whom almost 90 % of the cases of hepatocellular carcinoma are associated with cirrhosis, less than a third of adolescent or young adult HCC patients are associated with hepatitis or other inflammatory liver disease. Furthermore, the majority of these young patients is in good state of health and has normal liver function. Therefore, treatment choices for these patients should have a curative goal even at the expense of increased toxicity.

Tumor resection should be the therapy of choice for adolescents and young adults with localized disease. For those patients for whom up-front surgical resection is not feasible, the use of percutaneous tumor ablation or intra-arterial chemoembolization has been associated with a high response rate and increased survival; however, failures are usually associated with local tumor recurrence. Therefore, future studies are needed to determine if the association of surgical resection of these lesions following local control measures, like chemoembolization or percutaneous ablation, can improve these results.

Differently than for those with localized disease, treatment for patients with advanced unresectable or metastatic disease has not been associated with an improvement in the response rate or overall survival. Since conventional chemotherapy have yielded limited results to date, advancement in systemic therapies will come from the use of newer agents that target the numerous signaling pathways implicated in the pathogenesis of HCC. Future studies are needed to explore the efficacy of these targeted agents alone, in combination with other targeted agents or with conventional chemotherapeutic agents.

Given the rarity of malignant liver tumors in the adolescent and young adult population, national and international collaboration will be essential to evaluate these novel therapeutic approaches, to establish the role of liver transplantation for these patients and to continue to improve our understanding of the biology of HCC in this population.

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Other Carcinomas

19

Archie Bleyer

Chapters 12, 13, 14, 15, 16, 17, 18, and 19 summarized the most frequent carcinomas in AYAs. This chapter reviews the remaining carcinomas of importance in AYAs: carcinomas of the head and neck, lung, and stomach. Given the limited space for this chapter, diagnosis, staging, and treatment are considered in brief.

19.1 Head/Neck Cancer in AYAs in the United States

Head and neck cancer includes 11 sites: lip, tongue, salivary gland, floor of the mouth, gum and other mouth, nasopharynx, tonsil, oropharynx, hypopharynx, other oral cavity and pharynx, nose, nasal cavity, and middle ear. In American AYAs, the most common anatomical sites of occurrence are the salivary gland, tongue, nasopharynx, gum, and nose/nasal cavity/middle ear (Fig. 19.1). This pattern differs from that of older patients in whom carcinoma of the tongue predominates and salivary gland and nasopharyngeal carcinoma are relatively less common (Fig. 19.1). Much of the difference is likely due to a biologically different type of head/neck carcinoma in AYAs at least in part is related to human papillomavirus (HPV) and the Epstein–Barr virus (EBV) (discussed below).

19.1.1 Incidence

Figure 19.2 shows the incidence of head and neck (oropharyngeal; oral cavity and pharynx: lip, tongue, salivary gland, floor of the mouth, gum and other mouth, nasopharynx, tonsil, oropharynx, hypopharynx, other oral cavity, and pharynx) cancer during 2000–2011 in the United States as a function of age and sex. The incidence of head/neck cancer had a distinct sigmoid relationship with age. From age 10 to 40, the increase was exponential (Fig. 19.2, inset). Above the age of 30, males had a greater incidence of head/neck cancer; by age 40–50, the incidence was twice that in females. Before age 30, the incidence in males and females was the same.

Figure 19.3 depicts the incidence in the United States as a function of extent of disease at diagnosis. In AYAs, the most common stage at diagnosis was localized (inset), whereas in older persons, it was a regional disease. Less than 10 % of AYAs presented with distant metastases (Fig. 19.3, inset). In situ histology accounted for only 2 % of head/neck cancer in AYAs (inset). In AYAs, Asians/Pacific Islanders had the greatest incidence of head/neck cancer and native North Americans the least. This is in contrast to persons

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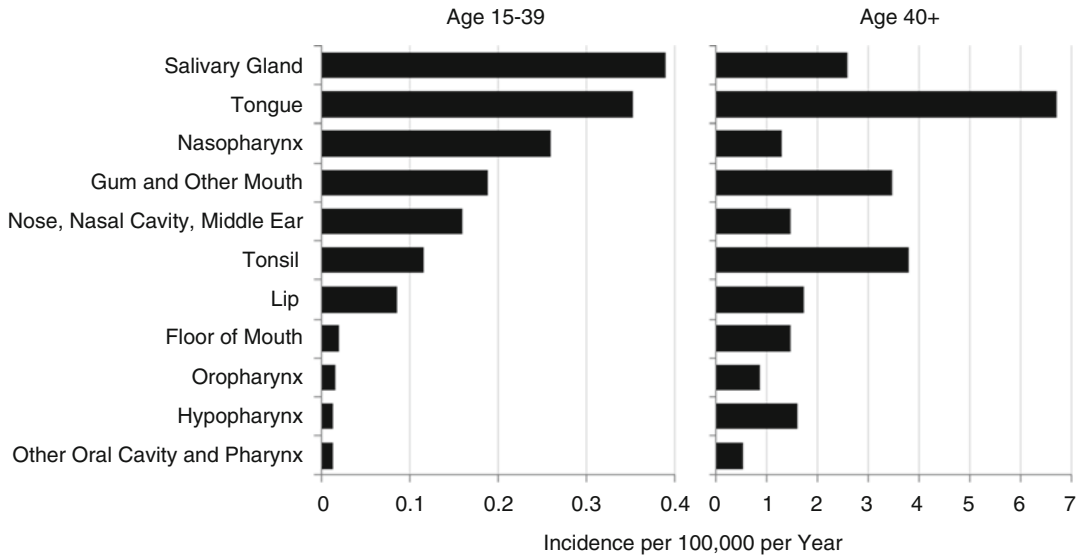

Fig. 19.1 Incidence of invasive head and neck cancer in AYAs (age 15–39), 2000–2011, SEER18, by anatomical site

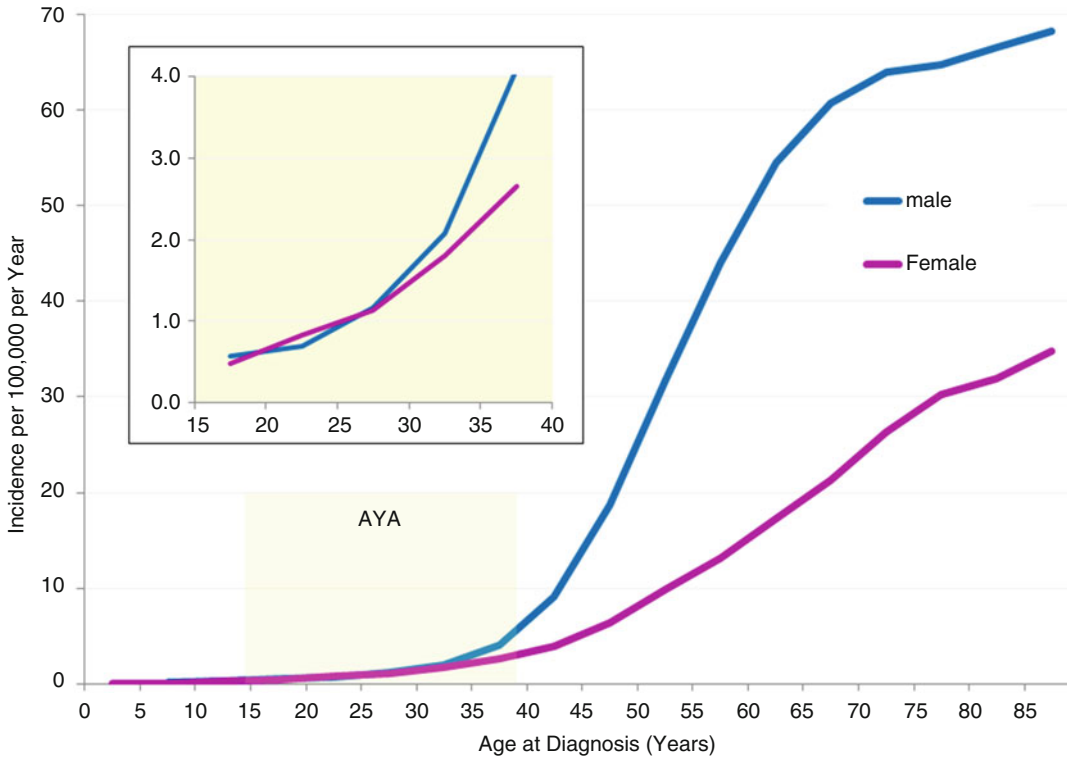

Fig. 19.2 Incidence of invasive head and neck cancer, 2000–2011, SEER18, by stage and age. The *inset* depicts the AYA age range

of older age in whom non-Hispanic whites and blacks distinctly had the highest incidence. In AYAs, males had 56 % of the malignant head/neck cancers, Asians/Pacific Islanders had 32 %, non-Hispanic white had 24 %, and blacks had 21 % of the cancers.

During 2000–2012, Asians/Pacific Islanders in the United States had the highest incidence of

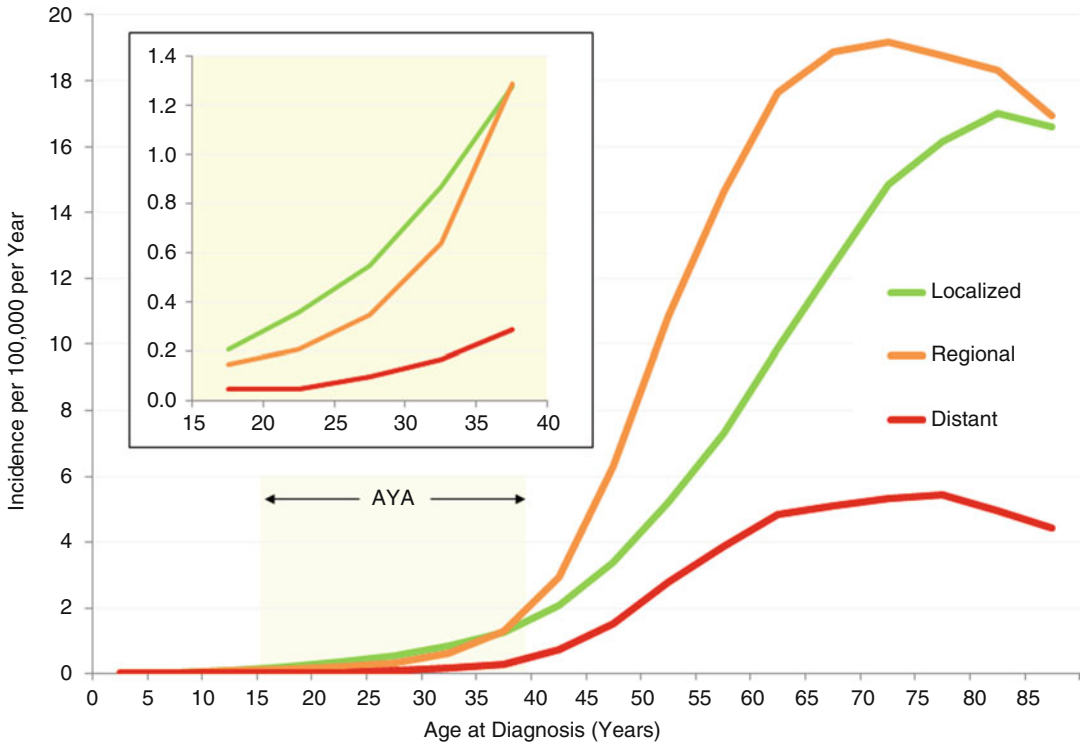

Fig. 19.3 Incidence of invasive head and neck cancer, 2000–2011, SEER18, by stage and age. The *inset* depicts the AYA age range

head/neck cancer in AYAs, in contrast to the non-Hispanic whites and blacks in older adults (Fig. 19.4). Hispanics had the lowest incidence at all ages (Fig. 19.4).

The proportion of head/neck cancer that is Epstein–Barr virus associated (EBV+) and human papillomavirus associated (HPV+) (Table 19.1) is greater in AYAs than in any other age group [1, 2]. Nearly half of head/neck cancers in AYAs are HPV+.

19.1.2 Incidence Trends

Whereas the incidence of head/neck cancer in both males and females older than 40 decreased steadily during the 1980s and 1990s, attributed to the decline in smoking in the United States, the incidence of head/neck cancer in AYAs from 1975 to 2011 was relatively constant in males; it increased steadily in females, however (Fig. 19.5). The lack of continued decrease in older adults since 2000 is disappointing and may indicate a failure of anti-smoking campaigns since then. All of the age subgroups in AYAs have had a constant incidence of head/neck cancer since 1975.

In the United States, the incidence of cancer in the oral cavity and pharynx was reduced successfully with public health programs that diminished the prevalence of tobacco use. In 2007, the prevalence of smoking dropped below an age-adjusted age rate of 20 % from as high as 57 % for men in 1955 and 34 % for women in 1965 [3, 4]. Recently, however, this progress in reducing the incidence of oropharyngeal cancer has declined in some population subgroups as the tobacco-related cancers have been replaced by those related to the human papillomavirus (HPV) [5, 6]. HPV, the causal factor in nearly all carcinomas of the uterine cervix, is also known to have a role in the pathogenesis of squamous cell carcinomas of the oral cavity and pharynx [7–15]. In vitro, HPV serotypes 16 and 18 are capable of transforming epithelial cells derived from both the genital and upper respiratory tracts [16], and HPV has been demonstrated to alter

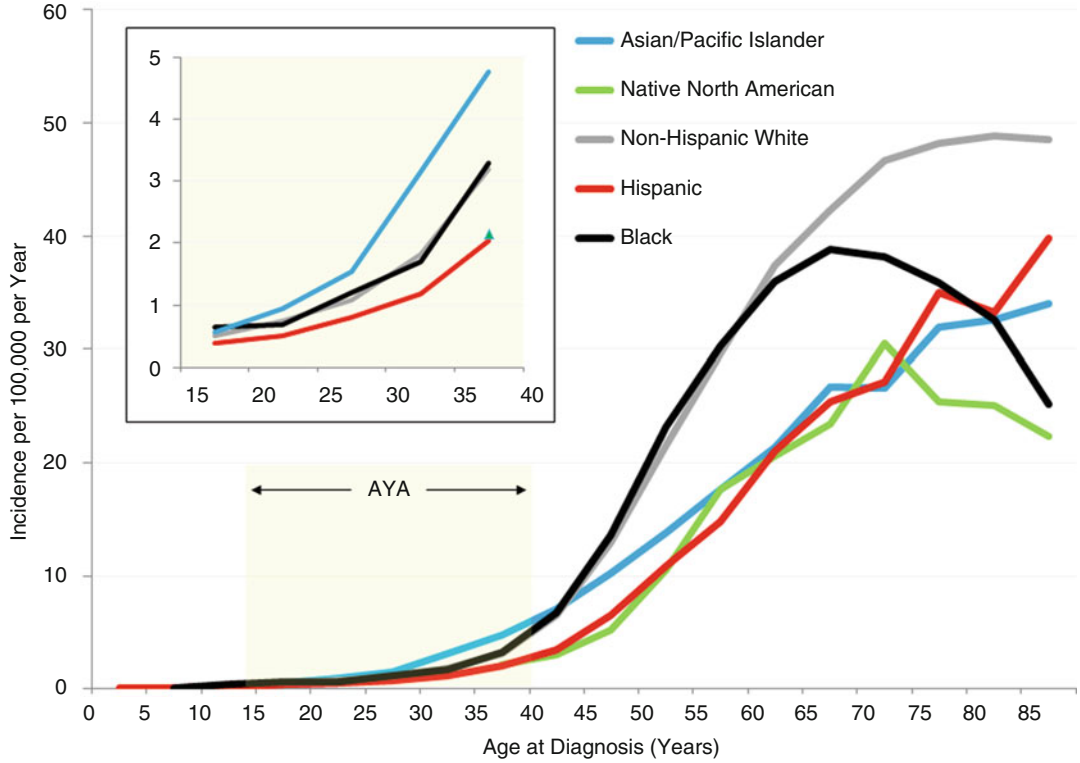

Fig. 19.4 Incidence of invasive head and neck cancer, 2000–2011, SEER18, by stage and age. The *inset* depicts the AYA age range

Table 19.1 Proportion of head/neck carcinoma that is HPV+, 2005, by age at diagnosis

	Age at diagnosis (years)			
	<45	45–54	55–64	65+
Incidence HPV–[a]	0.5	5.8	8.5	12.0
Incidence HPV+[a]	0.4	9.0	20.0	30.0
% HPV+	44 %	39 %	30 %	29 %

Data obtained from Cole et al. [2]
[a]Per 100,000 per year

p53 and Rb human oncogenes [17, 18]. The higher incidence of oropharyngeal cancer in females than males is consistent with orogenital sexual activity that puts females at higher risk of HPV transmission.

The increase in oropharyngeal cancer is apparent in females as young as 15 to 19 years of age [19]. The oldest 5-year age group demonstrating the acceleration was the 30- to 34-year-olds [19]. The recent acceleration in incidence among females is most obvious from age 15 to 34 [19]. The increase in females was due primarily to squamous, mucoepidermoid, and acinar carcinomas and not adenocarcinoma or other epithelial and glandular carcinomas of the head and neck [19]. The incidence trends were statistically significant for the squamous and acinar morphologies [19]. The anatomic sites within the oral cavity and pharynx that were most affected by the increase in females were the salivary glands and tongue, followed by the nasopharynx and tonsils [19]. The oropharynx and other sites classified in the ICD-O-3 designation did not demonstrate an increase in the age group. When the last decade is compared with prior decades, nearly half of the increase occurred in the salivary glands and more than a third in the tongue [19].

The decreasing incidence of oropharyngeal cancers since the 1980s in both men and women [20] was reversed in females less than 40 years of age in the early 1990s and resulted in an accelerating increase at least until the most recent year

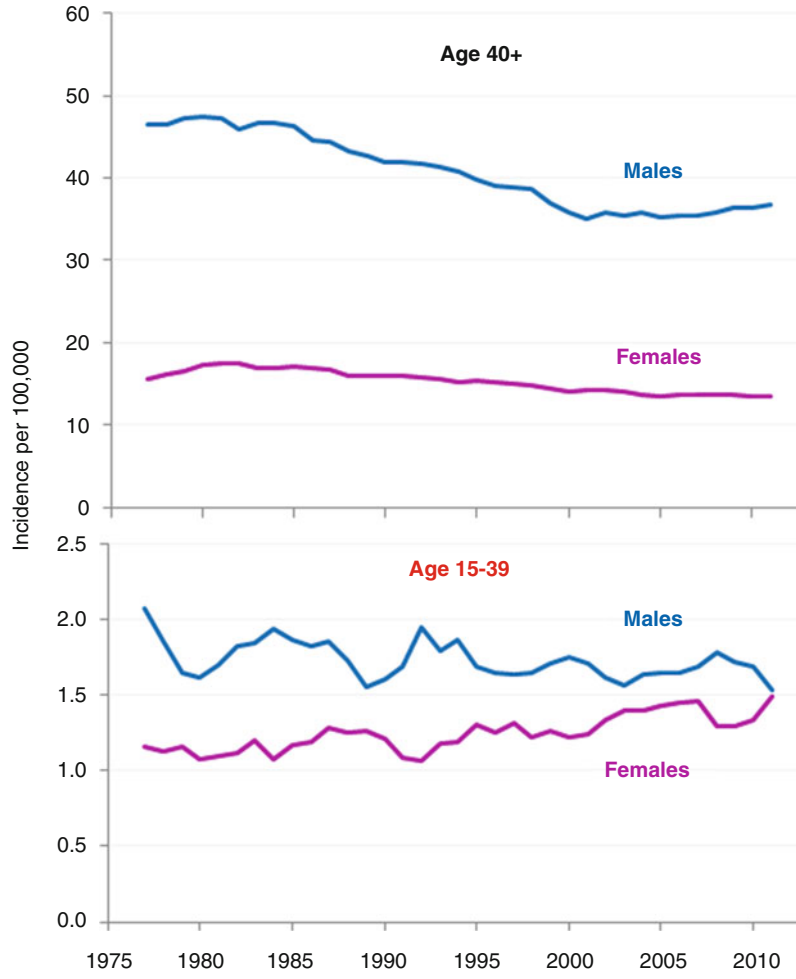

Fig. 19.5 Annual incidence of invasive head and neck cancer in AYAs (age 15–39) and older adults (age 40+), 2000–2011, SEER18, by sex 3-year moving averages

of available data. This pattern coincides with the national increase in orogenital sexual intercourse in young females and earlier age of sexual intercourse, in part because oral sex has had increased acceptability among adolescents and young adults and in some it is an alternative to vaginal intercourse. In an outpatient setting, the risk for developing HPV infection in 18- to 23-year-olds was found to increase with the number of lifetime oral sex partners ($p < 0.007$) [20].

Specific sexual behaviors have been associated more strongly with the risk of an HPV+ tumor, including a history of performing oral sex and oral–anal contact [21–24]. In a hospital-based population, patients who reported having had one to five oral sex partners were 3.8 times more likely to have an HPV-related oropharyngeal cancer, and if six or more partners were reported, the increase was 8.6-fold (95 % confidence interval of 2.2–34.0 times) [11].

That the most common anatomic sites within the oral cavity and pharynx that were affected by the increase in incidence in females were the salivary glands and tongue is also consistent with a transmission of a virus by direct topical contact via the genital–oral route. Other sites that contributed to the increase are the nasopharynx and tonsils. Sites that have not had an increase in females include the floor of the mouth, oropharynx, and hypopharynx, which are not involved as directly with this route of transmission. On the other hand, the majority of HPV+ tumors in males with oropharyngeal cancer have been reported previously to occur mainly in the lingual

and palatine tonsils of the oropharynx [8, 9, 17, 25–30]. The difference with the results of the study reported here is probably due to the fact that oropharyngeal predilection may be limited to males [21] and this study demonstrates an overall increase only in females. The incidence trends observed in this report may implicate the more anterior compartment of the oropharyngeal carcinoma in the pathogenesis of HPV-related, genital–oral-induced human neoplasia. Most of the increase in females was due to squamous carcinoma and, in the salivary glands, mucoepidermoid and acinar carcinomas. The predilection for squamous epithelium is consistent with what has been reported previously as the tropism for HPV [10, 12, 13, 18].

The dramatic decrease in the incidence of oropharyngeal cancer in 25- to 39-year-old males is likely due to the reduction in tobacco use and reversal of the HIV/AIDS epidemic. The decrease in older persons, both male and female, is likely primarily due to decreased tobacco use, which in males includes chewing tobacco. The increasing rate of oropharyngeal carcinoma in young females found in this study does not appear to have been reported previously. That a second order polynomial regression had the best fit with the available data is consistent with a reversal in incidence trend. The shape of the curve – of a decrease followed by an increase – implies an etiologic shift for which decreasing tobacco exposure being replaced by an increasing sexually transmitted disease is a reasonable explanation. The youngest females demonstrating an increase in oropharyngeal carcinoma, 10–19-year-olds, had the least evidence for a trend reversal increase, with 10–14-year-olds having had a linear trend. Since it is unlikely that tobacco exposure results in oropharyngeal cancer this early in life, the trends are consistent with a new oncogenic etiology in the age group such as HPV. That such a young age group is affected by HPV-induced cancer is consistent with the decreasing age of onset of sexual activity and with a more than twofold greater risk of oropharyngeal carcinoma when the age of first sexual intercourse is before 18 in comparison to 18 or older [11].

All of the racial/ethnic groups had evidence for the trend reversal in young females. That Asians had the highest incidence of oropharyngeal carcinoma is consistent with known epidemiologic patterns that in older persons have been attributed to a high prevalence of cigarette smoking and tobacco chewing [31]. Non-Hispanic whites appear to have had the greatest increase since the 1990s, and Hispanics/Latinos have had the lowest rates, racial/ethnic differences that may be attributable to orosexual behaviors.

HPV 16-positive oropharyngeal cancer has been associated with an increasing number of oral sex partners [11] and with increasing marijuana use and not with tobacco smoking and alcohol drinking. Reciprocally, HPV 16-negative oropharyngeal cancer has not been associated with sexual behavior or marijuana use, but has been associated with tobacco and alcohol use [32]. The HPV+ patient also appears to be distinct from the HPV− patient with regard to alcohol and tobacco exposure history. HPV+ oropharyngeal cancer is more likely than HPV− oropharyngeal cancer to occur in the nonsmoker and nondrinker [13, 17, 21, 27, 33, 34]. In a study restricted to patients with oropharyngeal cancers, nonsmokers were approximately 15-fold more likely to have a diagnosis of HPV+ oropharyngeal cancer than smokers [35]. Similarly, several studies have reported an inverse association between HPV status and alcohol use [17, 27, 33, 36, 37].

19.1.3 Survival

During 2000–2011 in the United States, AYAs had a better overall 5-year oropharyngeal cancer survival than older and, to the extent evaluable, younger patients (Fig. 19.6). They also had a better stage-per-stage survival (Fig. 19.6 inset), with 5-year cancer-specific survivals of >90 % for stage I and 40–60 % for stage IV. At all ages from 10 to 80 years, males had a worse 5-year head/neck-cancer-specific survival rate than females. At all ages above 10, the 5-year head/neck-cancer-specific survival was strongly and directly dependent on stage at diagnosis. Among AYAs, the 5-year survival of those with distant disease at diagnosis was 50 %, whereas those with localized disease had a >90 % 5-year survival.

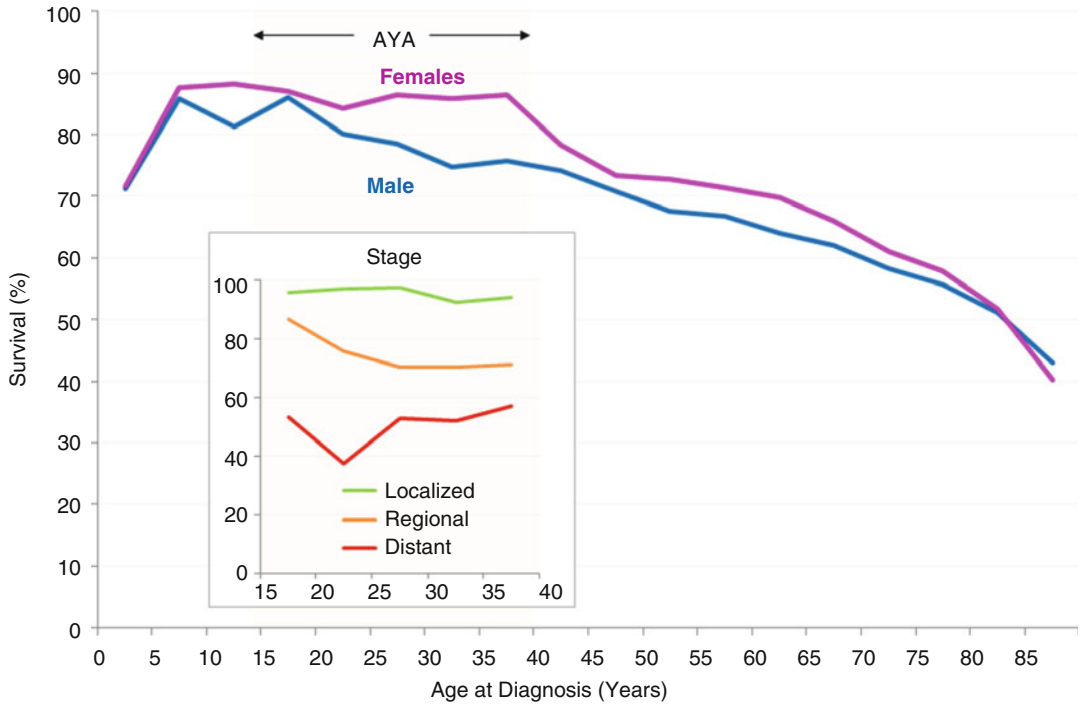

Fig. 19.6 5-year cancer-specific survival of patients with invasive head and neck cancer, 1975–2011, SEER18, by sex, stage (*inset*), and age; only age intervals with >10 patients are shown

The 5-year head/neck-cancer-specific survival of AYAs with head/neck cancer was independent of race/ethnicity with the exception that non-Hispanic white AYAs had a relatively better survival rate (Fig. 19.7). In older adults, blacks had the worst survival rate.

The 5-year head/neck-cancer-specific survival of AYAs was distinctly worse for those who presented with hypopharyngeal primaries (Fig. 19.8). It was best for those with primaries of the salivary glands, lip, gum, and tonsil.

19.1.4 Survival Trends

During 1976–2011 in the United States, AYA males have had less improvement in the 5-year head/neck-cancer-specific survival rate than older adults, but AYA women have had virtually no improvement in the 5-year head/neck-cancer-specific survival rate. Black and Asian/Pacific Islander AYAs with head/neck cancer have had an improvement in their 5-year cancer-specific survival rate, whereas white AYAs have not and Hispanic AYAs appear to have suffered a worse survival with each 8-year interval since 1976.

There is evidence that patients with HPV-related oropharyngeal carcinoma have better long-term survival than those with HPV-unrelated head and neck squamous cell carcinoma (e.g., 5-year overall survival rate of >80% versus ~40% for patients with stage III-IV tumors) [38]. This is especially true with tumors of the oropharynx [32, 37, 39–42]. This may be due in part to the fact that patients with HPV-related tumors are younger, with fewer comorbidities, and are less often alcoholics and smokers [17, 27, 36, 39, 40]. It may be also that the underlying biology of the HPV-transformed cell and its Rb- and p53-based [17, 18, 43] mutations render the carcinoma that results more prognostically favorable or because of other age-based biological distinctions summarized recently [42], resulting in a different type of cancer in adolescents and young adults than in older patients. In the analysis reported here, the increase in incidence in adoles-

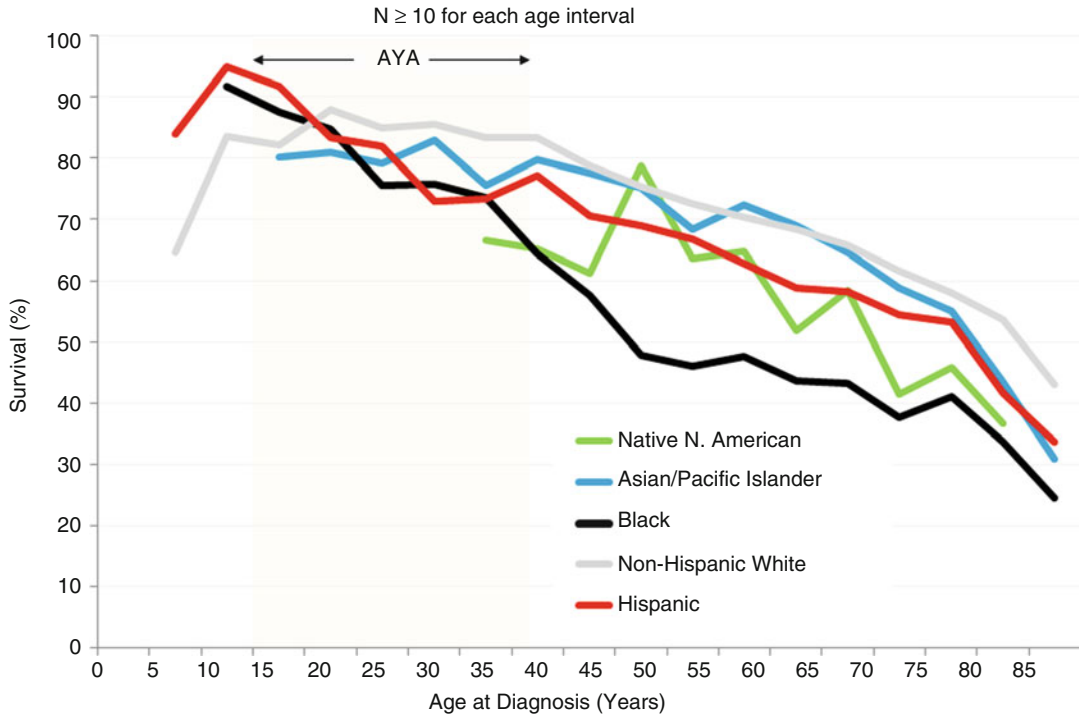

Fig. 19.7 5-year cancer-specific survival of patients with invasive head and neck cancer, 1975–2011, SEER18, by sex, stage (*inset*), and age; only age intervals with >10 patients are shown

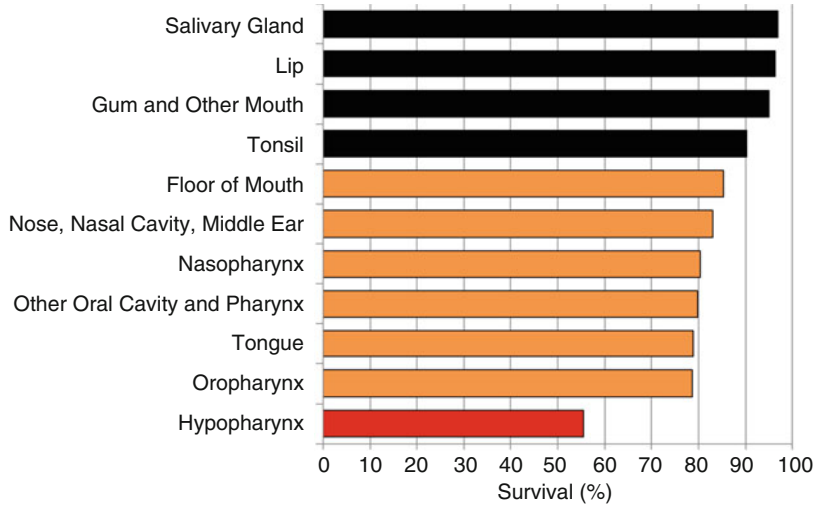

Fig. 19.8 5-year cancer-specific survival of patients with invasive head and neck cancer, 1975–2011, SEER18, age 15–39, by anatomical location

cent and young adult females with oropharyngeal cancer was not associated with an improvement in survival, especially in comparison with older females and with males who have had a 17–24 % increase in 5-year survival during the past 25 years (Fig. 19.2, lower panel). If the increase in oropharyngeal cancer among adolescent and young adult females is due to HPV-mediated

tumors, the higher reported survival rates may be limited to those receiving treatment at academic cancer centers that are studying and treating head and neck cancer, rather than in the general population as represented by the SEER registries. It could be also that the patients reported to have a better survival are older than the age most affected by the increasing incidence. Thus far, nearly all of the HPV-associated cases reported to have a better survival were over 40 years of age when diagnosed [30, 37, 40, 41].

The relative lack of survival progress in young adult females with oropharyngeal carcinoma is consistent, however, with the relative lack of progress in the SEER database for all cancer in the age group relative to younger and older patients [44] The inability to apply progress in older (and younger) patients to the adolescent and young adult age group, which has been ascribed to lack of health insurance, delayed diagnosis, low clinical trial participation, psychosocial challenges, and multiple factors unique to these patients [45], may just as well apply to oropharyngeal cancer as it does to other malignancies. Given the roles of tobacco, alcohol, and HPV in the oropharyngeal cancer population, it may well be that many of these factors are more problematic.

19.1.5 Mortality

Figure 19.9 summarizes the head/neck cancer death rates in AYAs during 2000–2011 in the United States according to sex, race, and anatomical site of the primary tumor. Nearly twice as many AYA males died of head/neck cancer than AYA females. Among AYAs with head/neck cancer, native North Americans and Asians/Pacific Islanders had the greatest death rate, followed by blacks and, with the lowest rate, whites. By far, most AYAs who died of head/neck cancer had primary cancer in the tongue and nasopharynx. Cancers of the oropharynx, hypopharynx, lip, and floor of the mouth were uncommon causes of death in AYAs.

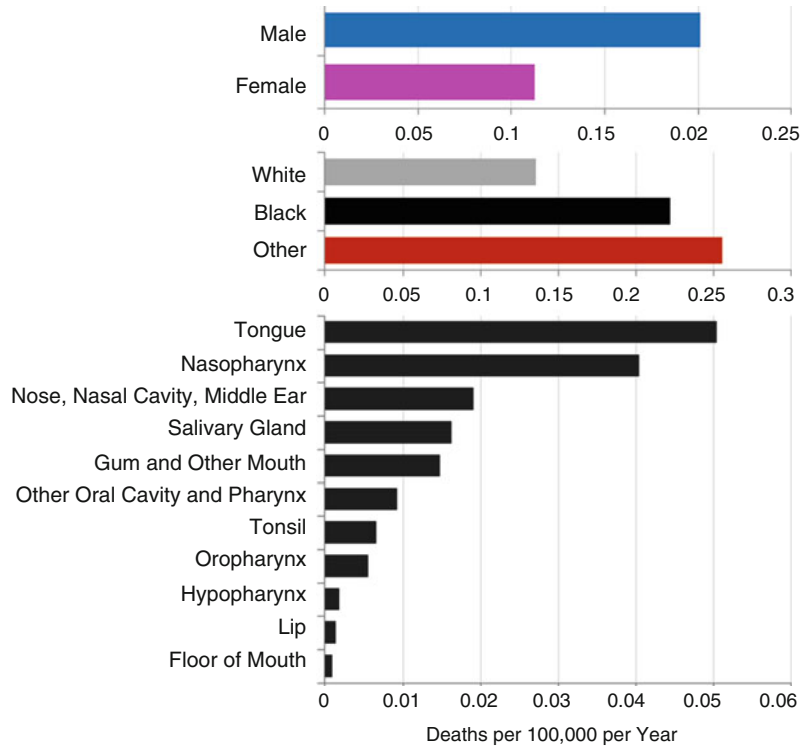

Fig. 19.9 5-year death rate of AYAs (age 15–39) with invasive head and neck cancer, 1975–2011, SEER18, by sex, race/ethnicity, and anatomical site

19.1.6 Risk Factors

Tobacco use and alcohol consumption are the main risk factors associated with head/neck SCC in older persons, due to their cytotoxic and mutagenic effects on the exposed epithelia of the upper aerodigestive tract. In AYAs, Epstein–Barr virus (EBV) and high-risk human papillomaviruses (HPVs), both encoding viral oncoproteins able to interfere with cell cycle control, have been recognized as the etiological agents of nasopharynx carcinoma and oropharyngeal carcinoma, respectively [46]. EBV and HPV transmission occurs predominantly via oral–oral (saliva and upper respiratory secretions) and orogenital routes, respectively.

19.1.7 Biology

The World Health Organization classification has three basic types of head/neck carcinomas: squamous cell carcinoma (SCC), non-keratinizing carcinoma, and undifferentiated carcinoma. The non-squamous types predominate in AYAs, whereas SCC occurs primarily in older adults. The molecular heterogeneity of head/neck SCC includes methylation profiles, microRNA expression, and mutated genes that may represent new targets for cancer-tailored therapies [46]. Most nasopharyngeal and some oropharyngeal carcinomas in AYAs are EBV+, whereas oropharyngeal carcinomas are more likely to be HPV+. [The other carcinoma that is likely to be EBV+ is gastric carcinoma, reviewed later in this chapter.] The biology of HPV+ oropharyngeal cancer is distinct: p53 degradation, retinoblastoma pathway inactivation, and p16 upregulation [47].

19.1.8 Treatment

Because the majority of AYAs present with early-stage disease, head/neck cancer in most AYAs patients is usually treated with surgery and postoperative radiotherapy or chemoradiotherapy. The minority of AYAs with advanced-stage head/neck cancer receive postoperative cisplatin-based chemotherapy and, increasingly, molecularly targeted therapy such as anti-epidermal growth factor receptor (EGFR) therapy. Most patients with HPV+ oropharyngeal carcinoma or EBV+ nasopharyngeal carcinoma present with cystic nodal metastases with a small primary tumor and respond well to all treatment modalities including primary surgery and chemoradiotherapy [48]. As of 2016, cetuximab was the only FDA-approved anti-epidermal growth factor receptor therapy for the treatment of head/neck SCC. A number of monoclonal antibodies targeting AKT, mTOR, and PI3K pathways and therapeutic vaccines against HPV 16 and EBV proteins are under evaluation. Furthermore, virus-associated oropharyngeal cancers may benefit from new developed immunotherapies targeting HPV E6 and E7 oncoproteins [49]. The higher survival rate also renders AYAs more likely to experience chronic therapy-induced morbidity [38]. Current research is evaluating de-escalation of treatment and follow-up evaluation to reduce long-term treatment-associated morbidities [48, 50]. In patients with EBV+ nasopharyngeal cancer, plasma levels of EBV DNA are both prognostic and helpful in guiding postoperative chemotherapy [51, 52].

The more favorable survival of AYAs with head/neck cancer is due in part to the more favorable subtypes of HPV+ and EBV+ carcinomas in the AYA population. This biologic difference also provides preventive opportunities.

19.1.9 Prevention

The recent increase in oropharyngeal cancer among females escalates the need for HPV immunization, for which two vaccines are available in the United States, one a quadrivalent vaccine licensed in 2006 and the other a bivalent vaccine approved in 2009 [53]. Both protect against the HPV serotype 16 that accounts for the majority of HPV-related oropharyngeal cancers [54]. The bivalent is recommended for use in females aged 10 through 25 years and the quadrivalent for females aged 11 or 12 years and

catch-up vaccination for females aged 13 through 26 years [54]. Immunizing males should also help by reducing the transmission from males to females and to males who also engage in oral sex and for persons in whom the route of contagion may be oral-oral rather than orogenital [55–57]. Both vaccines also have a high efficacy against HPV 16- and 18-related cervical precancer lesions. HPV 4 also has high efficacy against HPV 6- and HPV 11-related genital warts and HPV 16- and 18-related vaginal and vulvar precancer lesions [53].

The societal challenge is to reduce the burden of HPV-related disease, estimated to be 25,000 cases of cancer annually in the United States [58], by vaccination against certain disease-inducing strains of the virus, combined with the community's interest in limiting the transmission of infectious diseases while promoting health on the one hand and social mores on the other [59].

19.2 Lung Cancer in AYAs in the United States

19.2.1 Incidence

During 2000–2011 in the United States, AYA males and females had a similar incidence of lung cancer, beginning at 15 years of age, whereas in adults older than 50 year, males had a greater incidence of lung cancer (Fig. 19.10). In AYAs the increase was exponentially dependent on age. For 2000–2011, an average of nearly 3,000 AYAs was diagnosed annually with lung cancer (Table 19.2). It is not a rare cancer in the older AYA age range.

Figure 19.11 shows the stage of lung cancer at diagnosis as a function of patient age in the United States, according to the AJCC 6th edition staging system since 2004. At all ages above 20, the most common stage at diagnosis of lung cancer was stage IV. The most common stage at diagnosis of lung cancer at all ages was localized

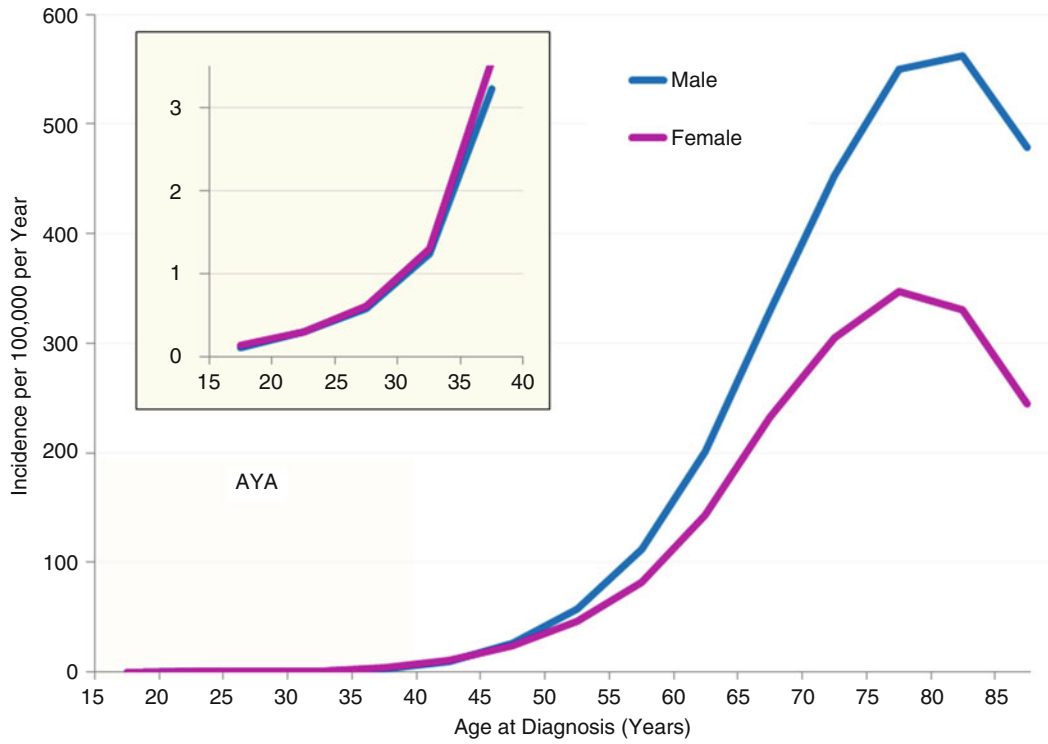

Fig. 19.10 Incidence of cancer of the lung and bronchus, 2004–2011, SEER18, by age and sex. The *inset* depicts the AYA age range

disease. 60 % of AYAs diagnosed with lung cancer had stage IV disease.

Figure 19.12 depicts the incidence of lung cancer in the United States as a function of race/ethnicity and age. The incidence among AYAs, Asians, non-Hispanic whites, and blacks had the highest incidence of lung cancer, and Hispanics and native North Americans had the lowest incidence. Among older persons, blacks had the highest incidence, followed by non-Hispanic whites. Among AYAs as a group, females had a slightly higher incidence of lung cancer. Among AYAs, blacks, non-Hispanic whites, and Asians/Pacific Islanders had approximately twice the rate of lung cancer incidence of Hispanics and native North Americans.

Table 19.2 Average annual number of AYAs diagnosed to have gastric cancer in the United States, 2000–2011

Age (years)					
15–19	20–24	25–29	30–34	35–39	16–39
65	144	321	716	1,597	2,844

Figure 19.13 shows the type of lung carcinoma in AYAs as function of age. Carcinoid and neuroendocrine carcinomas were far more prevalent in AYAs than in any older age group. Most 15- to 24-year-olds were diagnosed with either carcinoid or neuroendocrine carcinoma. AYAs were also more likely to be diagnosed with bronchoalveolar carcinoma than at any other age. Among the non-small cell lung cancers, adenocarcinoma and non-squamous tumors are more common in AYAs than in older patients [60, 61]. Non-small cell lung cancer of the anaplastic lymphoma kinase rearrangement is more common in AYAs than in older patients [62].

19.2.2 Incidence Trends

Figure 19.14 portrays the change in lung cancer incidence from 1976 to 2011 in the United States in AYAs and older patients. In older males, the incidence of lung cancer declined steadily from 1990 to 2011, whereas in older females, the

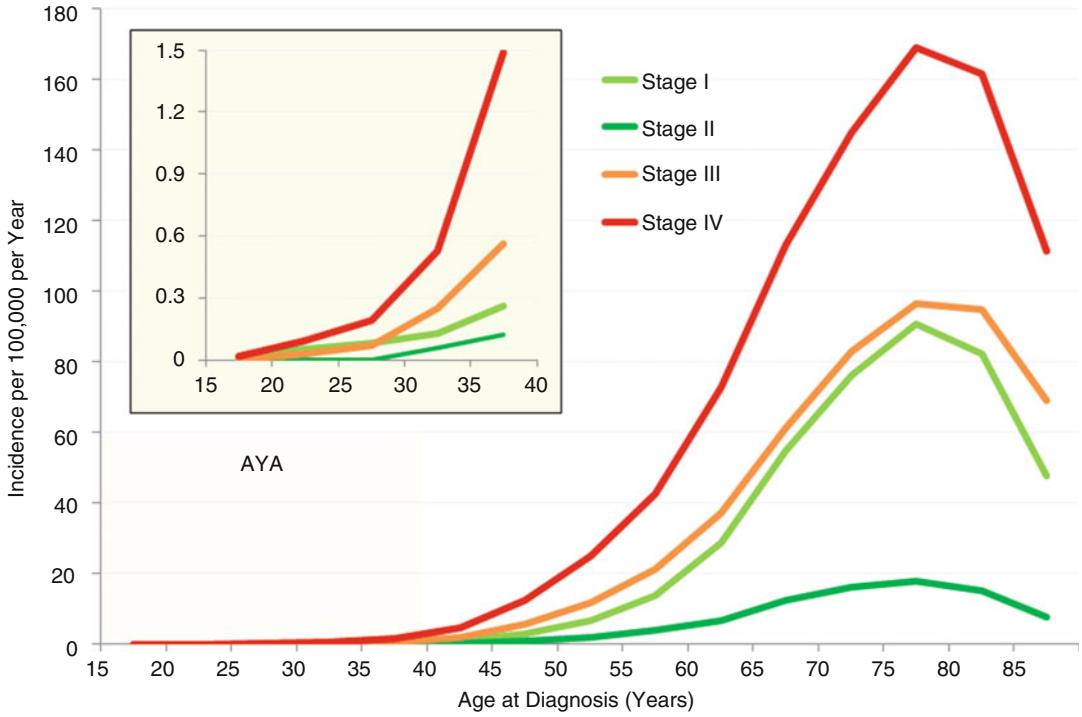

Fig. 19.11 Incidence of cancer of the lung and bronchus, 2000–2011, SEER18, by age and stage. The *inset* depicts the AYA age range

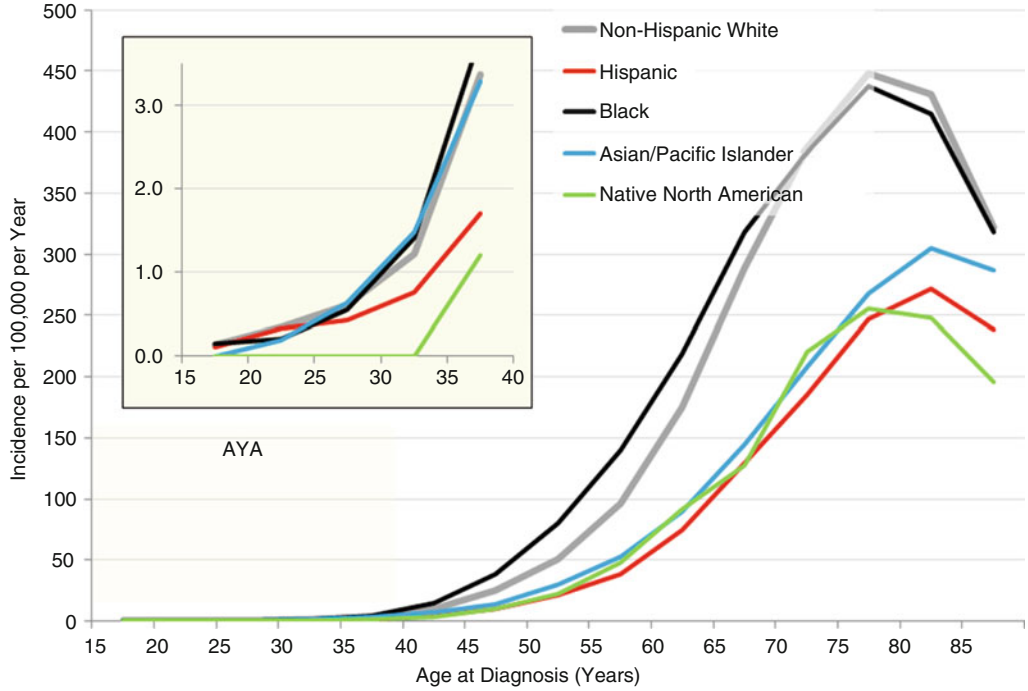

Fig. 19.12 Incidence of cancer of the lung and bronchus, 2000–2011, SEER18, by age and stage. The *inset* depicts the AYA age range

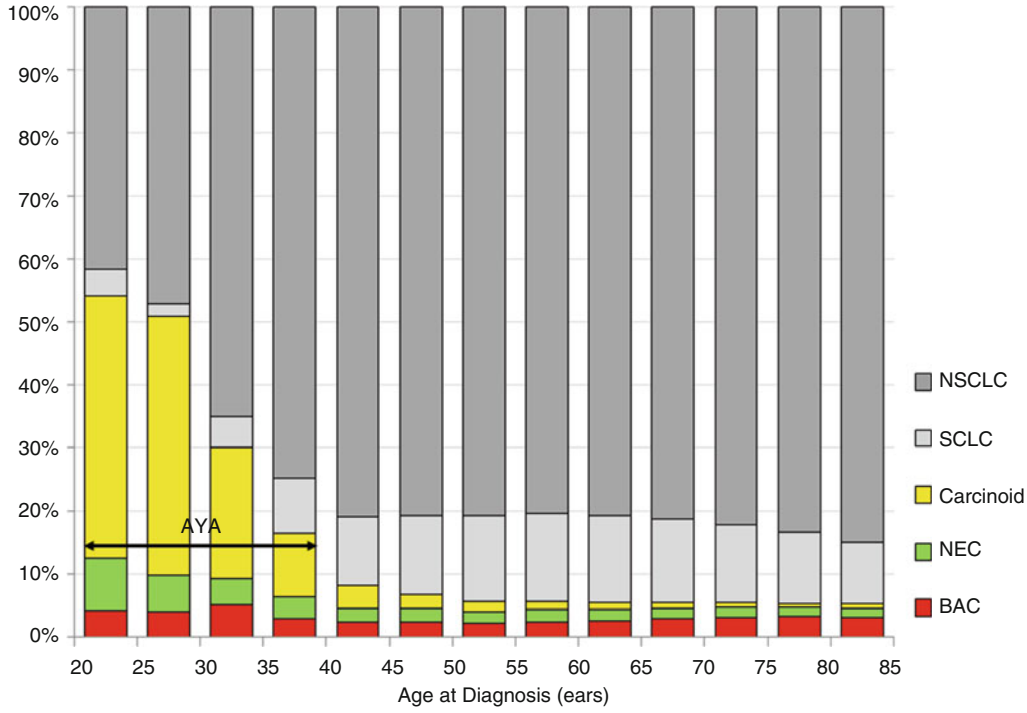

Fig. 19.13 Incidence of cancer of the lung and bronchus, 2000–2011, SEER18, by age and histologic type. *NSLC* non-small cell lung carcinoma, *SCLC* small cell lung carcinoma, *NEC* neuroendocrine carcinoma, *BAC* bronchoalveolar carcinoma

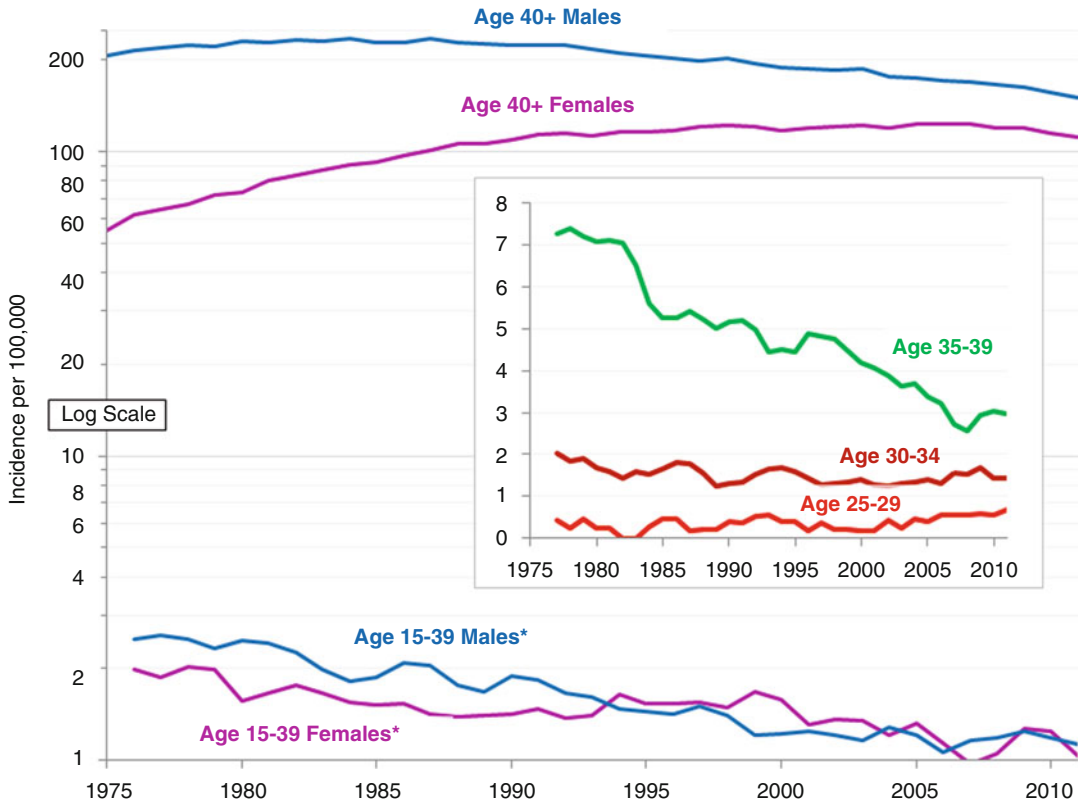

Fig. 19.14 Annual incidence of cancer of the lung and bronchus, 1975–2011, SEER9, by age and sex *2-year running average

incidence increased steadily, especially during the 1970s and 1980s and more slowly during the 1990s and early 2000s. For the first time during the past half century, the incidence in older females showed evidence for a decrease, since 2007. In both AYA males and females, however, the incidence steadily declined since 1975, especially in males. In females AYAs, the decline in incidence attenuated during the 1990s such that both male and females AYAs had the same incidence since the mid-1990s. Among AYAs, the decline in incidence of lung cancer was limited to the 35- to 39-year-old age group. In 25- to 34-year-olds, the incidence was constant since 1980 (Fig. 19.14 inset).

19.2.3 Survival

Figure 19.15 shows the cancer-specific survival of patients over 15 years of age with lung cancer diagnosed in the United States during 2000–2011 by sex (upper panel) and race/ethnicity (lower panel). Most of the decline in the cancer-specific survival rate as a function of age occurred in AYAs, dropping from 80 % in 15- to 19-year-olds to <30 % in 35- to 39 year-olds. At all ages above 20, the 5-year lung-cancer-specific survival rate was strongly and directly dependent on stage at diagnosis. At all ages above 20 years, females had a better 5-year survival than males. At all ages above 40, the average 5-year lung-cancer-specific survival rate was similar among the major races/ethnicities. Among AYAs however, Asian/Pacific Islanders had the worst survival rate.

Figure 19.16 portrays the 5-year cancer-specific survival rate for lung cancer as function of extent of disease at diagnosis by age. Stage for stage, AYAs have a better 5-year survival rate than older patients. Among AYAs, the average 5-year lung-cancer-specific survival rate of those

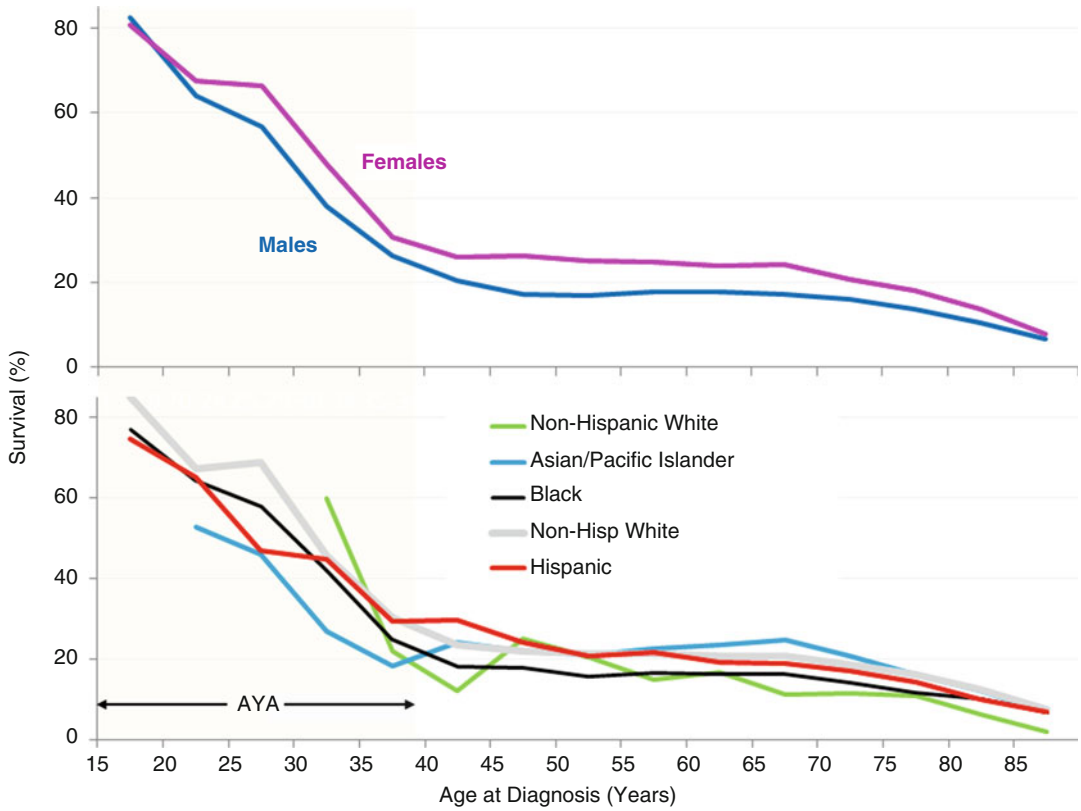

Fig. 19.15 5-year cancer-specific survival of cancer of the lung and bronchus, 2000–2011, SEER18, by age, race/ethnicity, and sex. Only age intervals with >10 patients are shown

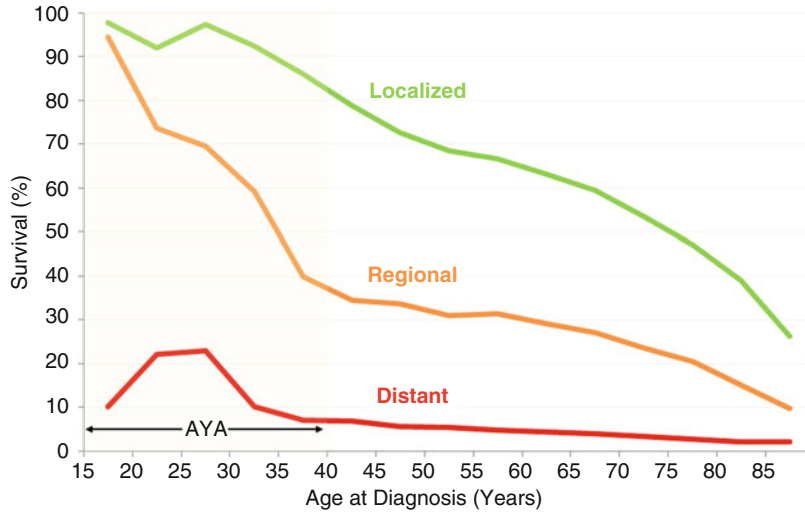

Fig. 19.16 5-year cancer-specific survival of cancer of the lung and bronchus, 2000–2011, SEER18, by age and extent of disease at diagnosis

with distant disease at diagnosis was 10–25%, whereas those with localized disease had a >90% 5-year survival. Among AYAs with localized disease, the 5-year rates were over 90% declined sharply in older patients as a function of age. The group in between with regional diseases at diagnosis had an average 5-year lung-cancer-specific survival rate that declined precipitously with increasing age during the AYA years, from 95% to 40%. The higher survival rates occur despite the higher incidence of adenocarcinoma and non-squamous tumors in AYAs which are generally regarded as carrying a worse prognosis than squamous cell carcinoma [63, 64].

19.2.4 Survival Trends

During 1976–2011 in the United States, there was a significant improvement in the overall 5-year cancer-specific survival rate since 1976 among AYAs with lung cancer that was relatively greater than among those 40 years of age and older (Fig. 19.17). The relative improvement in the survival rate among AYAs since 1976 was greater in males than females, especially since the early 1990s.

Asians/Pacific Islanders with lung cancer had little to no improvement in their 5-year lung-cancer-specific survival rate since 1985 despite an improvement in older Asian/Pacific Islanders that was similar in all major races/ethnicities (Fig. 19.18).

19.2.5 Mortality

Whereas male AYAs used to have twice the death rate from lung cancer than females, the relative improvement in females since has been so much slower that females AYAs have died of lung cancer at the same rate as male AYAs since the late 1990s (Fig. 19.19, upper panel). Black AYAs have had an extraordinary reduction in the decline of deaths due to lung cancer, especially since the early 1990s (Fig. 19.19, lower panel). Other races (non-White Hispanics, Asians/Pacific Islander, native North Americans) have had, as a group, a very different mortality rate profile, having had an increase prior to 1990 and no evidence for reduction since (Fig. 19.19, lower panel). Remarkably, by 2010, there was no racial inequity in lung cancer deaths among AYAs.

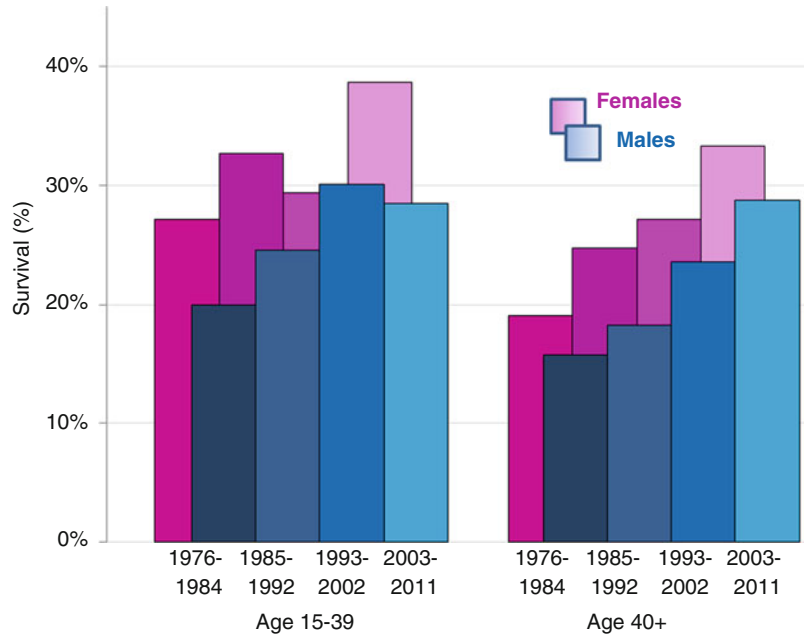

Fig. 19.17 Change in 5-year cancer-specific survival of cancer of the lung and bronchus, 1976–2011 by 8-year intervals and sex

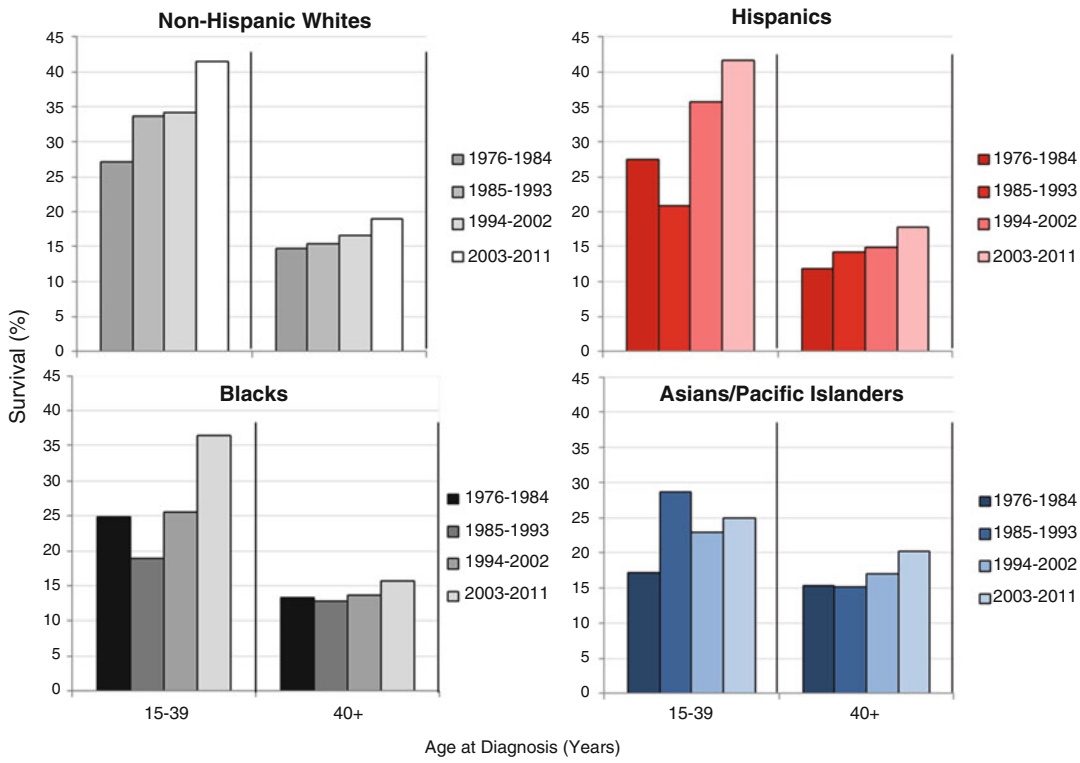

Fig. 19.18 Change in 5-year cancer-specific survival of cancer of the lung and bronchus, 1976–2011 by 8-year intervals and race/ethnicity

In the United States, the death rate from lung cancer paralleled the incidence of lung cancer from age 15 to 85+ (Fig. 19.20). Young AYAs had the lowest death rate relative to incidence, consistent with their more favorable prognosis. Among AYAs, the number dying of lung cancer relative to the number of new cases increased steadily by age, from 30 % in the 15 to 25 year age group to 90+% in the 35 to 39 year age group.

19.2.6 Biology

A highly significant discovery is the greater prevalence of actionable mutations in the lung cancers of AYAs than in older patients. Initial findings in 44 AYAs had 75 % with actionable mutations, with ALK fusions in 20 % of AYAs vs. 4 % in older patients and MYC mutations in 14 % of AYAs vs. 7 % in older adults [65]. In another study in 68 AYAs with a median (range) age of 35 (16-39), of whom 79 % presented with stage IV adenocarcinoma, 44 % had ALK mutations, 26 % had EGFR mutations, and 6 % had ROSI mutations, suggesting that 76 % of the AYA lung cancer population have targetable mutations with today's antineoplastic agents [66]. Remarkably, 90 % of female AYAs had actionable mutations. New, potentially targetable, mutations are also being found in AYAs. EGFR-RAD1 fusion was discovered in a 33-year-old man who had a 7-month objective response with afatinib [67].

19.2.7 Hereditary Lung Cancer

Studies of families predisposed to lung cancer showed that the development of lung cancer in young individuals (50 years or less) was compatible with Mendelian codominant inheritance or a rare autosomal gene [68]. Otherwise there has been little to no evidence for a familial or genetic

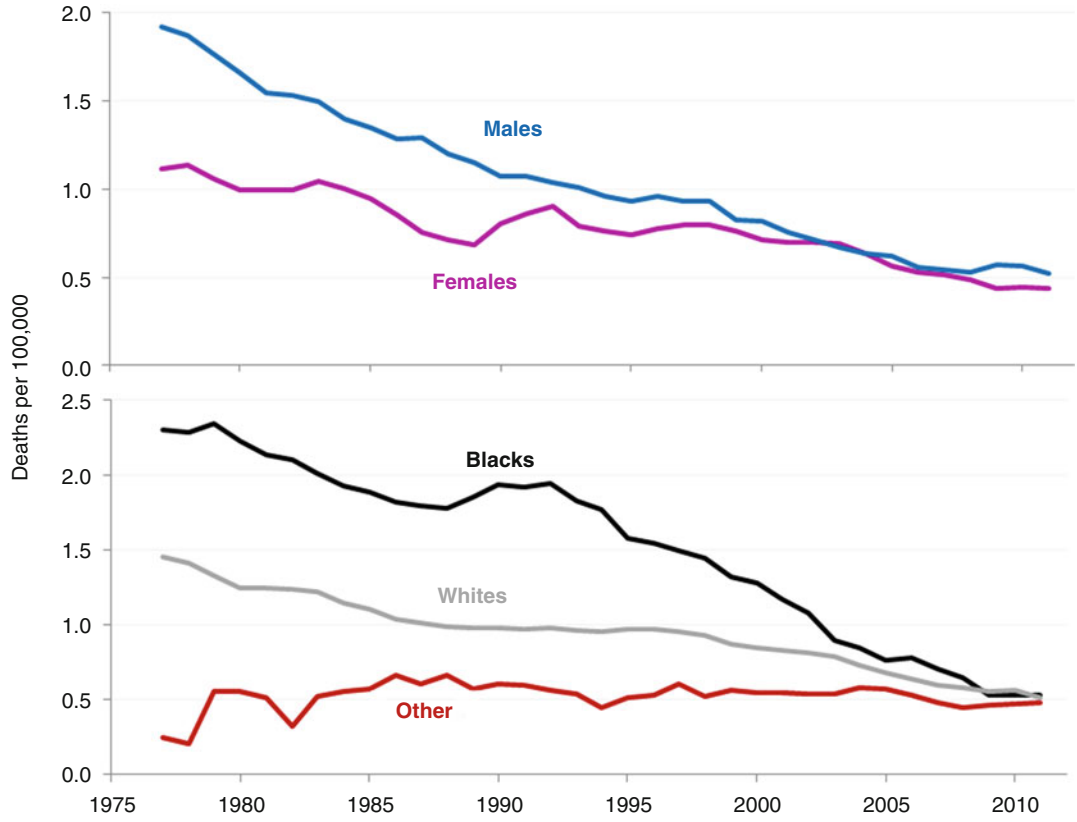

Fig. 19.19 Annual death rate of AYAs 15 to 39 years of age with cancer of the lung and bronchus, 1975–2011, United States, by sex (*upper* panel) and race (*lower* panel). "Other" includes non-white Hispanics, Asians/Pacific Islander, and native North Americans. Regressions are 3o polynomials

basis of lung cancer. Yet, not all heavy smokers develop lung cancer. So it would seem that there are genetic explanations for susceptibility to and resistance of lung cancer that remain to be discovered.

19.2.8 Treatment

Given that AYAs are otherwise usually healthy, with no comorbidities, when diagnosed with cancer, this discussion will apply the current non-small cell lung cancer NCCN guidelines (v3.2016) [69] for the medically fit and surgical candidates. The combinations and permutations of surgery, radiation therapy, chemotherapy, and chemoradiation are entirely dependent on pretreatment evaluation, the findings at surgery, and the resultant stage of disease based on the TNM (primary tumor, nodal involvement, and metastasis evidence). As described above, AYAs have a better stage-for-stage prognosis, including those with the most advance state (distant metastases; stage IV according to the AJCC classification) at age 20–30 have a 20–25 % 5-year survival rate (Fig. 19.16). Hence, unless co-existing morbidity prevents, AYAs with lung cancer should be offered the full treatment strategy per NCCN guidelines and be treated aggressively. The "ALK-positive" tumors that were described above, which occur earlier in life and in nonsmokers, are significantly more treatable with commercially available ALK inhibitors agents such as crizotinib [70].

19.2.9 Prevention

There is no question that lung cancer prevention is the best strategy and that avoidance of smoking is a definitive preventive measure. Since the

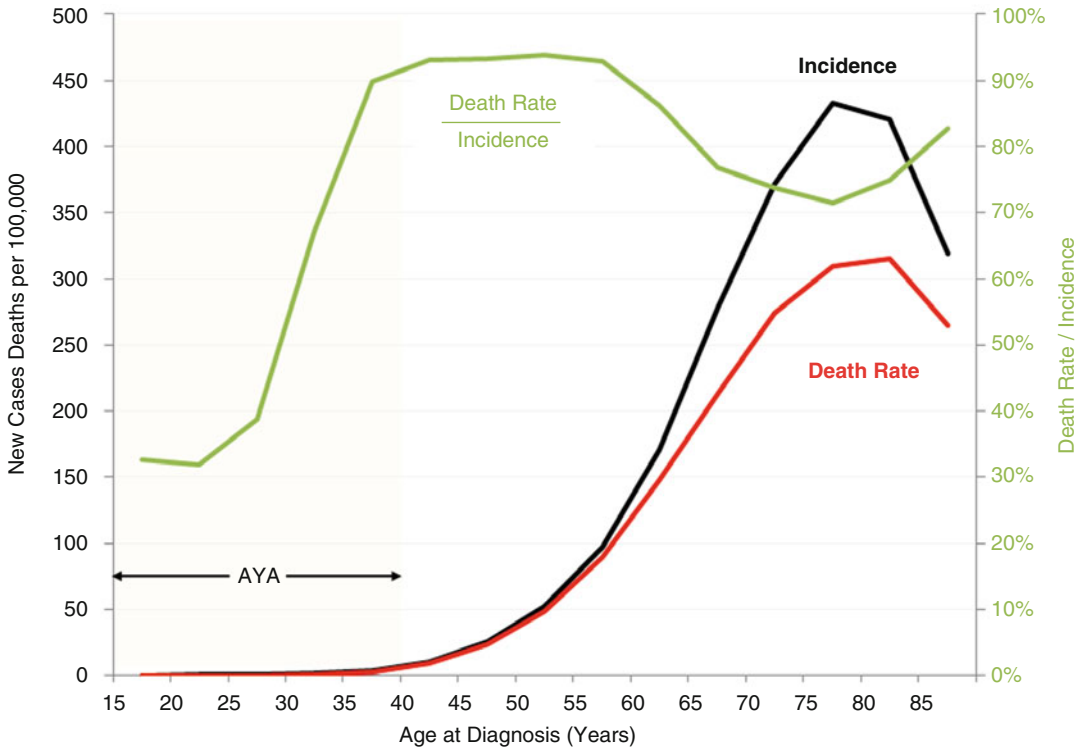

Fig. 19.20 Annual incidence, death rate, and death rate-incidence ratio of AYAs 15 to 39 years of age with cancer of the lung and bronchus, 1975–2011, United States, by age

series of carcinogenic steps in serial mutations that are required to result in lung cancer takes years to accrue, it is unclear how much of lung cancer in AYAs is attributable to smoking. Likely, those who develop cancer in the early AYA years are less likely to have smoking-related cancer. This may explain why there has been a clear reduction in incidence in 35- to 39-year-olds but no reduction in the incidence of lung cancer in AYAs younger than 35 (Fig. 19.14, inset). Thus, preventing the lung cancers that occur in young AYAs may be elusive.

19.3 Gastric Cancer in AYAs in the United States

19.3.1 Incidence Trends

In addition to prostate cancer (Chap. 16), gastric cancer is a newcomer to the AYA oncology discipline. As with prostate cancer, the incidence of gastric cancer in the United States has steadily and highly statistically significantly increased in AYAs in contrast to older persons in whom it has significantly decreased (Fig. 19.21).

19.3.2 Incidence

During 2000–2011 in the United States, AYA males and females had a similar incidence of gastric cancer, beginning at 15 years of age, whereas in adults older than 45 years, males had a greater incidence (Fig. 19.22). An average of more than 2,000 AYAs were diagnosed annually with gastric cancer, with three fourths of them over age 30. It is not a rare cancer in the older AYA age range (Table 19.3).

Figure 19.23 shows the above group by race/ethnicity and age. Above age 40, the incidence of gastric cancer was greater in Asians/Pacific Islanders, blacks, and Hispanics than in non-Hispanic whites and native North Americans.

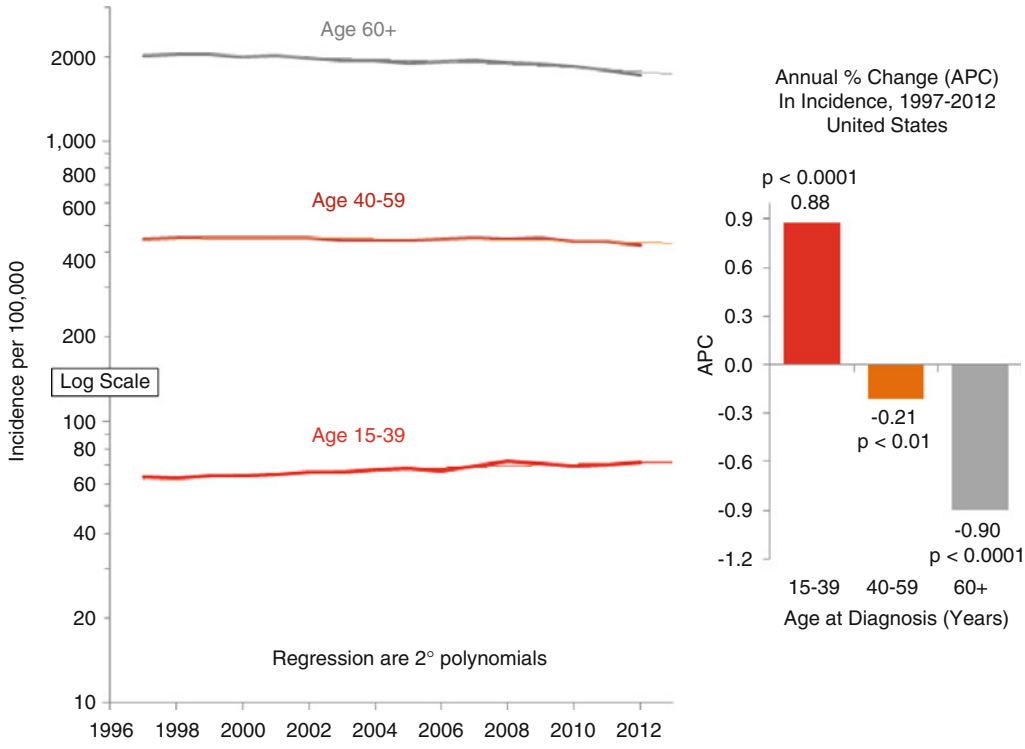

Fig. 19.21 Annual incidence of gastric carcinoma and its average percent change (APC) in incidence, 1975–2011, SEER9, by age

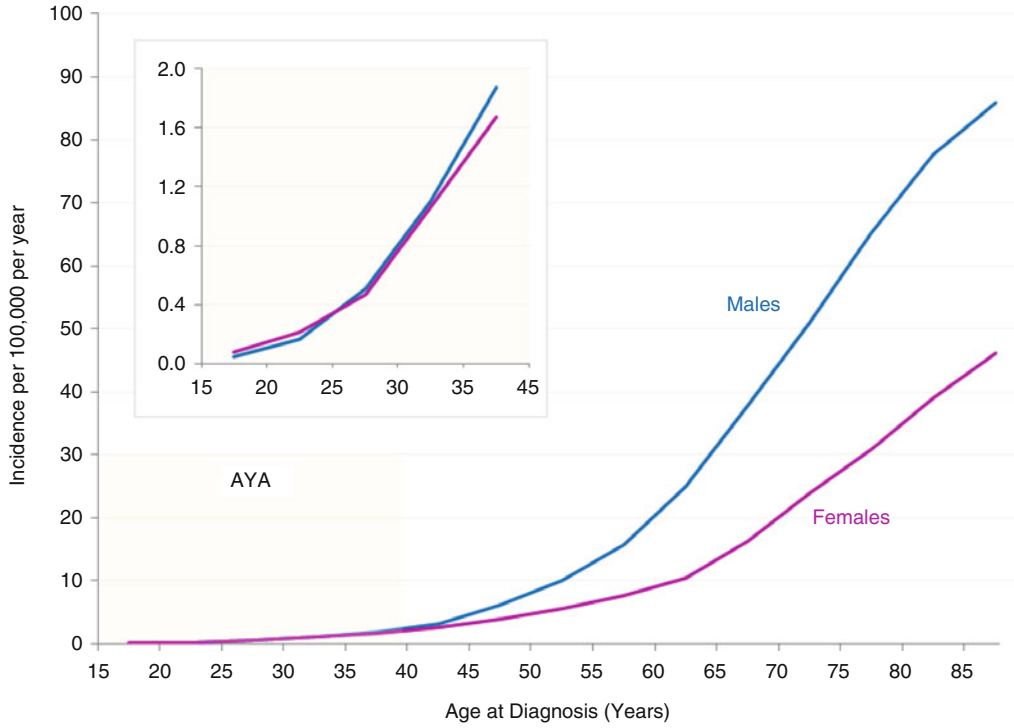

Fig. 19.22 Incidence of gastric carcinoma, 2000–2012, SEER18, by sex and age. The *inset* depicts the AYA age range

Among AYAs, however, the incidence was distinctly higher in Hispanics and least in native North Americans (Fig. 19.23, inset).

Figure 19.24 shows the stage distribution as a function of age at diagnosis during 2004–2012 in the United States. AYAs had the highest proportion of stage IV cancer and the lowest proportion of stage I cancer. With every 5-year interval above age 15, the proportion of patients with stage IV is inversely proportional to age. With every 5-year age interval above 30, stage I is directly proportional to age.

Figure 19.25 shows the distribution of gastric cancer histologies as a function of age at diagnosis during 2000–2012 in the United States. AYAs had a higher proportion of signet ring carcinoma but not of gastrointestinal stromal tumor (GIST), carcinoid, or neuroendocrine cancer. Of the two general types (intestinal type and diffuse type), the diffuse type has a worse prognosis, tends to occur in young patients, and can occur anywhere in the stomach [71]. Peritoneal and bone metastases have been reported to be more common among AYAs than among older patients [72, 73], with bone metastasis more likely to occur in patients with signet ring histology [70], the more common type in AYAs.

Table 19.3 Average annual number of AYAs diagnosed to have gastric cancer in the United States, 2000–2012

Age (years)					
16–19	20–24	25–29	30–34	35–39	16–39
46	104	235	528	1,187	2,100

19.3.3 Survival

Figure 19.26 shows the 5-year cancer-specific survival of patients in the United States with gastric cancer by sex, extent of disease at diagnosis,

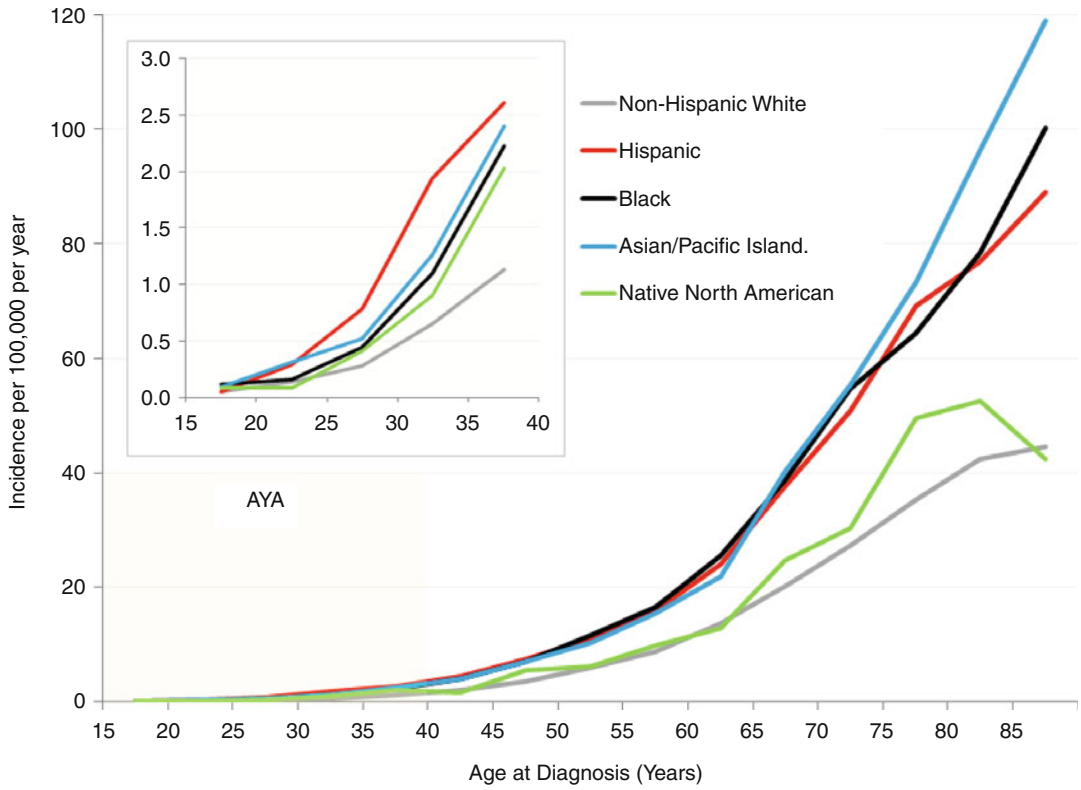

Fig. 19.23 Incidence of gastric carcinoma, 2000–2012, SEER18, by race/ethnicity and age. The inset depicts the AYA age range

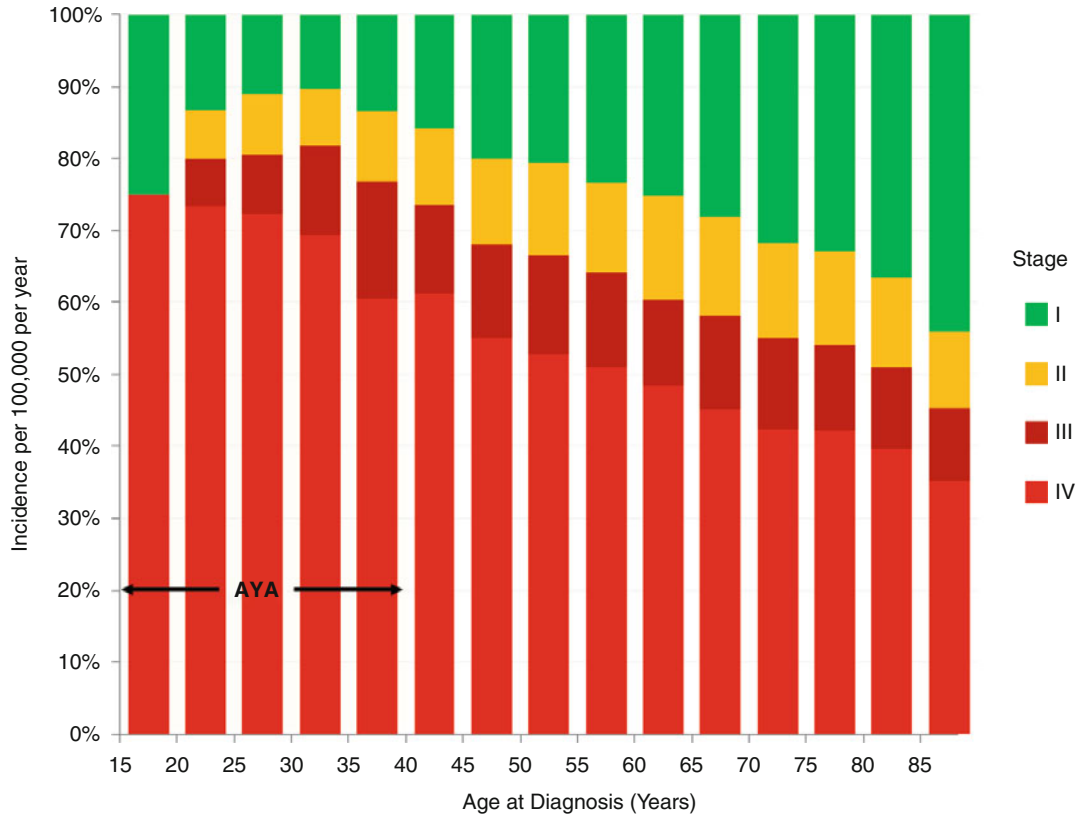

Fig. 19.24 Incidence of gastric carcinoma, 2004–2012, SEER18, by stage (AJCC 6th edition) and age

and age. Above age 20, the survival rate was less than 40 % throughout the age span, with females having had a slightly better outcome at all ages (upper panel). AYAs with those with localized disease had 5-year rates above 70 %, but those with distant metastases at diagnosis had a very poor outcome, with 5-year rates below 10 % (lower panel).

Figure 19.27 shows the 5-year cancer-specific survival of patients in the United States with gastric cancer by race/ethnicity and age. With the possible exception of Asian/Pacific Islanders having a lower survival rate, there is little difference in the survival of AYAs with gastric cancer between the major races and ethnicities. The suggestion that Asians have lower survival not only in AYAs but also in older adults (Fig. 19.27) may have a relationship to Asians having a high incidence of gastric cancer in their countries. In many Asian countries, it is the most common cancer and accounts for the greatest number of cancer deaths.

19.3.4 Survival Trends

The 5-year cancer-specific survival of patients with gastric cancer in the United States has steadily increased since 1976 in both AYAs and older patients and in both females and males (Fig. 19.28). This implies that the failure of the mortality rate in AYAs to decrease is due to the increasing incidence. Hispanic AYAs with gastric cancer have had no improvement in their 5-year cancer-specific survival since 1976, whereas other race/ethnicities and older Hispanics have had steady progress (Fig. 19.29).

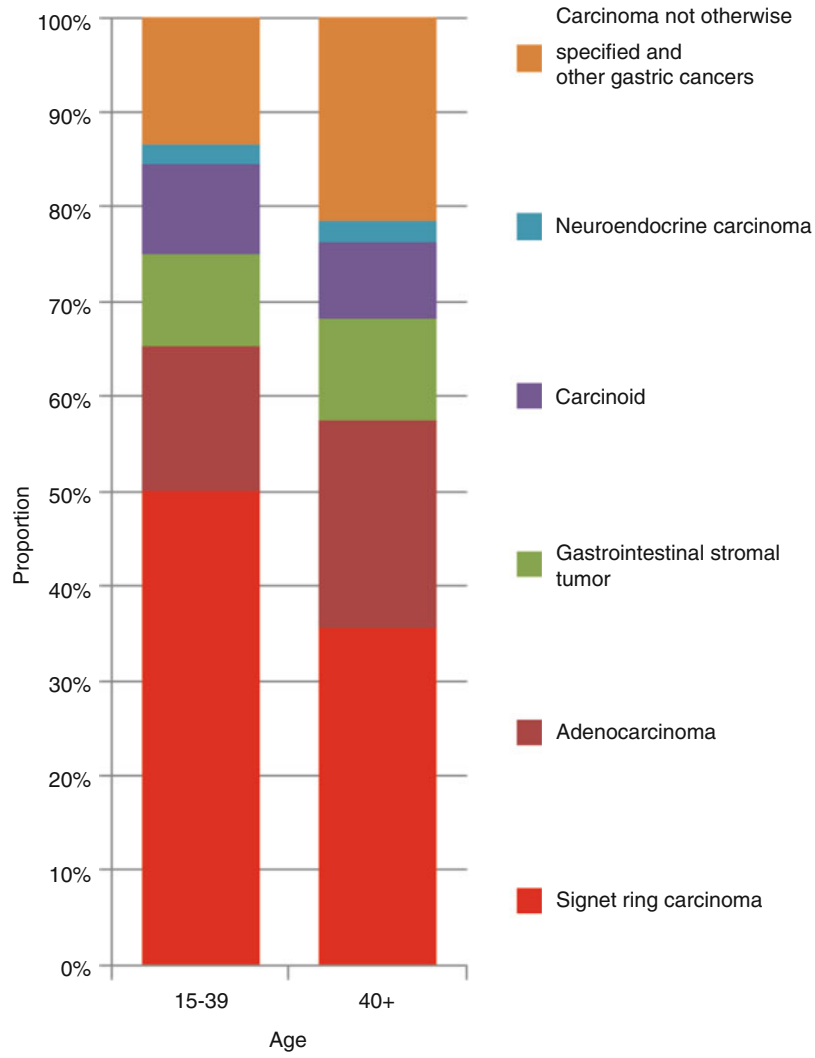

Fig. 19.25 Incidence of gastric carcinoma, 2004–2012, SEER18, by histologic type (ICD-O-3) and age

19.3.5 Mortality

In addition, the gastric cancer death rate among AYAs in the United States has not declined since 1997 despite significant decreases in its national death rate in older persons (Fig. 19.30).

19.3.6 Gastric Cancer Genomics

The Cancer Genome Atlas for gastric adenocarcinoma has four molecular subtypes and groups, each with a predilection for different sites within the stomach and histologic distributions (Fig. 19.31) [74]. Two of the four have direct therapeutic implications, those positive for Epstein–Barr virus (EBV) (9 % of the tumors) and those with high microsatellite instability (MSI) (22 % tumors). The former has PIK3CA mutations, DNA hypermethylation, and PD-L1 and PD-L2 amplifications. The latter are hypermutated (more than 50 mutations per megabase compared with <5 in the other groups). Both may therefore respond to PD-1 inhibitor therapy, such as pembrolizumab that has been found to be effective in MSI-high colorectal cancer [75]. The extent to which AYAs with gastric cancer have a different distribution of

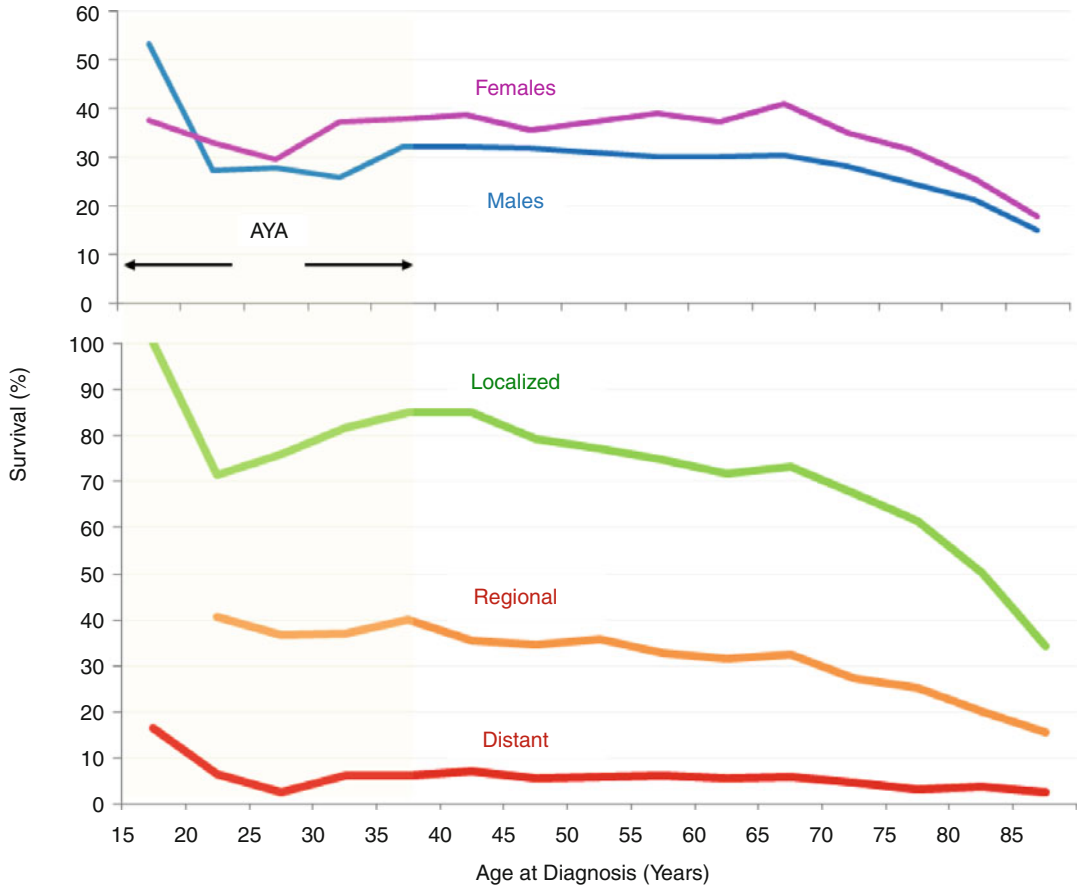

Fig. 19.26 5-year cancer-specific survival of patient with gastric carcinoma, 2000–2013, SEER18, by sex, extent of disease at diagnosis, and age

these four types and may therefore be more or less likely to benefit from the new targeted therapies remains to be determined.

19.3.7 Hereditary Gastric Cancer

Approximately 10% of gastric carcinomas show familial aggregation and 1–3% have had a documented hereditary basis [76]. The hereditary forms include those associated with polyps, *familial adenomatous polyposis* (FAP)/*attenuated familial adenomatous polyposis*, *Mutyh-associated polyposis*, *Peutz–Jeghers syndrome*, *juvenile polyposis syndrome/hereditary hemorrhagic telangiectasia*, and *familial gastric polyposis* [76]. Hereditary forms not associated with polyps are *hereditary diffuse gastric cancer* (HDGC), *hereditary non-polyposis colorectal cancer* (HPNCC) *syndrome*, *familial intestinal gastric cancer* (FIGC), *gastric adenocarcinoma and proximal polyposis of the stomach* (GAPPS), *Li–Fraumeni syndrome*, and *BRCA1 and BRCA2 hereditary breast and ovarian cancer* [76, 77]. Each has distinctive constellations of gene line mutations, and most are autosomal dominant abnormalities and as such are candidates for screening during the AYA years. The genes thought to be pathogenetic for gastric cancer are numerous, including APC, MUTYH, SKT11, CDH1, DCCgene, FHIT, RUNX, and PTEN. Like

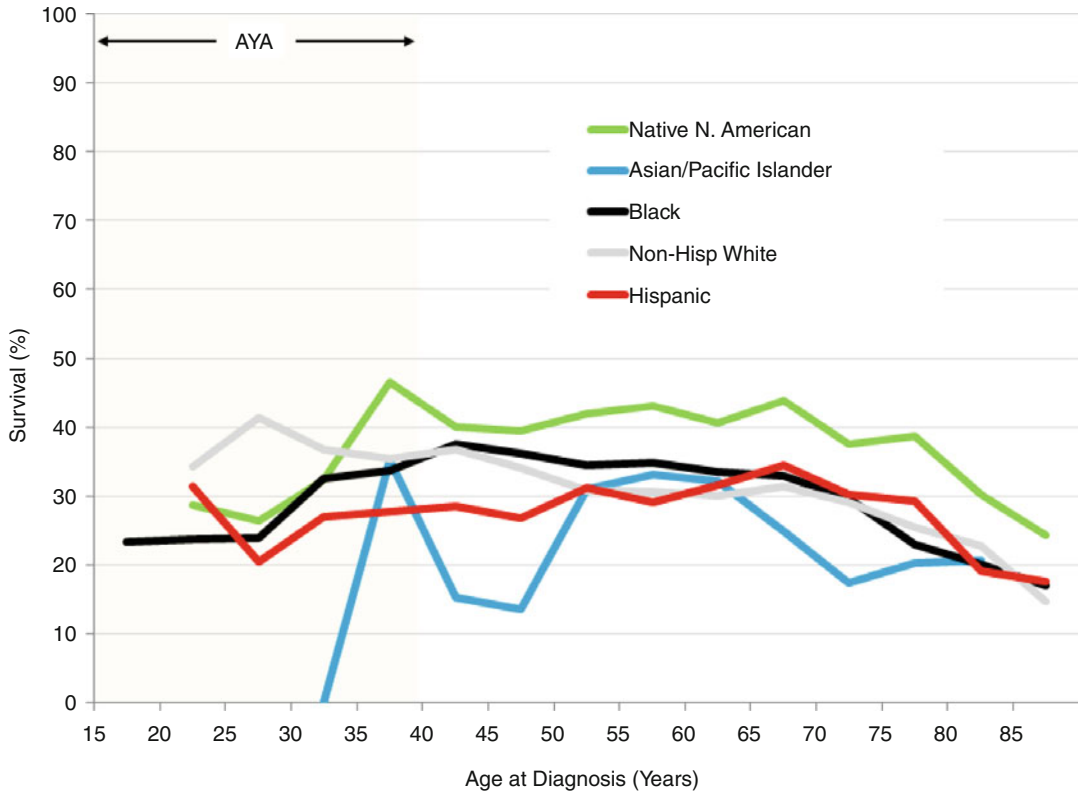

Fig. 19.27 5-year cancer-specific survival of patient with gastric carcinoma, 2000–2013, SEER18, by race/ethnicity and age. Only age intervals with >10 patients are shown

colorectal cancer, the incidence of hereditary gastric cancer is demonstrably higher in AYAs for some of the hereditable forms such that screening with upper endoscopy is indicated [76]. Prophylactic gastrectomy as early as adolescence is recommended for HDGC [76].

19.3.8 Sporadic Gastric Cancer

Most patients with gastric cancer have aberrant hypermethylation of E-cadherin, HMLH1, p16, and other genes. Although some investigators have reported microsatellite instability (MSI) to be more frequent in gastric cancer from young patients [79], others have found no significant age difference among patients with MSS or MSI phenotypes [80, 81].

19.3.9 Diagnosis and Treatment

Early diagnosis is difficult to achieve, since the symptoms of gastric cancer are usually nonspecific: vague gastrointestinal distress, episodic nauseas, vomiting, anorexia, unexplained weight loss, and dysphagia. Physical examination may reveal a palpable epigastric mass, jaundice, periumbilical or Virchow adenopathy, acanthosis nigricans, or multiple seborrheic keratoses. The diagnosis is usually made via endoscopic biopsy of the gastric tumor, and staging requires computed tomography and/or magnetic resonance imaging, endoscopic ultrasonography, and laparoscopy.

Given that AYAs are otherwise usually healthy, with few if any comorbidities, when diagnosed with cancer, the current gastric cancer NCCN

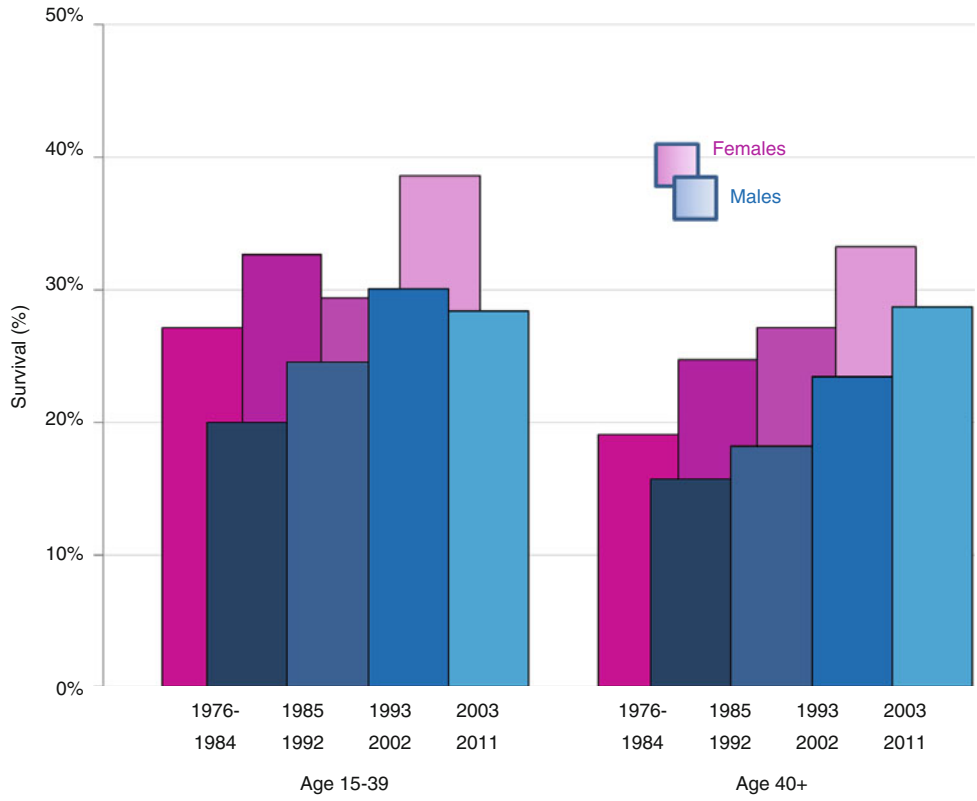

Fig. 19.28 Change in 5-year cancer-specific survival of gastric carcinoma, 1976–2011 by 8-year intervals and age

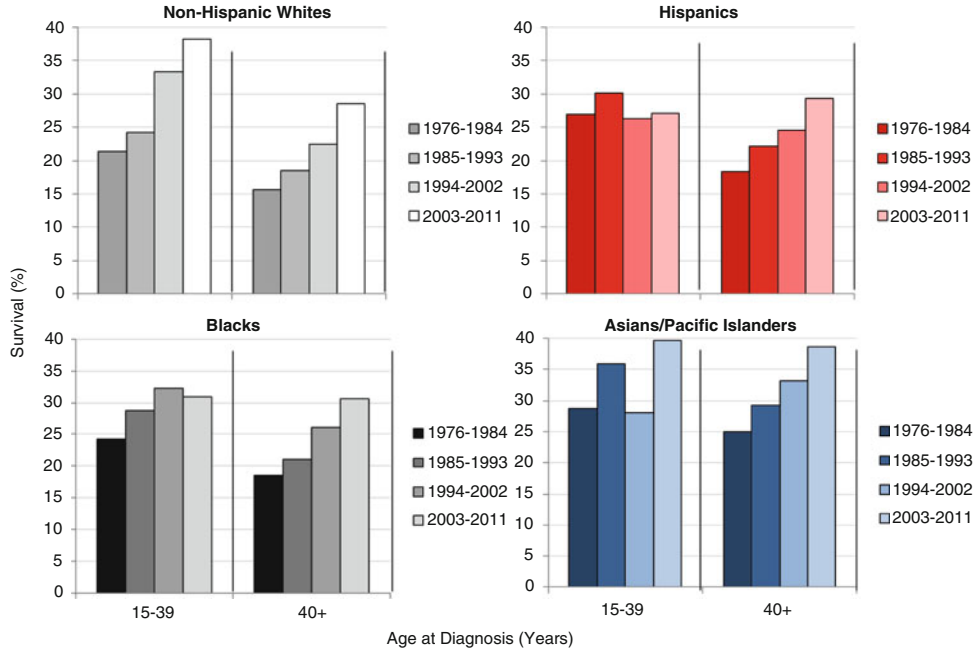

Fig. 19.29 Change in 5-year cancer-specific survival of gastric carcinoma, 1976–2011 by 8-year intervals, race/ethnicity, and age

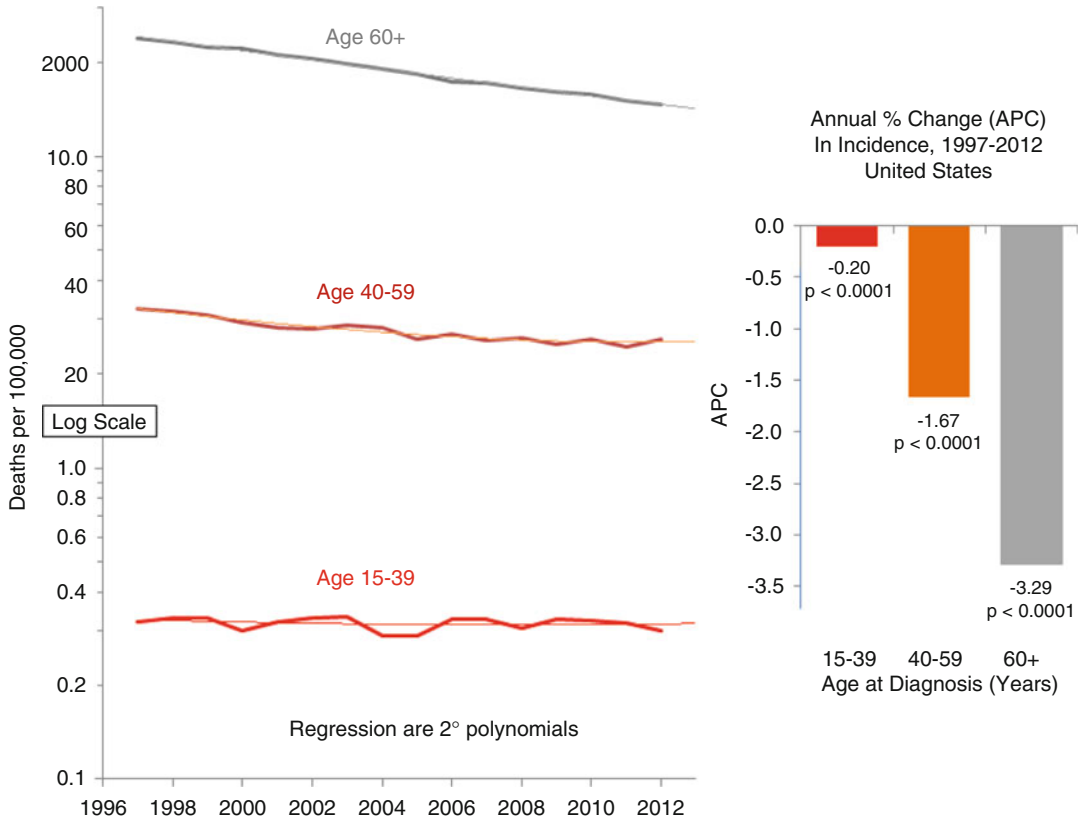

Fig. 19.30 Annual death rate of gastric carcinoma and its average percent change (APC) in death rate, 1975–2011, SEER9, by age

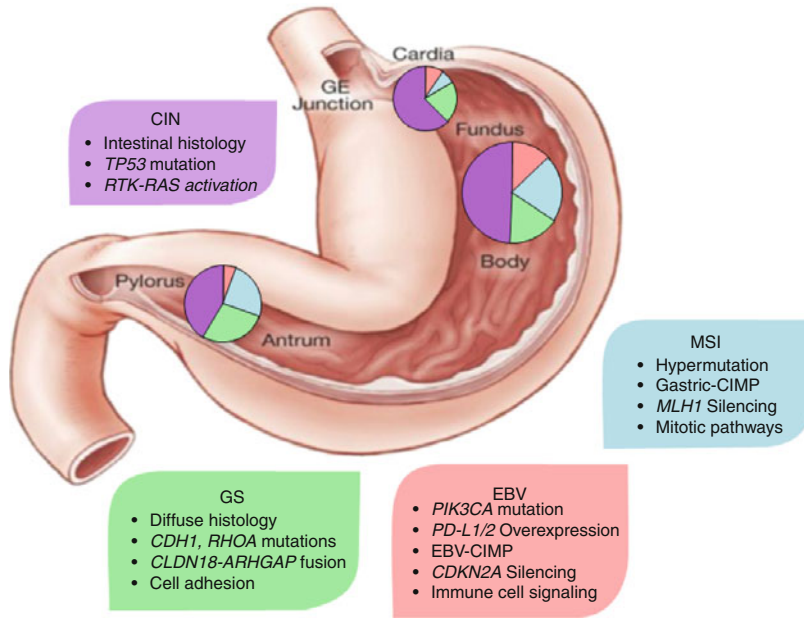

Fig. 19.31 The four molecular subtypes described in The Cancer Genome Atlas gastric cancer study, their mutational patterns, and location (Modified from Goldberg [72]). *CIN* chromosomal instability *EBV* Epstein–Barr virus, *GE* gastroesophageal junction, *GS* genomically stable, *MSI* microsatellite instability

guidelines (v3.2015) [82] for the medically fit and surgical candidates are generally applied to AYAs. In addition, AYAs are treated with the same strategies as older patients but should be assumed to tolerate all forms of therapy better than older patients and be more aggressively treated. T1b tumors are managed surgically, and more advanced stages may be treated with preoperative chemotherapy, preoperative chemoradiation, or primary surgery. Patients who are not treated with preoperative chemotherapy or chemoradiation and either have large primaries (T2+) or nodal metastases or have evidence for residual tumor after surgery receive postoperative chemotherapy with 5-fluorouracil + leucovorin or capecitabine with or without chemoradiation. Patients who received preoperative chemotherapy also receive postoperative chemotherapy or chemoradiation if they have a large primaries, nodal metastasis, or subtotal resection.

19.3.10 Discussion

Why is gastric cancer increasing in AYAs and decreasing in older persons? The latter has been attributed to the widespread availability of refrigeration, which has led to changes in dietary patterns and food preservation methods [83–85]. Refrigeration may have reduced dietary exposure to various carcinogens such as nitrates and nitrites, by reducing bacterial and fungal contamination of food or by allowing a reduction in the consumption of smoked, cured, and salted foods.

The decrease in incidence of gastric cancer from 1930 to 1976 has also been associated with a decline in incidence of distal lesions. There has been a general shift in presenting anatomic location from noncardia sites to cardia sites [86], which also has increased the likelihood of TP53 and RAS mutations (Fig. 19.31). Since 1976, the incidences of proximal cardia and (GE) junction adenocarcinomas in the United States and Europe have increased at a rate that exceeds that of any other malignancy [87]. The rise in incidence of GE junction and cardia lesions suggests a common pathogenesis that is distinct from that of distal gastric lesions, but the etiology is unclear. Gastric cancer is the second leading cause of cancer-specific mortality worldwide; in China, South America, Eastern Europe, and Japan, it has been the most common malignancy [88].

Increased meat consumption and longer cooking times of meat have been associated with increased incidence of gastric cancer [89], whereas diet diversity, especially with regard to fruits and vegetables, has been reported to be protective [90]. *Helicobacter pylori* and Epstein–Barr virus infection have been implicated in gastric cancer causation [91, 92]. For *H. pylori* infection, the increased risk is for noncardia lesions only [93], which is the more prevalent site in AYAs. Risk factors include a specific strain, cagA-positive *H. pylori* [94, 95] and infection early in life [96]. Whether any of these factors have increased more in AYAs than older adults remains to be determined, but AYAs and their dietary habits would seem plausible, especially since the International Agency for Research on Cancer (IARC) rated processed meat as carcinogenic for colon cancer and red meat as a probably carcinogenic for colon, pancreatic, and prostate cancer [97]. Although gastric cancer was not mentioned in the IARC report, its similarity to colon cancer raises the issue.

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Access and Models of Care

20

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20.1 Access to Care

The United States Institute of Medicine Committee on Monitoring Access to Personal Healthcare Services defines *access* as "the timely use of personal health services to achieve the best possible health outcomes" [1]. A dissection of this definition is important to tease out all the complexities of access and to illustrate AYAs' disadvantaged access to care. *Timely* care requires that there is no disproportionate lag-time to diagnosis or commencing treatment, either due to patient or provider/health system factors. The phrase "use of" is included in the definition because the existence of services is irrelevant if they are not *utilized*, due to lack of affordability, geographical inaccessibility, inconsistent referral pathways, and so forth. The elements of "health services" that achieve best outcomes are complex and remain to be well defined for AYAs with cancer. This chapter will address the way in which various barriers and enablers interact with each component of this definition of access, i.e., timeliness, utilization, and structure of health services, to influence outcomes for this patient group (Table 20.1). This will be followed by a summary of the various models of AYA cancer care which have been implemented internationally.

The above definition of access assumes that we know the "best possible health outcome."

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While survival is the most objective health outcome, it should not be forgotten that other outcomes, such as quality of life and societal outcomes (e.g., costs incurred providing a desired level of quality of care), can and should be measured. Survivors of cancer diagnosed in adolescence and young adulthood may experience difficulties returning to work and study [3] as well as a higher incidence of chronic illness and psychological morbidity [2]. Event-free survival (EFS) estimates from large clinical trials are often held as the gold standard, but as there are few AYA-specific trials, and even fewer incorporating patient-reported outcomes and health economic evaluations, an estimate of best possible outcome is difficult to determine in this group.

Even if we focus on survival alone, "real-world" survival data from population or large registry studies may not always reflect "best possible" survival outcomes. The historical example of acute lymphoblastic leukemia (ALL) is useful. Surveillance, Epidemiology, and End Results (SEER) registry data continue to show a decline in survival from ALL by age; the 2000–2004 5-year overall survival (OS) was 81 % for 10- to 14-year-olds, 61 % for 15- to 19-year-olds, 45 % for 20- to 29-year-olds, and 34 % for 30- to 44-year-olds [4, 5]. These population level data suggested that biological factors prevented AYAs from achieving better outcomes. However, Stock et al.'s seminal analysis comparing outcomes of AYAs with ALL treated on pediatric or adult studies from 1998 to 2001 challenged this assumption [6]. They found that 16- to 20-year-olds treated on a Children's Cancer Group study had a 7-year EFS of 63 % (comparable to that of 10- to 14-year-olds in that time period), whereas those treated on adult trials had an EFS of 34 %. Recently, several prospective AYA ALL studies have confirmed that, by the use of pediatric-inspired treatment, the "best possible" outcomes for AYAs with ALL are an EFS and OS exceeding 60 % [7–14]. Therefore, while adolescent age may be a surrogate for biological and other factors that influence survival, the adverse prognostic impact of these factors can be overcome partially by access to appropriate care. This, in turn, shifts our definition of the "best possible" currently achievable survival outcome.

Table 20.1 Potential barriers to accessing care encountered by AYAs with cancer

Healthcare system factors
Low awareness of AYA cancer in primary care providers
Arbitrary referral patterns to pediatric vs. adult medical oncology providers based on age alone
Rigid upper age limits set by pediatric hospitals
Minimal collaboration between pediatric and adult medical oncologists/hematologists
Complex and often fragmented systems
Lack of relevant clinical trials (or restricted access due to age-eligibility criteria, etc.)
Inadequate access to psychology, social work, and other support services
Poor understanding of normal adolescent development and behavior
Limited research into the unique tumor biology in AYAs
Inadequate transition, survivorship, and late-effects programs
Patient-related factors
Low awareness of AYA cancers and symptoms/signs
Lack of a regular, identified primary care provider
Normal adolescent developmental traits, e.g., fixation on the present, sense of immortality, limited self-management skills
Poor self-advocacy and variable parental involvement
Limited awareness of healthcare choices
Limited ability to navigate the healthcare system
Social concerns (e.g., education, job, peers, family) outweighing health concerns
Risk-taking and adherence issues
Geographic and societal factors
Rural or remote location
Lack of insurance
Financial insecurity
Cultural and race-related inequities

20.1.1 Structure of Health Services

In recent years, the AYA oncology community has directed considerable effort into understanding the elements of healthcare services – including provider, setting, and treatment – which are most critical to achieving the best outcome. There are elements of quality cancer care that should be universal for patients of all ages, which AYAs may not be accessing equally (e.g., clinical trial enrolment), and there may be age- or development-

specific requirements that are unique to AYAs. Unfortunately, attempts to measure the optimal provider, setting, and treatment are complicated, and these variables are probably confounding. Ideally, studies would incorporate very large, disease-specific samples, adjustments by case mix, and long follow-up. Ongoing analyses from the AYA HOPE (Health Outcomes and Patient Experience) (United States), BRIGHTLIGHT (United Kingdom), and Patterns of Care and Experiences of Care for AYAs with Cancer (Australia) studies should contribute further to the literature on this topic.

20.1.1.1 Where and from Whom Should AYAs Access Care?

Historically, pediatric and adult cancer services have operated relatively independently of one another, with each developing its own idiosyncratic model of care, as discussed in Sect. 2.2 of this chapter. In many regions there are overlapping age limits allowing AYAs between age 15 and 20 years (and occasionally up to 30) to access either site. There are increasing data suggesting that the choice of healthcare setting influences outcome. Specifically, AYAs with tumors more commonly seen in childhood appear to have a survival advantage when treated in a pediatric center, while those with carcinomas and other "adult" tumors fare better when treated by adult oncologists [15, 16]. Although differences in regimens of chemotherapy appear to explain much of the variation in outcome in ALL between pediatric and adult centers, the survival benefit may relate also to pediatric oncologists' greater familiarity with the complex protocols, centralization of care to tertiary/academic centers, and rigid adherence to prescribed dose and schedule [17]. These factors may explain the results of a retrospective review of German Ewing sarcoma trials which found a survival advantage for older AYAs treated in a pediatric center compared with adult centers, despite all patients receiving the same protocol of therapy [18]. Hence, it is likely that site of care is a proxy measure for clinical expertise in both disease-specific management and the psychosocial care of AYAs.

The importance of access to clinical expertise and centralized care is emphasized by several registry studies of AYAs with cancer which have reported that the adverse impact of age is abrogated by treatment at National Cancer Institute (NCI)-Designated Comprehensive Care Centers or Children's Oncology Group institutions [15, 19–21] in the United States. While the majority of children with cancer received treatment in such centers, the proportion fell to approximately 38 % of 15- to 21-year-olds and a mere 10 % of 22- to 39-year-olds. This difference was particularly pronounced for older adolescents with low socioeconomic status, public or no insurance, and increased distance to care.

Site of care is also a strong determinant of access to clinical trials. While it is unclear whether participation in a cancer clinical trial is associated with improved survival at an individual level [22], there is no question that collaborative group trials have facilitated stepwise improvements in survival for many cancers at a population level and that AYAs have been historically underrepresented in such studies [23–27].

Decisions regarding site of care are determined frequently by the initial referring physician, who will often not be familiar with the issues discussed in this chapter, given the relative rarity of cancer in AYAs. Consequently, patterns of referral are often arbitrary and based primarily on the patient's age, with the specialty of the referring physician, their years in practice, and location of training also potentially influencing this decision. While studies from Utah and Ohio found that 15- to 19-year-olds with "pediatric"-type tumors were somewhat more likely to be referred to pediatric oncologists than those with tumors more common in adults, two-thirds of patients from this age group were never referred to a pediatric oncologist. Furthermore, utilization of pediatric centers dropped with each additional year of age [28, 29]. This is despite consensus guidelines from the American Academy of Pediatrics [30] and the American Federation of Clinical Oncologic Societies [31] recommending that pediatric oncologists are the most appropriate providers for adolescent cancer patients.

Although there is broad agreement that pediatric oncologists are best placed to care for adolescents with cancer, the picture is less clear for

young adults. Pediatric oncologists probably have the most clinical expertise in managing pediatric-type tumors, including ALL, rhabdomyosarcoma, Ewing sarcoma and osteosarcoma, and medulloblastoma, but pediatric hospitals are often not a developmentally appropriate location in which to treat young adults. Equally, one could argue that many adult hospitals lack the time and expertise to address the psychological and social challenges faced by this age group. The development of Teenage and Young Adult Cancer Units in the United Kingdom, and subsequent adaptations in other countries, may provide an ideal combination of disease-specific and psychosocial expertise as well as an age-appropriate environment. This is reflected in the British National Institute for Health and Care Excellence guidelines recommending that "young people (aged 16–24 years) with cancer have their diagnosis, treatment and support agreed and delivered by a cancer-site-specific multidisciplinary team and a young adult multidisciplinary team" [32]. The Clinical Oncology Society of Australia has released similar guidelines [33].

Extrapolating from the evidence presented above, care by physicians with expertise in AYA oncology may improve outcomes, but as yet there is little empiric evidence to support this hypothesis. The concept of what constitutes "expertise" in AYA oncology is still evolving but could be assessed by specific training (pediatric, medical, or AYA oncology), practice volume (number of AYAs seen at a center or by a provider), expertise in the cancer diagnoses that affect AYAs (regardless of patient age), and expertise in the psychosocial and developmental needs of AYAs [34, 35]. Preferably, AYA patients should have care from clinicians possessing both age-appropriate and tumor-specific expertise.

AYA oncology training programs are continuing to be developed in medical, social work, mental health, and nursing disciplines. Online and conference AYA educational opportunities to earn academic credits or continuing medical education points are becoming increasingly available for all providers (e.g., LIVESTRONG's "Focus Under 40"), and online courses are offered internationally through Coventry University and the University of Melbourne. For physicians in the United States, a very limited number of "AYA fellowship" programs have been implemented, but are not yet recognized by credentialing boards. Until there is AYA-specific training and credentialing, the debate whether pediatric or adult medical oncologists are better placed to care for AYAs will probably continue.

Much of this discussion has focused on optimizing access to the best possible medical treatment, but AYAs with cancer also have unique psychological and social needs related to their life stage which are not always well met by either pediatric or adult models of care. As such, access to age-appropriate psychosocial care is crucial for this age group, with the critical elements summarized by Zebrack et al. [36] (Table 20.2). Anecdotal reports suggest that young people, their families, and the treating team greatly value the involvement of designated AYA cancer care coordinators (with a nursing or social work background). These health professionals can guide the patient through the often fragmented healthcare system, ensure that psychosocial issues are being addressed, help advocate for the patient, and provide general adolescent health guidance (e.g., sexual health, substance use). This is particularly important for the majority of AYAs who are treated at non-pediatric institutions, where a culture of holistic care is less engrained and self-management skills are often presumed. Early

Table 20.2 Critical elements of quality cancer care for AYAs with cancer

Early detection and diagnosis
Timely referral, initiation of treatment, and adherence
Healthcare providers knowledgeable of biomedical and psychosocial issues specific to AYAs with cancer
Supportive care and palliative care
Clinical trials and AYA oncology research
Fertility preservation and counseling
Cognizance among providers of the unique psychosocial context for AYA growth and development
Assessment and attention to cognitive, psychiatric, and psychosocial needs of AYA patients
Referral to available age-appropriate educational, peer support, financial, and legal resources
Facilitation of transition to survivorship

Adapted from Zebrack et al.

referral to psychologists and/or social workers with experience in treating AYAs is likely to help alleviate distress, promote coping strategies, and possibly support adherence to treatment. Access to other allied health staff such as an educational/vocational counselor, exercise physiologist, and dietician may assist in the transition to healthy survivorship, and it is acknowledged increasingly that exploring fertility preservation options is a fundamental component of AYA cancer care [36, 37]. AYAs with cancer endorse the benefits of meeting other young people with cancer universally [38], emphasizing the importance of facilitating access to peer support programs coordinated by not-for-profit organizations, such as Stupid Cancer (United States), CanTeen (Australia), and Teenage Cancer Trust (United Kingdom).

20.1.1.2 Delivery of Therapies Which Provide Optimal Outcomes for AYAs

Research in this area is sparse, largely because of the lack of consensus on the most appropriate therapy for specific cancers in the AYA population. Many studies document variation by age in the treatment of cancer; for example, AYA sarcoma patients characteristically receive less intensive therapy than children [39–41], younger breast cancer patients are more likely to undergo mastectomy [42], and younger rectal cancer patients receive radiation more frequently [43]. As noted above, there is consensus that a pediatric-based treatment is the appropriate therapy for a young AYA with ALL; however, there is less agreement on whether this pertains to AYAs aged 30–40 as well.

The AYA HOPE Study Collaborative Group reported recently that 25 % of a population-based sample of AYA did not receive "appropriate" initial courses of treatment, as defined by expert clinical consensus [44]. In multivariate analysis, clinical trial participation and cancer type were associated significantly with appropriate treatment, with 100 % of early stage male germ cell tumor, 79 % of sarcoma, and 56 % of ALL patients receiving appropriate therapy.

This study highlights the paucity of empirical research on the appropriateness of such variation in treatment. In some clinical cases, less therapy may be more appropriate, whereas in other cases, AYAs should be treated equally or even more intensively than children. Translational and clinical research should not assume that the biology of specific cancers in AYAs is the same as in other age groups, and host genetic variations influencing treatment response may also differ in AYAs with cancer [45]. For example, the incidence of Philadelphia-like ALL increases from <3 % of children to 27 % of young adults with ALL [46]. Additionally, specific germline susceptibility alleles are overrepresented in AYAs, suggesting an inherited predisposition to high-risk disease in this age group [47]. Likewise, it is plausible that tumor genetics and host polymorphisms contribute to a more aggressive disease phenotype in AYAs who develop the epithelial cancers that more characteristically occur in older individuals. Furthermore, AYAs exhibit distinct pharmacokinetic differences to children or older adults, which may contribute to age-specific variation in drug efficacy and toxicities [48]. Whether it is appropriate to differentiate therapy for AYAs by age alone or whether more emphasis should be placed on other biologic parameters that may sometimes be correlated by age, such as hormone receptor status in breast cancer, will have to be determined for each cancer type. Clearly, this area is ripe for future translational research.

20.1.2 Timely Diagnosis

When AYAs are compared with pediatric cases, there is a clear increase in time to diagnosis (TTD) by age [49–53]. There are many more studies in adults examining TTD, some including AYAs (usually aged 30–39); they do not conclude uniformly that there is a longer TTD for AYAs compared with older adults. A comprehensive study of nearly 100,000 patients over age 30 found an increase in advanced stage at presentation in young patients with colorectal, lung, and bladder cancer, but not breast, renal, melanoma, ovarian, or prostate cancer [54]. It is unclear whether increased TTD is associated with adverse outcomes in AYAs, with tumor biology probably being more relevant. Nonetheless, it may contribute to increased

morbidity in occasional cases, and perceived delays may cause heightened anxiety.

Within the AYA age group specifically, little is known about the factors influencing TTD. In a Canadian study, the delay to treatment was longer for adolescents when they were treated in an adult center than at a pediatric institution (92 vs. 57 days) [55]. The NCI Patterns of Care (POC) Study of 1,358 AYA patients with ALL, lymphoma, sarcoma, and germ cell tumors found less advanced cancer, and treatment in a hospital setting shortened the time from diagnosis to treatment [55]. Health insurance status was not a determinant of TTD in the POC study, although it was highly significant in other studies [56]. A study from the MD Anderson, for example, reported that AYA patients with public insurance had a 124 day lag-time compared with 76 days for private and 32 days for self-pay patients [57].

The interval that appears most responsible for delays in AYAs is the time from first symptom to presentation to a healthcare system [58, 59], although some studies on this topic may be subject to recall bias. Research seeking to decrease patient delays could investigate the impact of having an identified primary care provider, insurance status, cancer awareness, and self-advocacy skills. Educational interventions in healthy young people appear to increase cancer awareness [60], but it is unknown whether this results in earlier presentation. Studies in older adults have found limited evidence that education results in earlier presentation [61].

Because of the rarity of a cancer diagnosis in AYAs, primary care providers may not be sufficiently aware of common cancers in this age group, thereby contributing potentially to provider-associated delays. Research is needed to determine which symptoms should alert primary care providers to consider cancer in AYAs [62], as has been done in colon and lung cancer, and to a lesser extent in pediatric cancer [63, 64]. Clearly defined and simple referral pathways to an appropriate oncologist may also limit delays. Recent efforts in the United Kingdom and Australia have attempted to raise awareness of AYA cancer in primary care providers to facilitate early detection and referral [30, 65].

20.1.3 Affordability, Geography, and Socioeconomic Barriers to Care

There is a growing body of literature demonstrating an independent association between insurance status and access to healthcare and survival in AYAs with cancer in the United States. A study of 45,777 cases of Hodgkin lymphoma in the National Cancer Database found that uninsured/Medicaid patients had a 5-year OS of 54 % compared with 87 % in cases who had private insurance, managed care, or Medicare; this association persisted after adjustment for covariates. Uninsured patients presented at a more advanced stage had higher comorbidity scores, were less likely to receive radiotherapy and start chemotherapy promptly, and were less commonly treated at academic/research centers [66]. Likewise, a SEER review of 57,981 AYAs identified that young adults aged 25 to 39 years who had Medicaid or no insurance had a 2.9 times greater risk of death for stage I/II patients and 1.7 times greater risk of death for stage III/IV patients compared with their privately insured counterparts [67]. Another SEER analysis of 20- to 40-year-olds with cancer found that any insurance coverage, including Medicaid, was associated with a decreased likelihood of presentation with metastatic disease (odds ratio 0.84), increased receipt of definitive treatment (odds ratio 1.95), and decreased death resulting from any cause (hazard ratio 0.77) [68].

Despite the risks of recurrence and late effects of treatment, many AYA cancer survivors do not access follow-up care due to cost and underinsurance. The AYA HOPE collaborative study reported that >25 % of AYA cancer survivors experienced some period without insurance in the 35 months after diagnosis [69], and those without insurance were less likely to receive cancer-related medical care after completing treatment [70]. Even if insurance status is a marker for racial or other socioeconomic factors which may contribute to worse outcomes, this marked inequity remains extremely troubling. Furthermore, the economic impact of care is often more burdensome for AYAs. A recent survey found that, compared with their peers,

young adult cancer survivors had excess annual medical expenditures of $US 3170 per person and excess annual productivity losses of $US 2250 per person [71].

For many years, young adults in the United States have had the highest uninsured rate of any age group, falling in the gap between parental coverage augmented by programs designed to provide universal health insurance to children (Medicaid and the Children's Health Insurance Plan) and the coverage supplied by a full-time secure job [72]. The Affordable Care Act has resulted in a dramatic improvement in the number of insured young adults. Firstly, in 2010, insurance plans that include dependent coverage were required to cover adult children until their 26th birthday [73].

Early on, in 2011, 39 % of young adults aged 19–29 years remained without health insurance, primarily because their parents did not have healthcare plans that they could join. This was particularly pronounced in low-income families, with 70 % of young adults from the lowest income bracket reporting an insurance gap in the preceding year. Gaps in health insurance were associated with being less likely to have a regular doctor (85 % for those insured all year, 72 % for those with a gap in insurance, 38 % for uninsured) and delaying or forgoing healthcare because of costs [74]. Gradually more young adults took advantage, and by October 2013, the uninsured rate for 19- to 25-year-olds had dropped from 34 to 27 % [75]. In 2014, modifications to the Affordable Care Act expanded eligibility for Medicaid to young people who were unable to join their parents' plans, as well as subsidizing private health plans for low- to middle-income individuals, thereby providing near-universal coverage for AYAs. Additional millions of young adults have gained coverage this way, and a 2015 survey reported uninsured rates for 19- to 34-year-olds at 19 % [76]. While this is cause for great optimism, gaps still exist (e.g., for young adults older than age 26 years and poor individuals in non-Medicaid expansion states), and it is important that AYAs are provided with information and assistance in navigating the process to access coverage and benefits, as many survivors remain unfamiliar with the provisions of the Affordable Care Act [77].

Studies addressing the influence of socioeconomic status on AYA cancer outcomes in countries with universal healthcare have found more mixed results. In the United Kingdom, there was no association between deprivation and survival for most AYA cancers, with the exception of leukemias and carcinomas, especially colorectal and head and neck cancers. The authors postulated that a higher incidence of smoking and unhealthy lifestyle factors in deprived regions may explain the lower survival from carcinomas [78]. For Australian AYAs with cancer, socioeconomic status is associated significantly with relative survival, but not with cancer-related mortality per se [79].

Geographic isolation may also limit access to appropriate care. In an Ohio registry study, distance was associated with a greater likelihood of adolescents being treated in a non-pediatric institution [29], although a similar study from Utah reported a negligible effect [28]. In Australia, where the relatively small population is dispersed across an enormous area, geographic isolation is linked with cancer-related mortality [78], although it is unclear to what extent this relationship is explained by the greater proportion of Aboriginal Australians living in rural and remote locations. Aboriginal Australian AYAs have higher cancer-related mortality (hazard ratio 1.47, CI 1.23–1.76), and those diagnosed with germ cell tumors have nearly seven times higher excess mortality [80]. This likely reflects the myriad of social inequities contributing to worse health outcomes in this group, somewhat analogous to the disproportionately poor survival experienced by African American AYAs and other ethnic minorities in the United States.

It is important to remember that most of the world's cancer burden is faced by developing countries, where access to care, and consequently survival, lags well behind high-income countries. As most AYAs are in the working age group, they play an important role in their countries' economy both now and in the future, as well as frequently supporting their families [81]. As such, broader societal consequences follow deaths from curable cancers, which were either

undetected, referred at an advanced stage, or treated inadequately due to poverty, lack of access to chemotherapy and supportive care, radiotherapy, surgeons, and pathology services; abandonment of treatment; or inefficient health services. Twinning programs with high-income countries and the development of safe, efficacious, and cost-effective treatment protocols are likely to provide substantial benefits [82].

20.1.4 Adolescent Behavioral Traits

Adolescence is characterized by remarkable neurocognitive maturation and social role transitions; however, some of the normal adolescent behaviors which emerge during this process can compromise access to care. Delays in presentation may relate to the adolescent's strong sense of invincibility, denial, or embarrassment, and they may give an incomplete history, especially to a physician untrained to "read between the lines" of an adolescent history.

The disparity between maturation of the prefrontal cortex, which is responsible for executive control and rational decision-making, and the pleasure-seeking limbic system might underlie young AYAs' orientation to the here and now as well as risk-taking behaviors such as prioritizing social events over treatment and poor adherence [83]. The actual rate of nonadherence in AYAs is unclear due to difficulties in defining and measuring it objectively. However, it appears that a supportive family relationship, promoting involvement in treatment decisions, and supporting participation in normal activities might enhance adherence, while a chaotic social environment is likely to have the opposite effect [84]. This underscores the importance of pre-emptive referrals of AYAs with cancer to social work and psychological services.

Adolescents are often poor self-advocates, preferring to "blend in" and not upset the status quo or question authority. Additionally, their parents may not advocate to the same degree as they would for younger children. This is exacerbated by the fact that most AYAs have poorly developed self-management skills and hence may struggle with medication management, arranging appointments, and other tasks which they relied on their parents to perform previously. These factors may result in disengagement with the health system and poor adherence. This highlights the importance of a designated cancer care coordinator to help advocate for the young person and promote the development of self-management skills as they navigate the complex healthcare system.

20.1.5 Summary

In sum, we are beginning to learn more about the components of quality care for AYAs and the barriers they face in achieving access to that care. Although there is some knowledge gained from studies comparing care at pediatric versus adult centers or from pediatric versus adult providers, this is limited, both because it does not tell us what components are responsible for any differences in outcome and because only the youngest of AYAs will be eligible for pediatric care. Recent efforts to develop AYA programs, as detailed below, will teach us much about the essential elements of "personal health services to achieve the best possible health outcomes" and will require us to shift our assessment of access.

20.2 Models of Care

It is recognized currently that AYAs with cancer are a unique group, with special characteristics and special health needs [85, 86]. With the recognition of their complex psychological and social needs [87], together with the awareness of their inadequate access to optimal cancer services and the lack of improvement in survival rates [88], it has became evident that AYA patients are particularly complicated to care for and that the traditional healthcare models address their needs poorly [89, 90].

The teenage and young adult period is an age of transition, and AYA patients are often the older patients in children's services or the younger in adult services. In terms of healthcare delivery, it

has been said that these patients inhabit a "no man's land," neither belonging to the pediatric nor to the adult worlds of oncology. On the other hand, they may also become subject to professional competition for patient "ownership," paying the price of the shortcoming in communications and collaborations between these two worlds.

Nevertheless, it is evident that the last decade has been a key time for AYAs, and several dedicated projects have been developed in an attempt to address the unmet needs of this age group. Starting a specific project, however, remains a challenge: the enthusiasm of people has to be able to counterbalance the obstacles of ingrained cultures (or even strong opposition), physical space constraints, administrative and logistic issues, low prioritization, and costs [91].

20.2.1 What Makes Adolescents and Young Adults Different?

There is substantial evidence of specific clinical and psychosocial features, and also specific challenges in patient's management, that mark out being an AYA with cancer. Patients in this age group have specific clinical features because of their cancer types, tumor, and host biology; because of the insufficient awareness that cancer may occur in this age group and the complex diagnostic pathways; and because of the specific psychological and social characteristics that care providers must address adequately (Table 20.3) [92–99]. On the other hand, there is growing evidence that these patient features combine unfavorably with the features of many current healthcare systems (Table 20.4) [91, 100–110].

One of the main challenges for young people with cancer is the possibility to continue to live as normal a life as possible and to achieve developmental tasks. This critical concept needs to be taken into account when developing age-specific models of care. In this group, people change their perception of the world and need to test their limits. A recent review described brilliantly the AYA's world with the reference to the famous phrase of "sex, drugs, and rock 'n' roll" [111]. Care providers should be able to address the need of young people to live their experiences and rites of passage, that cannot be postponed due to the event of a cancer diagnosis. Care providers should be able to establish an open relationship with their patients to help them to revisit these aspects in the light of their cancer history. Young patients need to feel comfortable disclosing sensitive matters. Talking about "sex" – about sexual identity and sexual practices but also sexual dysfunction related to the disease or treatment – may be particularly complicated for a teenager in front of a doctor. A sensitive, nonjudgmental, and confidential relationship is essential also regarding "drugs" – alcohol and drug exploration and use. Clinicians must be aware of aspects such as the negative impact of alcohol and drug use (or abuse) in relation to the patient's health, the interactions with medical drugs, and the associated psychosocial morbidity; but they should be able to address this issue in a timely and appropriate manner, avoiding a paternalistic approach and prohibition that, for example, may have a negative impact on treatment adherence. Alcohol consumption and recreational drug use may have a role for socialization and for feeling normal and being part of the crowd. An adequate balance should be considered appropriately to help young people in developing their sense of self and their feelings of connection to the world. The "rock 'n' roll" lifestyle distinguishes young people from children and from older adults. The crucial concept that care providers dealing with AYAs should have in their mind is that a patient is first a normal young person who happens to have a cancer: this concept should be at the foundation of the model of care. Promoting normalcy means adequate spaces and rules in the ward to facilitate the relationship with peers and prevent the isolation that long periods of hospitalization may imply: social zone and multifunctional spaces with technical equipment (TVs, computers, musical instruments, books, magazines, and DVDs appealing to the age group concerned), for example, as well as kitchen/dining zone or "chill-out" zone. It means accessible visiting times and easy access to the hospital. It means the availability of activities and events as take away evenings. But it means also the opportunity to respect the

Table 20.3 Clinical and psychosocial parameters specific to adolescents and young adult (AYA) cancer

Feature	Comment and open questions
Epidemiology: this age has a unique spectrum of cancer types: AYA may have pediatric-type and adult-type tumors; then there are tumors with a peculiar incidence pick in this age [92]	Multiple parts of cancer research and care need to work together to improve outcomes for AYA. Detailed outcomes are poorly understood, because of international variations in cancer registration, and limited linkage of registration to treatment and outcomes
Tumor biology and clinical behavior of various tumor types are not the same in AYA as in younger or older people [45]	Management not simply the application of a children's or adult standard of care
	Most AYA tumors may have unexploited identifiable specific tractable biological targets. There is little detailed prospective biological data linked to treatment and outcome for AYA tumors
The *biology* of an AYA *patient* (not just their cancer) is distinct. AYA may have specific pharmacology and toxicity profiles that may be relevant in treatment protocols [94]	Treatment protocols tailored for children (or adults) may be not simply applied to AYA
	It remains to be clarified whether these differences in biology (in cancer and host) may explain the differences in outcome
There is *insufficient awareness* that cancer may occur in this age group, among teenagers, their families, and physicians [95]	Diagnostic pathways may be complex, with multiple consultations and consequent therapy only after an unacceptable delay. Which improvements in professional and public education will reduce time from symptoms to diagnosis?
Unique complex *psychological needs* (physical changes, development of self-image, identity, relationships, and sexuality, seeking independence; communication challenges, compliance, and treatment adherence; peculiar behaviors of this age and risk-taking) (smoking, alcohol, substance use, sexual health) [87]	These normal needs may go unrecognized as what they are or even be resented by some professionals. Information and consent must be tailored to a patient's age and level of maturity. What are the predictors of psychosocial adaptation after AYA cancer?
Fertility preservation is a key issue for AYA [96]	Addressing this issue actively is an essential part of the overall management
	What is the balance of parental, sibling, and personal responsibility in adolescent decision-making for their future?
Distinct *late sequelae* (e.g., late cardiac toxicity, secondary tumors, psychosocial reintegration into life) [97]	Specific management and follow-up may be necessary. Which model should we follow for managing deferred risks in adolescents? Is lifelong follow-up the best option?
Transitional programs (to take care for children as they become older, and move patients through to adult services when older still) [98]	AYA services need open collaborative cultures and funding mechanisms to support care. How do we hold vulnerable people's implicit trust at the time of diagnosis while not hindering a transition of care to others in the future?
Peculiar aspects in *palliative care*, *death*, *and bereavement* (adjustment to a short life expectancy in the AYA age is complex) [99]	Balance of pediatric and adult palliative care skills. Do AYA services need more specific approaches to end of life care?

Table 20.4 Specific challenges in managing AYA cancer

Feature	Comments
AYA patients can benefit from expert management including a *specific integrated multidisciplinary team* [91]	This should include access to psychologists, education and vocational mentors, nurses, social workers, activity coordinators to continue developmental social activities during stays in hospital
Each professional needs *training* in the specific issues of AYA	Need of joint adult and pediatric credentialing organizations. Doctors trained in all of AYA care (regardless of their pediatric or adult oncology background) may provide better care
AYA with cancer may seem only to accept a *curative intent* [100]	Management of AYA cancer needs to reflect their frequent ambition to seek a cure (even in situations where the chance to reach this is low). A prolongation of life by some years with improved control of symptoms that is frequently achieved in older adults receiving effective modern cancer treatment is less relevant to AYA
Some data show a lack of recent improvement in *survival rates* for AYAs as compared to other age groups. For some tumor types, AYA survival is poorer than that of children with the same disease [101, 102]	The reasons of these differences probably combines factors linked to the biology of tumors, factors related to delivered treatment and factors due to the patients themselves (e.g., delay in diagnosis, adherence and specific pharmacology)
AYA may have limited *access to cancer services* which meet their needs [103]	Many patients are managed either as younger children or as older adults would be
	Policy changes at different rates in different nations may lead to improvements
In many healthcare environments, AYAs have low *accrual to clinical trials* [101, 104, 167]	Developing clinical research protocols is a fundamental part of cancer research. Entry in clinical trial has been suggested as a factor improving survival
	Need to facilitate and prioritize trial entry
Clinical *trial entry criteria* disadvantage AYAs [104]	Trial entry criteria reflect the practices of the clinicians designing the trials, not the disease under study. The trial entry criteria may reflect the practices of the clinicians designing the trials, not the disease under study. Trials in cancers should have age-related entry criteria that offer recruitment to all AYA with comparable tumor biology
Given the peculiar pattern of tumor types, the management of AYA patients requires effective *cooperation between pediatric and adult oncologists* [106, 107]	AYA may fall between children's and adult services, but may also be subject to professional competition for patient "ownership." It appears neither a pediatric nor an adult clinical group can manage this group of patients without the active collaboration of the other group. Currently however cooperation between pediatric and adult oncologists could/should be improved
Young people strongly prefer to be cared for alongside their *peers*, rather than with younger children or older adults [108]	An adequate setting and environment for this care is required as choice for AYA to make.
	There is the necessity to consider also AYA specific needs for privacy from other peers, but also their need for social contact
Many young patients are eloquent *advocates* for the services they value [109]	It may be helpful to actively promote the patient voice at the center of services.
	A partnership with AYA and their groups, parents and their associations where involved, and charities, may be critically important to shaping a service meeting AYA needs, and involving people who are harder to reach
AYA *specialization* is a recent consideration [110]	For AYA, and the clinical culture, investment and networks have existed for a shorter time and are therefore less mature than those dedicated to children or adults.
	There is a need for infrastructure investment to establish these services

need of privacy and the possible wish to refuse the involvement in social activities.

A further critical aspect relates to what young people say they need. In designing and delivering services, it is essential to take the experiences and views of patients into account. It is important that the young people are given a "voice and a choice" in their care, as this helps to inform and underpin everything that is developed for them. Given the opportunity, young people will say what they want from services and those who provide them.

20.2.2 Current Healthcare Delivery Models: Medical Oncology Versus Pediatric Oncology

Pediatric oncologists and adult medical oncologists usually adopt different organization models, particularly as concerns interaction with the patient. With a rough generalization, it could be said that the pediatric model is *family focused*, while the adult model seems to be *disease focused* (Fig. 20.1).

20.2.2.1 Pediatric Oncology Model

The pediatric model of care is based on a complex, sometimes dualistic, relationship between three leading actors, i.e., the child, the parents, and the healthcare professionals. The pediatric oncologist has to establish a deep relationship with both patient and family, but the interactions are on different levels: for instance, parents are fully informed about the child's condition and prognosis and involved in the decision-making process, while the child himself/herself is often not [112]. As children get older, their contribution to decision-making may become more

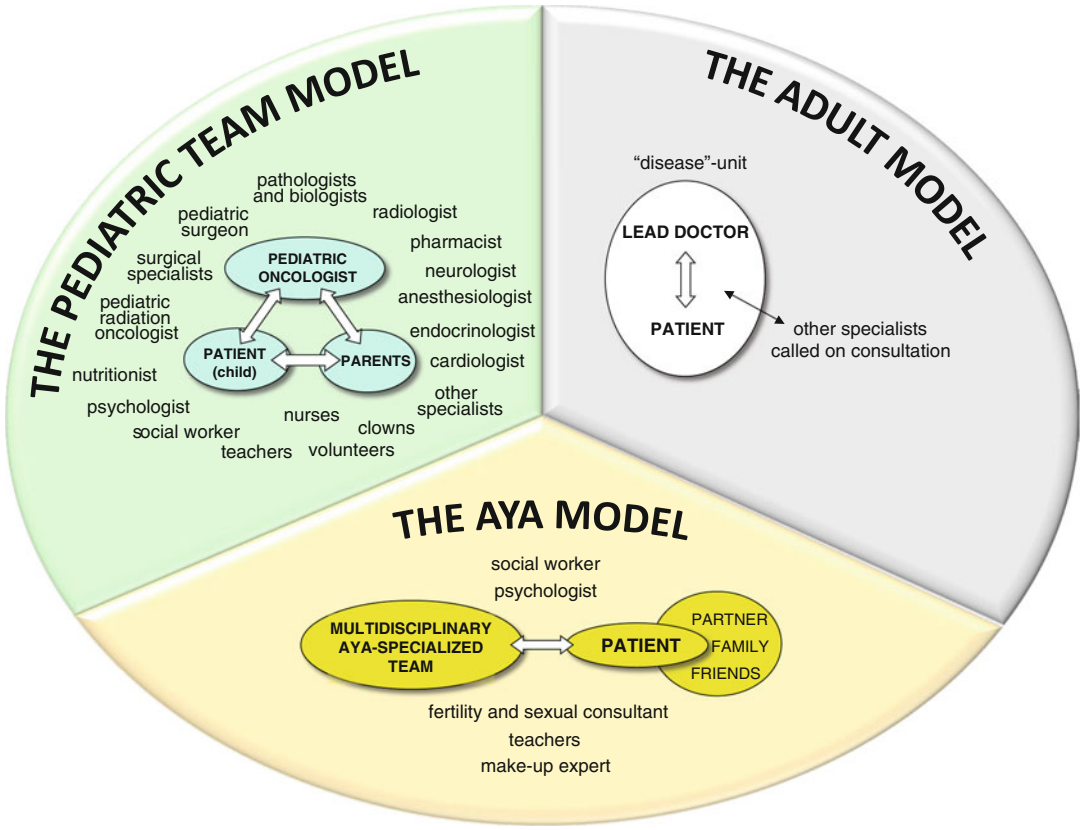

Fig. 20.1 Healthcare delivery models: the *family-focused* pediatric model, the *disease-focused* adult model, and a possible model for AYA

apparent, although decisions and discussions remain an intricate process in which parents' views tend to predominate [91].

Another important characteristic in pediatric oncology units is that, rather than assembling consultants piecemeal, the young patients are managed routinely by an integrated multidisciplinary staff of pediatric oncologists, surgeons, radiotherapists, nutritionists, and subspecialists in infectious disease, neurology, and endocrinology, as well as nurses, teachers, psychologists, social workers, and others.

Pediatric oncology teams have been relatively well resourced, with a high staff/patient ratio and a greater amount of time given in support and interaction with patients and families [91]. Though pediatric cancers account for less than 1 % of the total cancer burden, society and the healthcare system have accepted a disproportionate allocation of resources to children and their families in the view of the differential societal burden of years-of-life lost, which is estimated to be 69.3 years for childhood cancers compared to 15–20 years for the most common adult malignancies [113].

Finally, in pediatric oncology, care is often given on or according to standardized protocols or clinical trials, with centralization in a limited number of referral centers. Historically, pediatric oncologists have put a lot of effort into promoting national, and ultimately international, multicenter collaborative networks: pediatric patients usually have a good chance of being treated within cooperative clinical trials, whereas the proportion of adult patients entering multicenter clinical trials is far lower. This is partly a function of resources but also reflects fundamental differences in trials strategy. For example, adult medical oncologists place a relatively greater emphasis on phase 1–2 trials and research on new treatments (and on randomized phase 3 trials tailored to the "big killers"), while pediatric oncology trials are usually in phase 3 (randomized or risk based) and the emphasis is often on limiting the burden of therapy to reduce toxicity and sequelae (without jeopardizing the results achieved in some diseases).

20.2.2.2 Adult Medical Oncology Model

Professionals engaged with adult patients tend to work within a more classical medical model of a lead doctor interacting directly with the patient, often within units dealing with specific types of tumor. This doctor–patient relationship is at the core of practice and is based on confidentiality and consent. Patient autonomy is central to the therapeutic relationship: the patient rather than the family is at the center of this particular care paradigm, and other family members or partners interact with the professional team largely through the consent of the patient.

Although a multidisciplinary approach has been implemented increasingly at adult units too, particularly at referral centers, this often refers to the involvement of the surgery and radiation disciplines within a clinic program dealing with a specific type of tumor, while it remains rare to encompass psychosocial, nutritional, or educational support routinely.

Though there is more variability of care models in adult oncology, the staff/patient ratio is generally low, and resources have been more stretched. This implies differences in time and resource allocation (i.e., different amounts of time spent on interacting with patients) as well as costs. It remains to be seen whether it might imply also differences in global quality of care and patient satisfaction.

Historically much of the focus of adult teams has been on older patients (and there is much logic in this as the number of older patients who develop cancer is large). In many cases, the emphasis has been often on treating with largely palliative intent while paying particular attention to unwanted acute side effects. The proportion of patients entered into multicenter clinical trials is much lower than in pediatric oncology [88].

20.2.3 The Ideal Model of Care for AYA

Since AYAs are neither children nor older adults, and yet share many characteristics of both, it is not surprising that neither of the classic pediatric

or adult models of care is ideally suited to meet the needs of AYA patients. Certainly, it remains to be seen whether a single, ideal "new" model of delivery of care should exist for AYA patients and whether it could feasibly be implemented. Alternatively, there should be discussion about what adjustments should be made to one or both systems to better meet the needs of the AYA patient [114].

Ideally, an AYA-tailored model of care would have to be *patient focused*: the doctor needs to interact directly with the patient, with sufficient sensitivity to acknowledge each patient's level of maturity and independence and unique needs. Interacting with a patient's parents and/or other figures, such as a partner or friends, still has an extremely important role, given the wide range of independence encountered across the AYA stage of development. Moreover, sensitivity and flexibility are required to meet the needs of each individual, in view of the different levels of maturity and independence.

Due to the complexity of their care and the variety of their psychosocial issues, a multidisciplinary approach is necessary. In addition to the routine group of specialties, this may well include nurse educators, navigators, fertility experts, social workers (especially skilled in employment and insurance counseling), teachers, psychologists, sexual consultants, and even a cosmetics expert (Fig. 20.1).

Given that teenagers and young adults develop a wide range of cancers that encompass both pediatric and adult types of tumors, the multidisciplinary team should include the expertise of both pediatric and adult medical oncology. Providing both of these skills remains a challenge. On the one hand, the direct presence in the team of both pediatric oncologists and adult medical oncologists may be an apparently easy solution. On the other hand, the figure of a "new" tailored healthcare provider – an AYA oncologist – may be advisable. Barriers exist for both solutions [91].

Establishing a genuine collaboration and shared ownership between pediatric oncologists and medical oncologists remains a difficult goal. There are different backgrounds, different priorities, and different models of working: even when they deal with similar diseases, pediatric and adult oncologists often adopt different classification, staging, and grading systems, as well as different practices relating, for example, to data collection – and consequent difficulties when it comes to sharing data. Though both may have much to gain from cooperating with one another, competition often exists. Historical experience showed that AYA dedicated programs have developed in some cases as an adjunct to the local adult oncology facility, while in other cases they have developed predominantly as an adjunct to pediatric oncology services. It has been less common for units to be developed by joint collaboration between adult and pediatric oncology teams.

The ultimate solution to develop oncologists (and oncology centers) specifically dedicated to the care of AYA patients – to create a new discipline, i.e., AYA oncology, with its own training programs, clinical and translational research, and national and international organizations – still remains a challenge. For example, current training for either pediatric or medical oncologists does not provide the necessary skill, and a modification of current fellowships would be necessary.

However, more than regarding the specific training needed for AYA oncology, the key unresolved issue remains whether, in practice, the AYA oncologist ought to cross all disease boundaries, treating breast cancer, melanoma, rhabdomyosarcoma, and leukemias with equal competence. Given the complexity of modern oncology, this seems unlikely. As a matter of fact, a tension continues to exist between providing centralized care in a unit specializing in a particular malignant disease or in a unit specializing in the care and needs of young people. It might be thought that the best solution for young people would be to create an environment that combines these elements to ensure that teenagers and young adults benefit from both. The optimal model may be a unit designed specifically for young people and staffed by a skilled multiprofessional team expert in both the care of teenagers and young adults and their diseases and committed to working in new ways. In this way, the role of the AYA oncologist may be complementary to these of pediatric and medical oncologists. Patients would

be cared for in a unique space (inpatient and outpatient) with specially trained providers, within a culture that recognizes the various needs of young patients as well as the necessity to improve clinical trial enrollment [91].

20.2.3.1 Key Themes in Developing an AYA Oncology Program

Various experiences of AYA oncology programs have been developed – and are in development – all over the world, with differences and similarities (discussed above in this chapter). The possible identification of an ideal model of care for AYA oncology is still a challenge, in particular because AYA units cannot be formed instantly or in isolation. In practice, developing a dedicated program should reflect not only an ideal but also acknowledge local issues and variations in medical culture and resources which have and will continue to generate an interesting heterogeneity of solutions.

A recent review has tried to underline the key elements that needed to be considered and developed according to local issues in starting an AYA-tailored program:

- Cooperation between pediatric and adult medical oncologists – while it is true that many of the existing schemes have arisen in the pediatric oncology setting, several have succeeded when originating from the medical oncology side; real results can only be achieved if there is a genuine cooperation between, and leadership by, both pediatric oncologists and medical oncologists.
- Definition of "who AYA are" – any local project should be able to define in advance its target in terms of the age cohort (from 15 to 24, 29, or 39 years old?).
- Staffing – although appealing, it is unlikely that most programs will be able to create a new unit of AYA oncology with multiple specialties represented (each with an AYA focus and expertise), while it is possible that team members may be involved as "part-time" figures, with other responsibilities in a home department. In some cases, the decision has been that of focusing more on dedicated non-physician staff (nursing, psychology, social work, child life). The development of specialized teams should be based on the recognition that the staff needs special training
- Availability of clinical trials for all the tumor types occurring in the AYA age group – the inadequate inclusion in clinical trials has been demonstrated as one of the factors responsible for the lack of recent improvement in survival rates for AYA patients as compared to other age groups and should be seen as a critical theme to address. Providing dedicated physical areas – as done in some programs – as well as adequate psychosocial support facilities should be considered insufficient if patients are not enabled to enter clinical trials.
- Adequate dedicated space – one of the most common sentiments expressed by AYA patients is the feeling that they do not belong (cartoons and clowns, as in pediatric facilities, may be inappropriate, while adult clinics may be bare and depressing); tailored and adequate spaces are indispensable for them.
- Patient and family advocacy – establishing support from patients and their families is of critical importance for strategic planning.
- Research – research projects (e.g., psychosocial assessment, basic science studies of tumor biology across the age spectrum) may increase the level of an AYA program but may be also important to increase the degree of acceptance within the local context.
- Funding and metrics – AYA programs may be perceived as additional services (and so as additional costs), and it is therefore mandatory to consider economic implications in developing a tailored project/unit. Funding may be based on rearrangement of current resources (so demonstrating the lack of added cost), on new public investment (if it is possible to demonstrate the benefit of the program), on peer-reviewed research grants, or on philanthropic support. Philanthropic financial supports have been of great importance in developing many AYA programs, but it is clear that reliance on these may not be considered sufficient since a sustainable model of care needs institutional, community, and government support. In prin-

ciple, in systems in which the total health budget is limited, a program should be able to demonstrate possible revenue growth (e.g., increase in volume from new referrals, ability to bill for added services such as consults, fertility preservation, psychology services). This may be difficult, or it has been difficult in many cases. The other path to sustainability is to demonstrate the indirect benefit of the AYA program: How to demonstrate the value of the project? How to define and measure the desired outcome? These are not pointless questions since the proposal of building AYA dedicated units/projects may be met with enthusiasm by some people, but not by others. In some experiences, variously motivated opposition has emerged, often relating to administrative and logistic issues or costs. In other cases, barriers have been put up out of diffidence or because physicians are afraid of losing their patients or position of expertise. The metric of desired outcome should be defined and collected carefully. Since it is unlikely to reach the goal of demonstrating improved survival rates within a single local project, other values should be considered and measured: e.g., the development of ancillary services previously lacking (psychosocial support, fertility preservation program), the growth of the number of AYA patients seen at the institution, the proportion of AYA patients enrolled in clinical trials, the fraction of AYA patients receiving fertility preservation, the percentage of AYA patients receiving teaching support or participating in support projects, patient satisfaction (specific surveys, quality of life measurement), provider satisfaction, AYA research and publications, grants, community, and media recognition.

In any case, it is key to recognize that the sustainable development of AYA services will require acceptance as a standard of care at the community and government level. Local programs ought to be complemented by a comprehensive approach, involving a national program. Finally, though rules and recommendations might be defined to improve the chances of success, the human element remains essential: no progress will be made without the fundamental influence of forward-thinking, charismatic heads willing to dedicate their professional lives to AYA patients [91].

20.3 Examples from Several Parts of the World

Various multi-pronged comprehensive programs focusing on AYA oncology and involving numerous organizations, healthcare providers, academic societies, and governments have been developed in different countries, with different models according to the different local situations. Table 20.5 summarizes the major findings of some of these projects.

20.3.1 United States

AYA oncology in the United States garnered interest following the observation that, for patients diagnosed with cancer between 15 and 39 years of age, survival rates had been stagnant for more than two decades. In contrast, cancer survival had improved markedly in children and older adults during that same time interval [115]. To address this inequity, the National Cancer Institute (NCI) partnered with LIVESTRONG to hold a progress review group (PRG) in 2006 [116]. The PRG set priorities for research to define this survival gap precisely and combat the observed disparities [117]. The resulting studies, combined with energetic advocacy for AYAs by both individuals and nonprofit organizations, resulted in significant progress by the conclusion of the PRG in 2011 [118]. AYA oncology has now gained national attention, as evidenced by national initiatives, guidelines, and educational programs. The National Comprehensive Cancer Network (NCCN) developed clinical practice guidelines for AYAs [119], the Institute of Medicine (IOM) sponsored an AYA workshop [120], and there are now two AYA oncology-specific journals [121, 122]. Critical Mass (formerly LIVESTRONG's Young Adult Alliance) is an independent not-for-profit organization working to advance the AYA movement (www.

Table 20.5 Summary of National AYA projects in different countries

Parameter	Progress				
	United Kingdom	United States	Italy	Canada	Australia
Specialization	27 dedicated units with geographical coverage and NHS clinical standards	20 established programs, with many more in development	2 AYA units; national program (SIAMO) as initiative of the pediatric oncology society	6 regional action partnerships coordinated by a national task force	5 Youth Cancer Service lead sites with a number of additional partner sites
Definition of "who AYA are"	16–24 inclusive (flexibility for 13–15)	15–39, with some variation. Some centers serve a subset of this range	Initially 15–19 years, now 15–24 (some extending to 29)	15–29 inclusive	15–25 inclusive
Cooperation between pediatric and adult services	Multiprofessional psychosocial and case review meetings attended by both groups. Requirement for representation of both groups in MDT	Pediatric–adult collaboration is standard	Adult medical oncology societies have formally joined the national program	In 5 provinces	In most regions
Staffing	Dedicated multiprofessional teams, nationally funded	Supported by individual hospitals, local philanthropy, and nonprofit organizations	Specific MDTs are still lacking	In 4 provinces	Dedicated multiprofessional teams
Specific staff education	Professional membership organization "TYAC" provides education Nursing competencies published	Continuing education through ASCO's "Focus Under Forty" series and Critical Mass annual meetings	Specific education and accreditation still lacking	Royal College of Physicians and Surgeons of Canada AYA program	Melbourne University Graduate Certificate of Adolescent Health and Wellbeing (Oncology Stream); Youth Cancer Service national network meetings; Clinical Oncology Society of Australia AYA workshops
Leadership	Named funded lead clinician and nurse per center. Local leads identified for designated as well as principal treatment centers	Lead clinician in each center, some with designated funding	Lead in 2 centers	Lead physician with various support staff in several centers	Named funded lead clinician in each lead site

(continued)

Table 20.5 (continued)

Parameter	Progress				
	United Kingdom	United States	Italy	Canada	Australia
Availability of clinical trials	Funders review age entry criteria against disease epidemiology	Priority but no policy for review	Priority but no policy for review	US National Clinical Trials Network (NCTN) has an AYA Working Group with NCIC-CTG representation	Varies depending on site of treatment
Dedicated AYA space	27 specialized wards (co-funded by charity)	3–5 specialized wards (co-funded by charity), with more in development	In 2 centers	Not available	Drop-in/leisure space in most jurisdictions; dedicated inpatient rooms in some jurisdictions
Patient and family advocacy	Specified public consultation mechanisms required and examined by peer review	Offered by numerous AYA-focused national nonprofit organizations	Partnership with the federation of parents organizations (FIAGOP); online chat room	National initiative	Strong consumer input via Youth Advisory Groups in each jurisdiction and nationally
AYA-focused research projects	Specific national clinical study and cancer intelligence groups	Two AYA oncology-specific journals	Ongoing, supported by National Health Services, government, and charity	National epidemiology data	Competitive funding grants offered by ANZCHOG and CanTeen
		AYA committees in pediatric and adult clinical trial groups		Clinical trial accrual	
				Access to fertility preservation	
				Distress screening	
Funding and economic implications	Reorganization of existing resources, charitable investment	No funding from federal government	Developed *within* 1 pediatric oncology unit and 1 adult oncology unit, as an *offshoot*	Not at present	Funded by combination of Federal Government funding (over 4 years), ongoing state government funding, and not-for-profit organizations (CanTeen, Redkite, etc.)
			Local charities support		
Facilitators of improvement	Policy, national funding, routine peer-on-peer service reviews	Progress Review Group 2006	Strong leadership	Canadian Partnership Against Cancer	Policy; cooperation of clinicians, government, consumers, and professional organizations across adult and pediatric. Structured age-appropriate documented psychosocial assessments and care plans
Inhibitors of improvement	Low engagement from adult services	Lack of federal funding	Lack of policy	Lack of investment from provincial jurisdictions	Financial barriers to fertility preservation and regulatory barriers to trial participation

criticalmass.org). Large-scale programs for provider education such as "Focus Under Forty" were developed by the American Society of Clinical Oncology (ASCO) [123]. The National Clinical Trials Network (NCTN) now has AYA committees in each of its pediatric and adult clinical trial groups [124, 125]. In addition, there has been a brisk increase in the number of AYA programs at pediatric and adult hospitals, both at academic and community cancer centers [124]. An increasing number of 501c3 nonprofit organizations have been created to serve AYA cancer patients, support professionals who serve this population, and foster the development of new AYA oncology programs [124].

US AYA programs may be based on either pediatric or adult cancer treatment facilities, and they may serve patients in both pediatric and adult oncology from their inception [126]. In a 2013 survey of 20 established AYA programs in the United States, 10 were based on pediatric cancer centers, 7 were based on adult centers, and 3 programs bridged between pediatric and adult programs. These programs have varying age limits. Ten programs serve the entire 15–39-year-old age spectrum, and five programs serve young adult patients aged 18–39 years. The remaining five programs focus on younger AYAs, with two programs serving an age range of 15–21 years of age and three programs serving 15–29-year-old patients [127].

The services offered by AYA oncology programs in the United States have followed similar themes, which can be summarized by the acronym FACES(S): Fertility preservation, Access to Clinical Trials, Expertise in AYA cancers, and Support Services as the basic elements of US AYA programs. An ideal additional program element, designated clinical **S**pace, constitutes an additional "S" at the end of the acronym but is currently only available at a few facilities.

Fertility preservation is a major priority for US AYA centers, since AYAs often have not yet completed childbearing at the time of their cancer diagnosis [128]. Sperm banking [128] and oocyte and embryo cryopreservation [129] are now standard of care, and in females gonadotropin-releasing hormone (GnRH) analogs are used increasingly in combination with other fertility preservation strategies [130]. Experimental protocols for ovarian and testicular tissue cryopreservation and in vitro maturation of gametes have become available at some centers [131].

Access to clinical trials is crucial for AYAs with cancer, since data suggest greater survival improvement for populations with higher clinical trial enrollment [132]. At present, AYAs are the age group least likely to enroll in clinical oncology research studies in the United States [133], and many clinical trials for cancers that affect AYAs exclude part or all of the AYA population [134]. AYA programs therefore encourage clinical trial participation and offer personalized assistance to help AYAs locate appropriate clinical trials. The presence of an AYA oncology program in a comprehensive cancer center has been shown to improve clinical trial enrollment for AYAs treated in the adult setting at that facility [135].

Expertise in cancers that affect AYAs is essential in order to optimize outcomes. US AYA programs promote systematic communication between pediatric and medical oncologists because the disease spectrum, even in younger AYAs, includes both pediatric and adult cancers [126]. To foster the development of healthcare professionals with expertise in AYA cancer, a few US AYA programs offer post-fellowship training programs in AYA oncology, as well as AYA-focused summer programs for medical students [136].

Since expertise in multiple allied health disciplines is required in the management of AYAs with cancer, US programs have developed coordinated multidisciplinary teams. A recent survey assessed the composition of these teams, which varies by center based on institutional differences and the local availability of AYA-focused subspecialists [126] (Fig. 20.2).

Provision of educational and psychosocial *support services* is a major focus of US AYA programs, with offerings such as AYA-specific patient education materials and videos, facilitated face-to-face and/or online peer support, as well as camps, retreats, and social activities to encourage peer-to-peer interaction [124, 126]. Figure 20.3 shows the spectrum of services provided, according to a 2013 survey of 20 US AYA programs [127].

AYA oncology has developed into a well-recognized discipline in the United States, and continuing rapid growth is anticipated. Brisk progress is occurring despite the fact that, in contrast to several other countries that offer AYA oncology services, the United States currently has no funding from the federal government to support the development of a national infrastructure for AYA oncology service delivery. The number of AYA programs is increasing rapidly, reaching an expanding number of patients in a larger variety of academic hospitals, community cancer centers, and hospital systems. The independent not-for-profit organization Change It Back now offers formal accreditation for qualifying AYA programs in the United States [137].

20.3.2 United Kingdom

Early Years In the United Kingdom, recognition that the needs of teenagers were poorly met by hospital services emerged in the late 1980s and bore fruit when the first inpatient hospital unit specifically for teenagers was opened in London in 1990, at the Middlesex Hospital, a large multispecialty hospital including services for both children and adults with cancer [138]. This was possible due to the fortunate cooperation of far-sighted clinicians and a small charity, the latter born out of the personal experience of its founders. Twenty-five years later, there is national provision of similar dedicated services embedded in commissioned specifications for cancer. This is coupled with a dedicated AYA research infrastructure and maturing networks for professionals working in the field.

National planning did not however drive initial developments. These focused on the establishment of "units" – inpatient facilities based on hospitals which already hosted cancer facilities for children and/or adults. Permissiveness was essential, usually driven by enthusiastic individual clinicians brokering arrangements between

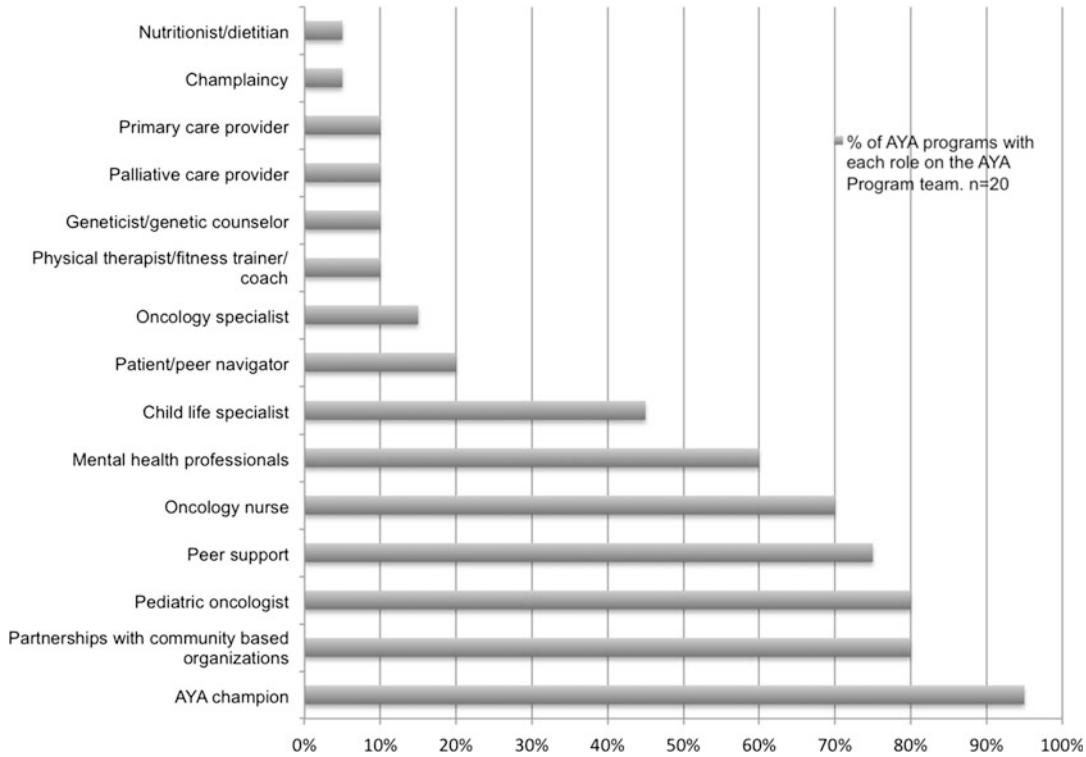

Fig. 20.2 AYA programs include a diverse team of professionals and paraprofessionals (Adapted from "Creating an adolescent and young adult cancer program: lessons learned from pediatric and adult oncology practice bases")

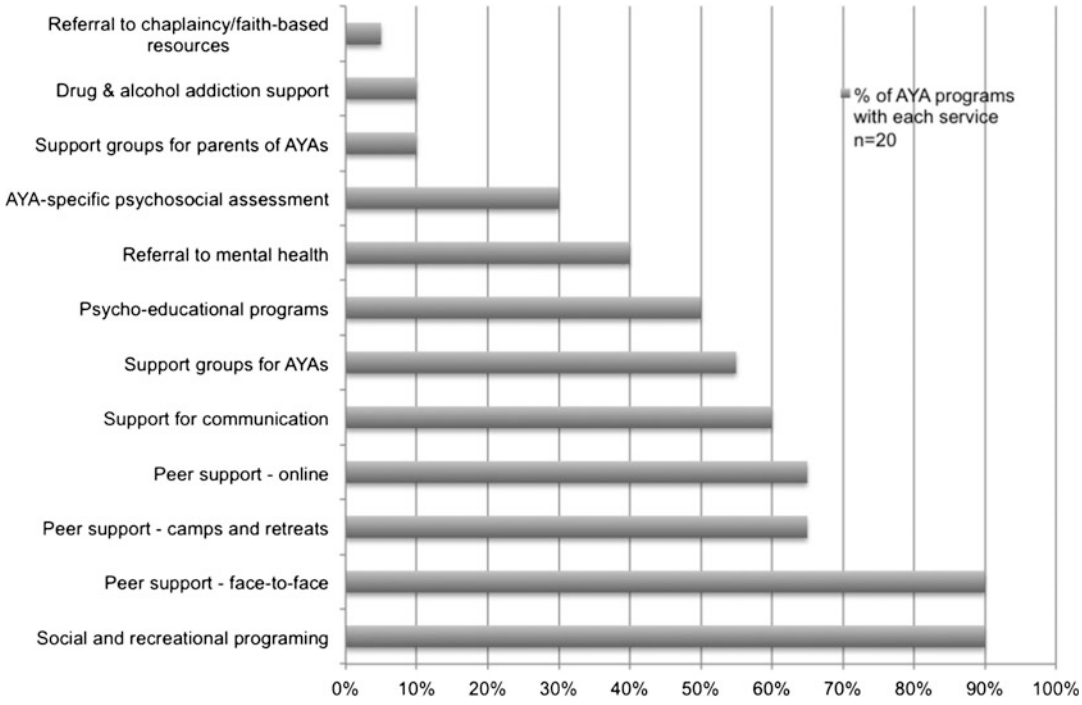

Fig. 20.3 AYA programs provide a variety of psychosocial service

the emerging national charity, Teenage Cancer Trust [139], and the hospital management of a potential National Health Service (NHS) Hospital Trust. Early units were characterized by being small, consisting of between four and ten beds with a staff- and parent-free recreation area. As well as providing a separate and unique environment, units were a focus for the members of various professional groups to develop team working with specific focus on the needs of young people. Although this multidisciplinary work was grounded in pediatric oncology, it flourished by recognizing the need to meet the quite different needs of an older population of patients.

The age range served by early units varied, largely depending on the type of host Trust and the key professional groups championing their foundation. For example, those set in children's hospitals served few patients over aged 18, while others, such as the original Middlesex Hospital unit, exercised considerable flexibility in early years, caring for patients between 13 and 25 years. With time, the age policies of units have hardened, taking account of national policies, increasingly restrictive safeguarding considerations but also retaining some local historical influence. Truly seamless inpatient units serving 15–24-year-olds, the age range for which commissioned NHS services must be provided, are some way from being universal.

In time, the number of units increased, and a narrative of the working of units emerged which started to define the characteristics of the needs of young people and of teams working to meet those needs. This was not research driven; indeed the value of the emerging UK model of specialist care is only being determined post hoc.

Professional Networks A network between clinical staff with interest in the field of care delivery for young people began soon after the opening of the first units in the early 1990s. This was not confined to those working in those units but included professionals working in other hospitals without dedicated facilities. This too was facilitated by the teenage Cancer Trust who supported the first national conference dedicated to teenage cancer in Leeds in 1994. A self-motivated federation of professionals also successfully campaigned for recognition of AYA in new national cancer

research structures. This cooperative approach was formalized in 2004 with the formation of a membership group, Teenagers and Young Adults with Cancer, a National Group for Professionals, known as TYAC (www.tyac.org.uk). This multidisciplinary group has subsequently engaged in training and education, good practice definition, policy, and advocacy work. However, one of its most notable achievements was to introduce a system of voluntary registration of AYA patients in treating centers to an extent mirroring the practice which had been initiated in the 1960s leading to a national children's cancer registry for patients aged up to 15 years old. This was conducted in partnership with a population-based cancer registry and was also designed to fill the gap arising from the historical practice of epidemiological reporting in quintiles of years and the limitations of disease classifications designed for either children's cancers or for those carcinomas principally affecting adults [140]. This allowed a national picture to build up about TYA care in particular in which centers they were being treated.

National Policy The National Institute of Health and Care Excellence (NICE) was set up in 1999, to reduce variation in the availability of elements of health and social care within the NHS. Its role included the production of a series of cancer service guidance documents to support implementation of national cancer plans. These "Improving Outcomes" documents each focused on a specific tumor type. These were designed to be taken into account in planning, commissioning, and delivering cancer services ultimately aimed to improve patient-centered outcomes. In August 2005, NICE published Improving Outcomes in Children and Young People with Cancer which provided a unique template for cancer services for AYA [141]. Among the many recommendations, the key ones described in detail a "multidisciplinary team" (MDT) that should be accessible to patients and additional recommendations mandated that teenagers under 19 should be treated in centers which had "age-appropriate facilities" and those aged 19–24 years should have "unhindered access" to such facilities. In practice this enshrined 14 "principal treatment centers" across England and Wales where MDTs delivered care in a young person-friendly environment.

Services for AYA in the United Kingdom continue to be based on the recommendations of the NICE guidance. In 2010, AYA services began to be subject to annual "peer review," a national program of independent service assessment against a series of standards or "measures" derived from the original Improving Outcomes guidance. In 2014, this was supplemented with a further document from NICE, a "Quality Standard," a list of seven statements which prioritize areas for service improvement. These include access to clinical trials, neuro-rehabilitation, and fertility advice [142].

Research In parallel with the developments in national policy for service improvement, greater coordination of research was supported by the establishment of the National Cancer Research Institute (NCRI) and its associated National Cancer Research Network (NCRN). Broadly tumor working groups were responsible for delivery of a portfolio of relevant clinical trials which were then supported by NCRN staff at a locoregional level. After successful lobbying, the NCRI established a crosscutting Teenage and Young Adult Clinical Studies Group, the primary remit of which remains to ensure that teenagers and young adults are considered for and have opportunities to enter disease-specific research protocols generated by other NCRI Clinical Studies Groups. In addition, the group was set up to develop research into the optimal provision of healthcare for AYA and in particular to provide the evidence base for current and future NICE Improving Outcomes Guidance for children and young people with cancer. Discussion took place about a specific population for which the group should be responsible, concluding: "No precise age boundaries are to be used. The lower end of the range is in the order of 16 depending on the nature of the study and the upper end is commonly placed in the mid-20s but may for some studies extend up to young adults of under 40 years of age."

One important study initiated by this group serves to illustrate the links between national policy, service improvement, and research. BRIGHTLIGHT is a nationally funded 5-year research program addressing the value of specialist care for young people through a multidimensional and mixed research method approach [[143]]. The outputs of this study are anticipated by NICE as it plans its cycle of reviewing guidance, looking to update the Improving Outcomes guidance described above as new evidence emerges from BRIGHTLIGHT in 2016–2017.

Progress and the Future Although there has been some disruption to strategic health policy developments in the United Kingdom as a consequence of increasing devolution of powers and responsibility to the four constituent nations, a large degree of convergence has been maintained with regard to AYA care, maintained by the strong interprofessional links and the supporting dedicated charities. There remain challenges to address particularly when young people find themselves straddling the interfaces of care, whether these be pediatric and adult or hospital and community. While the imposition of specific age boundaries has had a positive impact, for example, in facilitating the provision of dedicated AYA hospital care environments, the challenge from now is to ensure that such boundaries don't remain restrictive when addressing the unmet needs of young adults on the other side of the 24 years boundary.

20.3.3 Australia

The past decade has seen substantial progress in the care of 15- to 25-year-olds with cancer in Australia. There is now a network of five *Youth Cancer Services* located across the eight states and territories, each with a multidisciplinary team comprising medical, specialist nursing, psychology and/or social work, and other allied health staff. Most of these teams function across both the pediatric and adult sectors, as well as interacting with collaborating partner sites. Such a model promotes centralization of specialist care while still supporting equity of access for Australia's geographically dispersed population. In 2014, approximately 55 % of Australians aged 15 to 25 years with cancer were treated in conjunction with a Youth Cancer Service (YCS).

The development of the YCSs resulted from a coordinated national effort involving clinicians, the federal and state governments, consumers, and not-for-profit organizations, notably CanTeen, a consumer support organization for young people with cancer [144]. While the *ONTrac at Peter Mac Victorian Adolescent* and *Young Adult Cancer Service* at Peter MacCallum Cancer Centre had been championing AYA oncology for some time, significant momentum was gained in 2005 when an Australian government senate report recommended the establishment of specialized adolescent cancer care units [145]. The key next step was the development of the *National Service Delivery Framework for Adolescents and Young Adults with Cancer* by Cancer Australia and CanTeen together with expert clinicians and other stakeholders from around the country. This document detailed the essential features of a model which could be adapted consistently in each jurisdiction (summarized in Table 20.6) [146].

Table 20.6 Key features of the model proposed by the Australian National Service Delivery Framework for Adolescents and Young Adults with Cancer

1. Establishment of lead AYA cancer care sites across Australia, with a view to:
Developing a nationally mapped network to deliver high-quality cancer services for AYAs with robust links to local care
Improving collaboration between adult and pediatric services
Concentrating the treatment of rare cancers at lead sites
2. Access to support services and clinical trials
3. Comprehensive assessment at diagnosis
4. Coordinated care to empower AYA decision-making
Requires improved referral pathways
5. Expert multidisciplinary teams skilled in AYA cancer care
Requires integrated age-appropriate psychosocial support services as well as clinicians expert in the biomedical aspects and developmental needs of AYA with cancer

In 2007 the Australian Federal Government committed $15 million (AUS) to build a national network of YCSs, charging CanTeen with the responsibility of administering these funds to the state and territory-based jurisdictions. As well as facilitating the establishment of a nationally mapped network of lead sites, the funds were used to construct a small number of physical facilities, to develop a series of national guidelines in partnership with the Clinical Oncology Society of Australia [147, 148, 149], and to foster national capacity through professional educational meetings and an AYA oncology postgraduate diploma coordinated by the University of Melbourne.

Following these successes, in 2013 the Federal Government invested a further $18.2 million (AUS) over 4 years for CanTeen to continue to build the network of YCSs. One of the aims of this phase was to consolidate a nationally consistent model of care (Fig. 20.4). Rather than constructing stand-alone AYA cancer treatment centers (like the Teenage Cancer Trust units in the United Kingdom), the focus in Australia has been to develop multidisciplinary AYA cancer teams. These teams usually work together with conventional oncology and hematology services, adding value by their expertise in the medical and psychosocial aspects of AYA cancer and adolescent health. Each YCS has a *lead physician* whose role is to build networks with other cancer clinicians, promote the service, and provide AYA-specific medical expertise, a *service manager* with a strategic role and a focus on service development, and an AYA *cancer care coordinator* (with a nursing or social work background) to provide patient support and care navigation and to ensure that the patients' psychosocial needs are being addressed [150]. Most services also have other allied health

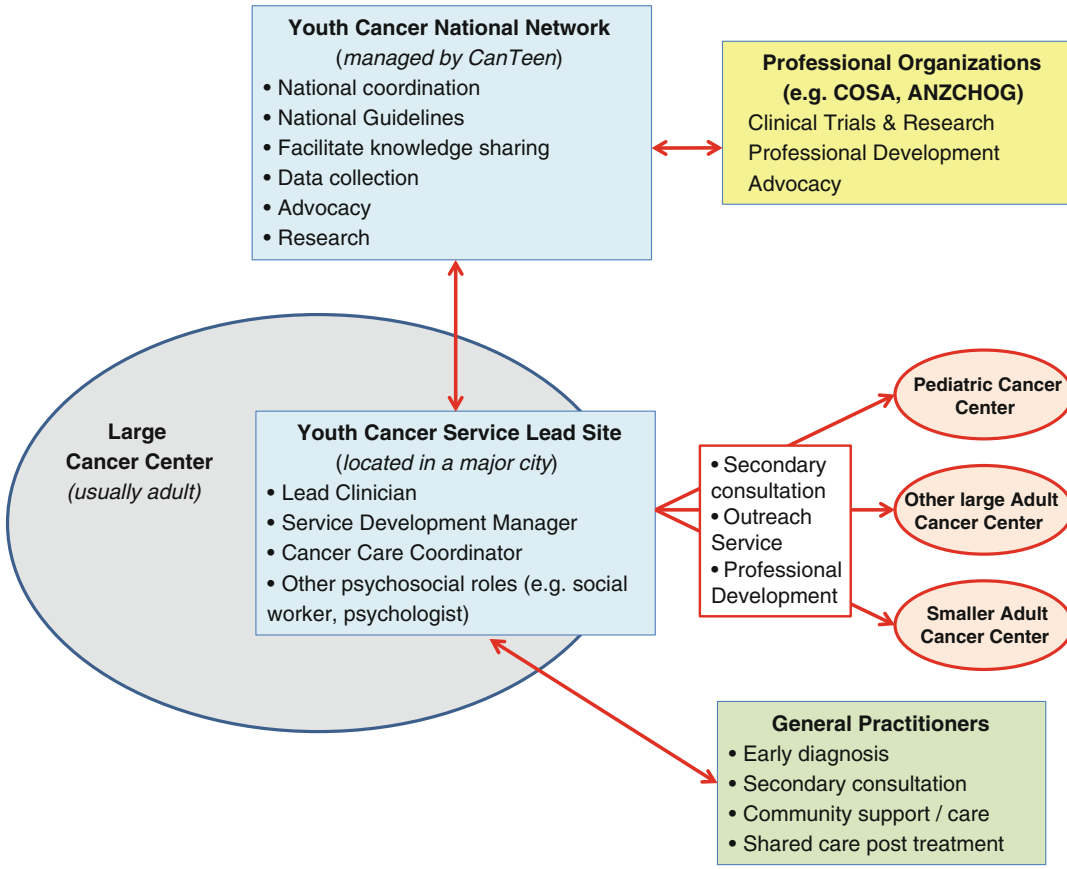

Fig. 20.4 Model of care utilized by Youth Cancer Services in Australia

staff as part of their team, including psychologists and social workers. In Australia, most states specify firm age limits to determine whether a patient is treated within a pediatric or adult hospital. As such, even though most of the Youth Cancer Services are located within a major adult hospital, most provide a comprehensive outreach service for teenagers who are treated in the pediatric sector. Most services also offer either an outreach service or secondary consultations to other adult cancer centers within their jurisdiction, and some services support the employment of a cancer care coordinator within these partner sites (e.g., the Northern Territory AYA cancer care coordinator is supported by the South Australian YCS). Consequently, young Australians should be able to access age-appropriate specialist cancer care irrespective of their treatment location. This is important given that Australian Institute of Health and Welfare data have indicated that young people with cancer from rural and remote locations experience inferior outcomes [151].

To ensure consistency of care among the YCSs, each site reports key performance indicators to the network, such as the proportion of patients receiving fertility preservation advice, being enrolled onto clinical trials, having a documented psychosocial assessment and care plan, and so forth. Most sites utilize routinely a formal AYA-specific psychosocial assessment tool and care plan, developed in Australia [152], to identify preemptively an individual's particular areas of need. Each YCS also provides professional development opportunities to clinicians working within their region, in order to enhance local awareness and skills. Biannual network-funded professional development days have also encouraged sharing of experience and collaboration between the states.

In addition, the YCS network has undertaken a number of national projects, including the development of a national dataset to measure the impact of YCSs and the establishment of a Research Advisory Committee to drive a national AYA research agenda and assist in directing funds to high-priority projects.

The impressive improvement in AYA cancer care across Australia over the last decade is attributable largely to the cooperation and consensus vision and approach shared among dedicated clinicians, CanTeen, state and federal governments, consumers, professional organizations (such as the Clinical Oncology Society of Australia and the Australian and New Zealand Children's Haematology and Oncology Group), and other not for profits. Clearly, the federal funds together with buy-in from some states have been major enablers, and CanTeen's management of the network has maintained momentum and promoted consistency and equity between the states. Central to this process has been the input of consumers, which has ensured the development of patient-centered models of care. Similarly, the highly coordinated approach that the network has taken to bringing together adult and pediatric oncologists, high-profile researchers, policy-makers from government health departments, and various advocacy groups has been critical to driving progress. Future challenges include sustainable funding, financial barriers to fertility preservation in some jurisdictions, and regulatory barriers to clinical trial participation.

20.3.4 Canada

Interest in AYA oncology in Canada accelerated substantially with the formation of a national task force in 2008 funded by the Canadian Partnership Against Cancer (CPAC) and supported by C17 (the consortium of all pediatric oncology centers in the country). CPAC is an "arms length" agency of the Federal Government charged with developing and overseeing a national strategy on cancer control. The task force, headquartered with a small secretariat at McMaster University in Hamilton, has established a series of working groups to address priorities in AYA oncology. These have evolved to address several topics (Table 20.7) since the task force was established with funding that continues from CPAC. Two international workshops have been held to date (2010 and 2012) with a third planned for February 2016. The proceedings of the first were published as a supplement to Cancer [153] and led to a series of recommen-

dations [154] akin to those developed by the Progress Review Group in the United States [155], formed in a collaboration between the National Cancer Institute and the Lance Armstrong Foundation/LIVESTRONG in 2005 and operating continuously since. The second workshop produced a Framework for Action [156], a plan to implement the recommendations developed previously. The third workshop has two goals: to establish a research agenda and to form an "alliance of stakeholders" modeled on Critical Mass in the United States [157].

Recognizing that the provision of healthcare in Canada is more a responsibility of the provinces and territories than of the federal government, the task force has helped to form 7 Regional Action Partnerships (RAPs) (Table 20.8). The RAPs are working with regional stakeholders, including provincial cancer agencies, to promote AYA oncology, with improvements in clinical care as a top priority (Table 20.9). The RAPs have identified several common themes, such as oncofertility, and are coordinated by the task force's secretariat. The national enterprise operates with three co-chairs and is supported by an international advisory group. Annual meetings of the task force are convened under the auspices of CPAC to which the task force has line accountability.

Critical to the success of the national initiative in AYA oncology in Canada has been the formation of collaborations and other initiatives to sustain and expand the development of this activity. These include:

Table 20.7 Working groups of the Canadian national task force

Survey of the delivery of active treatment and long-term follow-up in cancer centers
Systematic review of transitions in care
Plan for communication
Clinical trial accrual
Access to oncofertility services
Secondary prevention in AYA survivors
Developing a distress screening tool
Governance structure
Principles of active treatment and long-term follow-up
Components of supportive care

Table 20.8 Regional action partnerships in AYA oncology in Canada

British Columbia and Yukon
Alberta and North West Territories
Saskatchewan
Manitoba and Nunavut
Ontario
Quebec
Atlantic provinces – New Brunswick, Prince Edward Island, Nova Scotia, Newfoundland, and Labrador

Table 20.9 Clinical programs in AYA oncology in Canada

City	Site(s)	Features
Montreal	Jewish General Hospital and Royal Victoria Hospital	Wide age range (18–39)
		Multidisciplinary team
Toronto	Princess Margaret Cancer Centre and Hospital for Sick Children	Primary focus on sarcomas
Edmonton	Cross Cancer Institute and Stollery Children's Hospital	Primary focus on sarcomas
Vancouver	BC Children's Hospital, Vancouver General Hospital, and BC Cancer Agency	Consultative service provided to VGH and BC Cancer Agency from BCCH
Winnipeg	Cancer Care Manitoba	A provincial priority for development

- Postgraduate training. The Royal College of Physicians and Surgeons of Canada has approved a national program in AYA oncology as an Area of Focused Competence with related certification in the discipline.
- Improvement in access to oncofertility services. In cooperation with the Canadian Fertility and Andrology Society, Fertile Future, the oncofertility referral network, and other stakeholders, this goal is being pursued.
- Enhancing accrual to clinical trials. This objective is being addressed with support from the

National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). The NCIC-CTG is a partner in the Canadian Cancer Clinical Trials Network and in the National Clinical Trials Network (NCTN) in the United States. The NCTN has an AYA Working Group on which the NCIC-CTG is represented.

- Establishing national epidemiological data on AYA (15–29 years of age). The Canadian Cancer Society's special issue in 2009 [158] has achieved this target.

There is much that remains to be done. The challenges have been enunciated [159]. Issues relating to location of care [160], supportive care needs [161], transitions in care [162], and accessing oncofertility services [163, 164] have been described in detail and form part of the continuing agenda. Electronic communication has begun in the public domain with a website www.aya-cancercanada.ca and Twitter account @AYACancerAlly. Formation of an effective alliance is anticipated to provide further momentum in addressing AYA oncology in Canada.

20.3.5 Italy

Italy may be seen as a example of a relatively "young" country concerning the development of projects dedicated to AYAs with cancer. However, in recent years a growing awareness has emerged on the necessity of effective local programs and dedicated units [165, 166] but also forward-thinking national programs capable of bridging a gap in the quality of the care of patients in this age group.

The first national program arose in pediatric oncology. In 2010 the pediatric cooperative group Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) established a Committee on Adolescents with a view to assure adequate and equitable access to the best available care for Italian adolescents with cancer.

In the light of other research, a first plan of the AIEOP Committee was to investigate whether the limited access of adolescents to dedicated cancer centers and the underrepresentation in clinical trials already reported by other groups was confirmed in Italy. A comparison of the number of patients treated at AIEOP-affiliated pediatric oncology centers (over 22,000 cases, as recorded in their hospital-based registries in the 1989–2006 period) to the number of cases expected to occur in Italy judging from incidence rates (obtained from population-based cancer registries) showed an observed to expected (O/E) ratio of 0.77 for children (0–14 years old) and 0.10 for adolescents (15–19 years) [167]. A further study identified, as a possible reason for this discrepancy, the adoption of strict upper age limits for patient admission at pediatric cancer units: 46 % of Italian pediatric oncology centers used upper limits of 16, 15, or even 14 years of age (while 39 % had a rigid limit at 18 years) and reject patients over their upper age limit even if they suffer from tumors typical of children, such as rhabdomyosarcoma or acute lymphoblastic leukemia, for example [168]. These studies emphasized that the AIEOP network was far less effective in serving adolescents than children and prompted the committee to implement a strategy aiming mainly at (a) increasing access to AIEOP centers for adolescents (15–19-year-olds) and young adults (20–24-year-olds) when affected by pediatric-type tumors; (b) improving awareness (with a communication strategy at various levels, i.e., community, family physicians, oncologists, and institutions); and (c) improving cooperation with adult medical oncologists [169].

Meanwhile, the two AYA units developed in Italy improved their activity: (1) the Youth Area Project of the Centro di Riferimento Oncologico (CRO) in Aviano (www.areagiovanicro.it), a transdepartmental unit activated in 2007 within an adult medical oncology setting [170], and (2) the Youth Project of the pediatric oncology unit at the Istituto Nazionale Tumori in Milan (www.ilprogettogiovani.it) – this project was developed *within* the pediatric oncology unit, as an *offshoot* of the existing activities, without requiring major changes to the hospital's organization or new professional staff; it has the double aim to optimize clinical aspects (e.g., adolescents' inclusion in clinical trials, psychosocial support, fertility-preserving facilities) and also to develop a novel organizational and cultural approach to the chal-

lenges of treating these patients while paying attention to their quality of life, making time and space inside the hospital for them to be normal (Fig. 20.5) [171, 172].

In 2013, a more ambitious comprehensive national program was defined. The committee of pediatric oncologists was expanded, becoming a broad-based national task force dedicated to AYAs, forming strong links with adult cooperative groups and getting various stakeholders involved, including nurses, psychologists and social workers, advocacy organizations, cancer survivor associations, cancer agencies, and family physicians. In January 2014, the SIAMO project (Società Italiana Adolescenti con Malattie Oncoematologiche – Italian Society for Adolescents with Oncohematological Diseases) (www.progettosiamo.it) was started. Two main steps for the foundation of SIAMO was the formal partnerships with the federation of parents organizations (Federazione Italiana Associazioni Genitori Oncoematologia Pediatrica – FIAGOP) and the cooperation of the pediatric oncology group with the adult medical oncology societies (Associazione Italiana di Oncologia Medica (AIOM) and Società Italiana di Ematologia (SIE)) [173]. "SIAMO" in Italian means "we are," but it can be also "SI' AMO," which means "yes, I love." The SIAMO project is an ambitious new challenge, a sort of cultural movement as well as a platform of professional societies linked with the existing cooperative groups running clinical trials. SIAMO will serve as a logo in the media, attracting attention and improving public awareness but also as an official scheme that deserves the support of the national health services and governmental organizations. In fact, after only a few months of activity, SIAMO has achieved formal support from national

Fig. 20.5 Music was chosen as a means of communication with and for the adolescents taking part in the Youth Project organized at the Istituto Nazionale Tumori in Milan, Italy. With help from a famous Italian rock band (Elio e Le Storie Tese), young patients wrote a song called *Clouds of Oxygen*. The picture shows some of the patients posing for the photographer together with one of the musicians (photograph by Matteo Volta). The *Journal of Clinical Oncology* published the story of the song, with the words of the adolescents who explained the meaning of the lyrics. This publication is proof that the oncology community recognizes the importance of coping with the complex psychology of teenagers with cancer, providing dedicated projects and novel methods to communicate with their inner world

health services and governments, as well as a partnership with the big charity Fondazione Umberto Veronesi.

Among its several objectives, SIAMO aims to include the particular needs of adolescents in Italy's next National Oncology Plan, identifying the special criteria and facilities that centers (be they pediatric or adult units) need to treat adolescents with cancer, i.e., eliminating restrictive age cutoffs, giving adolescents access to clinical trials on different types of tumors, training multidisciplinary staff to cooperate actively with pediatric and adult oncologists, developing age-appropriate psychosocial support teams, and providing dedicated physical spaces, fertility preservation programs, and transition in care programs. The creation of a network of AYA dedicated centers is ongoing. Grants from the national health services as well as from charities will be provided to stimulate and support the development of new local projects. New projects dedicated to the involvement of general practitioners and to patient and public involvement are ongoing. A recent update of the evaluation of the access of 15–19-year-old patients to AIEOP centers has showed a significant increase from the 0.10 O/E ratio of the 1989–2006 period to 0.28 for the 2007–2012 period, as a result of the various initiatives launched recently.

20.3.6 A European Joint Project

Between 2011 and 2015, the European Network for Cancer in Children and Adolescents ("ENCCA"), a network of research institutes and clinical organizations in pediatric oncology (within the European Seventh Framework Programme for Research, FP7, Grant Agreement number 261474), has included a work package (number 17 of 18) dedicated entirely to AYAs. Entitled "Improving Outcomes for Teenagers and Young Adults with Cancer," this is completing six tasks (Fig. 20.6).

Although it will sunset in 2015, ENCCA will continue its work in AYA oncology with the creation of the European Network for Teenagers and Young Adults with Cancer (ENTYAC).

The development of TYA services and research has progressed at different rates and to different extents in different European Union (EU) nations. In addition to initiatives described already in United Kingdom and Italy, other dedicated projects have been launched in various EU countries.

In Germany the provision of TYA oncology has been characterized by distinct and separated infrastructures for pediatric and adult oncology and a usually quite strict age barrier of 18 years between them. However, a collaboration between adult and children's services to develop services and research dedicated to TYA has been activated recently (called AGYO). In France, the Institut National du Cancer (INCa) defines 11 French TYA centers with crosscutting clinical teams, disease-focused clinical trials open to TYA, and psychosocial programs. A national association – called Groupe Onco-hematologie Adolescents et Jeunes Adultes (Go-AJA) – has been funded, focusing on patients aged 15–25 and including patients and their representatives. In Spain, an Adolescents with Cancer Committee was founded by the Spanish Society of Pediatric Hemato-Oncology (SEHOP) in 2011, and more recently TYA oncologists, patients, and charities founded the charity AAA – "Spanish Association of Adolescents and Young Adult with Cancer" – to increase awareness. In the Netherlands, a national cooperative TYA project began in 2013, led by medical oncologists and nurses involving patients through a digital community and focused on late effects of treatment. In Denmark, building upon a nurse-initiated project since 2000, the Danish Cancer Society is considering a national initiative to establish TYA units with charitable funding. Elsewhere (e.g., Belgium, Bulgaria, Czech Republic, Eire, Greece, Hungary, Lithuania, Norway, Poland, Portugal, Rumania, Slovenia, Sweden), there is no coordinated national project but individual projects such as guideline development across Scandinavia, CanTeen in Ireland, an inventory of TYA needs within the Southern Swedish healthcare region, and a professional training scheme in the Czech Republic.

Many of these European national projects have joined ENTYAC [174, 175, 176–181]. ENTYAC

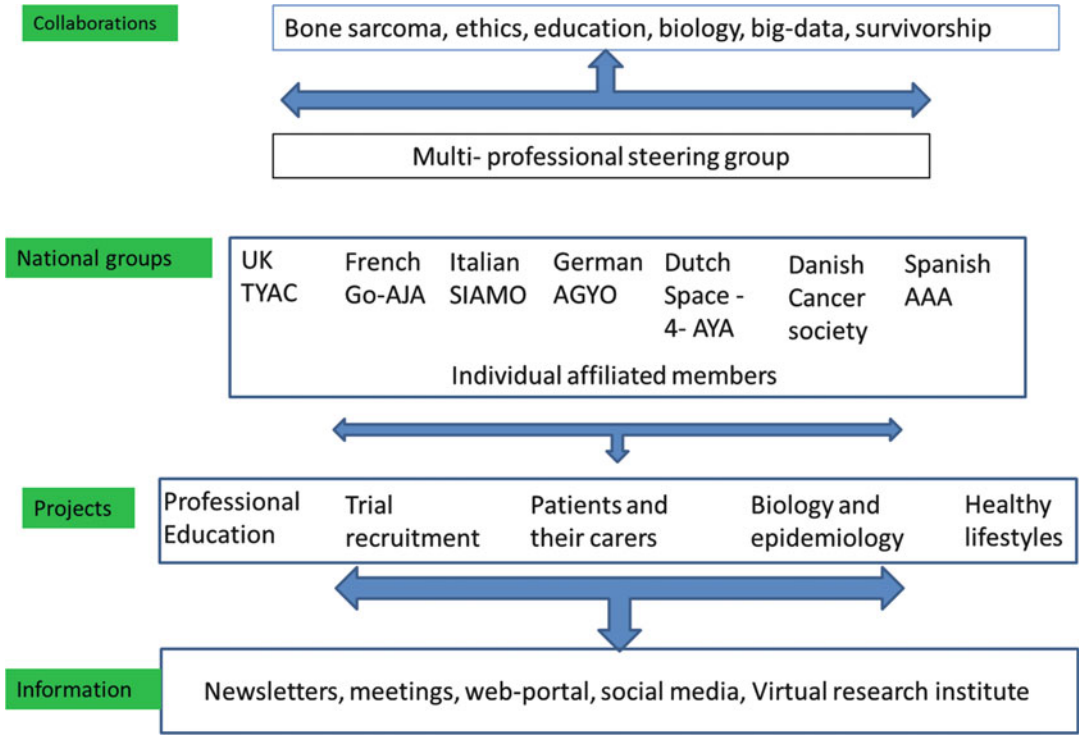

Fig. 20.6 The framework of the European Network for Teenagers and Young Adults with Cancer Legend: *ENTYAC* European Network for Teenagers and Young Adults with Cancer, *TYAC* Teenagers and Young Adults with Cancer, *Go-AJA* Groupe Onco-hematologie Adolescents et Jeunes Adultes, *SIAMO* Società Italiana Adolescenti con Malattie Onco-ematologiche, *AYA* adolescent/young adult, *AAA* Asociación Española de Adolescentes y Adultos Jóvenes con Cancer

leadership includes adult and pediatric oncologists increasingly delivering the major objective of developing synergistic working across fields. ENTYAC has also had the central involvement of patients, caregivers, and charities. They provide guidance about service improvements, suggest novel ideas, and advise on measureable standards of care and how to influence policy. Other larger professional organizations are also developing shared AYA initiatives, including the International Society of Pediatric Oncology (SIOP)-Europe and the European Society of Medical Oncology (ESMO). Several of these are linked through ENTYAC.

ENCCA has over 350 affiliated members [182] and has expanded from 3 to 18 involved EU nations. The project has surveyed service user and professional perceptions of service, education, and research priorities, including over 400 patients in 13 languages. It has led well-attended AYA-specific educational sessions at nine pan-European and global professional conferences and hosted two new European conferences specific to TYA cancer care. It has shared multiprofessional competencies internationally, is analyzing European trial design to assess the appropriateness of age-eligibility criteria, and contributed to enhanced contemporary EU-wide TYA incidence and outcome analyses. It is also running a prospective multicenter international pilot study of pathways to diagnosis and published reviews of best practice in survivorship.

While organization of specific TYA cancer care is developing in several European countries, there is a growing demand for further widening and strengthening. ENCCA-funded projects conclude in 2015, but ENTYAC will continue as a federation of national groups aiming to represent the European structure with regulatory authorities, providers, academics, cooperative groups, patients, and carer groups.

20.4 Appendix

Program/organization	Brief description	Website address
LIVESTRONG	LIVESTRONG Young Adult Alliance is the successor to the US Lance Armstrong Foundation. It coordinates the advocacy and support programs of approximately 150 organizations	www.livestrong.org
PRG – Progress Review Group	The Adolescent and Young Adult Oncology (AYAO) Progress Review Group (PRG) is a US public–private initiative established in 2005 by the National Cancer Institute (NCI), in collaboration with the Lance Armstrong Foundation and the LIVESTRONG Young Adult Alliance. It is composed of prominent members of the scientific, medical, and advocacy communities, and its purpose is to develop a national agenda for adolescent/young adult oncology	planning.cancer.gov/disease/AYAO_Report_2006_FINAL.pdf
HOPE – Health Outcomes and Patient Experience	The HOPE study is a joint undertaking of the US National Cancer Institute and the former Lance Armstrong Foundation. It is an observational cohort study based on a survey of population-based cancer registries on newly diagnosed AYA patients with cancer	outcomes.cancer.gov/surveys/aya/overview.html
Critical Mass	Formerly LIVESTRONG's Young Adult Alliance, it is the "Young Adult Cancer Alliance," an independent not-for-profit organization working to advance the AYA movement in the United States	www.criticalmass.org
Focus Under 40	A program of educational courses from the American Society of Clinical Oncology to increase awareness and enhance the understanding of care issues and challenges associated with this patient population	university.asco.org/focus-under-forty.html
Stupid Cancer	US nonprofit organization that addresses young adult cancer through advocacy, research, support, outreach, awareness, mobile health, and social media	http://stupidcancer.org/
Change It Back	US independent not-for-profit organization. It focuses on advocacy and education	http://hcri.org/programs/change-it-back
TCT – Teenage Cancer Trust	A UK charity advocating for young people and supporting development of dedicated care units in National Health Service hospitals	www.teenagecancertrust.org
BRIGHTLIGHT	A UK research program evaluating the value of specialist care for young people with cancer	www.brightlightstudy.com
Teenagers and Young Adults with Cancer TYAC	A UK multidisciplinary professional group undertaking networking, education, and policy work	www.tyac.org.uk
NICE – National Institute of Healthcare Policy and Excellence	Organization supporting provision of evidence-based healthcare in the UK National Health Service	www.nice.org.uk
Teenage and Young Adult Clinical Studies Group	Coordinates' national research portfolio in United Kingdom as part of National Cancer Research Institute	http://csg.ncri.org.uk/groups/clinical-studies-groups/
CPAC – Canadian Partnership Against Cancer, AYA Task Force	AYA Task Force of the CPAC, an independent organization funded by the federal government to accelerate action on cancer control for all Canadians	www.partnershipagainstcancer.ca
ONTrac	AYA program at the Peter MacCallum Cancer Centre in Melbourne, Australia	www1.petermac.org/ontrac
CanTeen	Australian national support organization for young people living with cancer, including patients, their siblings, young people with a parent with cancer, and those who have had a sibling or parent die of cancer	www.canteen.org.au

(continued)

Program/organization	Brief description	Website address
YCS – Youth Cancer Service	Australian hospital-based treatment and support services for 15–25-year-olds with cancer, funded by the Australian Government and administered by CanTeen. There are five lead services in Sydney, Adelaide, Brisbane, Melbourne, and Perth, and their work is complemented by national research, data, and professional development initiatives	www.youthcancer.com.au
SIAMO project – Società Italiana Adolescenti Malati Onco-ematologici	Italian Society for Adolescents with Oncohematological Diseases. Italian national program dedicated to adolescents with cancer, launched in 2014 by the cooperation of the pediatric oncology group with the adult medical oncology societies	www.progettosiamo.it
Go-AJA – Groupe Onco-hematologie	GO-AJA Groupe Onco-hematologie Adolescents et Jeunes Adultes (Groups of onco-hematology for adolescent and young adults)	www.goaja.fr
Adolescents et Jeunes Adultes	French national project dedicated to adolescents and young adults with cancer	
AAA – Asociación Española de Adolescentes y Adultos Jóvenes con Cáncer	Spanish Association of Adolescents and Young Adults with Cancer. Started in 2012 as a platform to connect patients, health professionals, charity foundations, and other associations, to improve the care of adolescents and young adults with cancer in Spain	www.aaacancer.org
ENTYAC – European Network for Teenagers and Young Adults with Cancer	Pan-European multilevel network of professionals, patients, and caregivers, established as a result of the European Network for Cancer in Children and Adolescents (ENCCA) WP17 project, with the goal of promoting and coordinating international research in this field	

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Clinical Trials

21

Annette E. Hay, Lorna Fern, Ralph M. Meyer, Nita Seibel, and Ronald Barr

Abstract

The concept of the 'adolescent and young adult (AYA) gap' in relation to recruitment to cancer clinical trials was first described in 1997. The 'AYA gap' refers to the association between lesser survival gains and poorer recruitment to cancer clinical trials for this group. Since then, many countries have reported lesser involvement of AYAs in cancer trials compared to children and older adults. Lately a number of initiatives have served to improve recruitment for AYAs with cancer, and barriers and facilitators to recruitment have been identified. This chapter summarises the concept of clinical trials and some of the challenges faced by AYAs with cancer and the healthcare teams caring for them.

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21.1 Introduction to Research and Clinical Trials

This chapter will emphasise the importance of promoting research for young people with cancer. Without research there will no further improvements in survival, quality of life and long-term effects for this group. What is research?

> To advance scientific knowledge directly or indirectly, leading to improvement in the prevention and treatment of disease. [1]

The chapter will focus on recruitment to clinical trials, but the principles of promoting recruitment of AYAs to studies apply to all types of research including prevention, epidemiology, basic laboratory investigations, applied health services research and end of life care.

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21.1.1 What Is a Clinical Trial?

Clinical trials are critical to evaluate scientific advances, generating evidence to inform optimal care of patients, and the development of health policies. A clinical trial is a study that attempts to answer a medical question, most often about the effect of a therapeutic intervention on the outcome of a disease. The study is carried out under conditions determined in advance by the investigator, with the trial's methodology aligned according to the hypothesis being tested [2]. Traditionally, clinical trials have been categorised into four types that are referred to as phase 1–4 trials; each trial type has a distinct purpose and contributes to the developmental pathway of a new intervention, as follows:

- The purpose of a phase 1 trial is to determine the safe dose and schedule of a new therapeutic intervention. The primary end point of these trials is toxicity, which is used to define the maximum tolerated dose (MTD) for a given schedule and route of administration [3]. It is common to perform pharmacokinetic studies as part of phase 1 trials.
- The purpose of a phase 2 trial is to estimate the efficacy of the agent against individual tumour types and to determine if the new agent is sufficiently promising to warrant further study [4]. The most common phase 2 end point is objective response which is assessed usually by the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [5]. More recently, phase 2 studies have included evaluation of an intervention's efficacy according to tumour or host-specific bio-specimen correlates referred to as biomarkers.
- The purpose of a phase 3 trial, also referred to as a randomised controlled trial (RCT), is to compare the efficacy or effectiveness of an experimental therapy with an existing standard of care; phase 3 trials may be conducted also to resolve uncertainty about best management when multiple standards of care exist [6]. The technique of randomisation is used to determine therapy so that bias in comparing treatments can be minimised. The ideal disease control end point for evaluation in an RCT is overall survival, but this may not be practical if deaths occur long after the treatment; in this case, end points such as 'event-free survival' or 'failure-free survival' are particularly common in childhood cancer trials [7]. Phase 3 trials may be used also to evaluate other trial domains, such as quality of life and economic analyses.
- The purpose of a phase 4 trial is to evaluate a new drug and consider the agent's long-term safety and effectiveness. Phase 4 trials are conducted typically after a new treatment has been approved and is on the market.

21.1.2 Why Do We Need Clinical Trials?

Clinical trials enable systematic evaluation of novel therapeutics or other interventions in a scientifically rigorous manner, providing reliable information on benefit and adverse effects. Close ethical and regulatory oversight ensures that patient safety is prioritised over the course of the study. Requirements to maintain a public record of active trials, such as that listed on clinicaltrials.gov, and expectation that results will be published in a peer-reviewed journal, facilitate global dissemination of findings. No other mechanism exists to provide such a comprehensive analysis accessible to policy makers, physicians and patients.

Advances in cancer care over the past 60 years have been realised through clinical trials, as exemplified by the dramatic improvement in survival in many different cancer types [8–13]. Beyond survival, clinical trials also evaluate interventions to improve the quality of life for individuals living with cancer [14, 15]. Such gains are of clear benefit to society and future generations.

Clinical trials offer earlier access to promising agents, prior to their approval by regulatory authorities and funding bodies. Expectation of individual patient benefit differs according to the phase of trial. Phase 3 trials in many disease types are associated with curative potential. Phase 1 trials are not, but yet may hold some benefit for the patient.

21.1.3 Are There Disadvantages of Clinical Trials?

For an individual with cancer contemplating enrolling in a clinical trial, there are many factors to consider: uncertainty regarding the efficacy of an intervention, risk of side effects, potential for more investigations than would be standard and, in the case of a randomised trial, loss of control of treatment assignment. This experience is shared by family members, particularly in the case of teenagers and young adults. Processing such information, especially in the setting of a recent serious diagnosis, can be overwhelming.

While clinical trials facilitate advances and improve outcomes for future patients, direct benefit to an individual participant cannot be guaranteed. Particularly in early-phase clinical trials, the majority of agents tested have not been proven to be useful and may not be efficacious.

From an operational perspective, major infrastructure is required to support traditional clinical trials which are regulated closely to ensure that the rights and safety of patients are upheld. Consequently, they demand large financial resources; securing research funding to support these endeavours is challenging.

21.1.4 Informed Consent

Ethical principles for medical research involving human subjects are laid out in the World Medical Association Declaration of Helsinki [16].

- While medical progress is based on research which must rest on experimentation involving human subjects, consideration related to the well-being of the human subject should take precedence over the interests of science and society.
- Each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential risks of the study. The subject must be informed of the right to abstain or withdraw consent without reprisal. After ensuring that the information has been understood, the subject's freely informed consent should be obtained and documented.

In keeping with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice [17], clear explanations of potential risks and benefits are mandatory, to ensure that patients are able to make an informed decision to participate or not. Competent individuals over a predetermined age sign their own consent. In the case of a child, willing cooperation or assent is sought alongside parental consent [18]. The age at which a child becomes legally competent to give their own consent varies across jurisdictions.

21.1.5 Clinical Trials, Adolescents and Young Adults

Thus far we have presented the basic concepts relating to clinical trials, their purpose and design as well as the advantages and disadvantages associated with running and recruiting to clinical trials. Taking into consideration some of these factors, it is not surprising that recruitment of AYAs to studies is challenging. Raising discussions around clinical trial participation and ensuring that young people know what they are consenting to can be difficult, given the impact of a recent (and often unexpected) cancer diagnosis. Communicating complex trial designs to patients of any age is a skilful and often time-consuming process. Consequently, under-representation of young people in trials is an international phenomenon. The remainder of this chapter is dedicated to exploring these issues.

21.2 Deficits in Accrual of Adolescents and Young Adults to Cancer Clinical Trials: An International Phenomenon

21.2.1 Background

The reasons behind lesser improvements in cancer survival amongst AYAs, compared to children and older adults, are likely to be complex and multifactorial. Unique cancer and host biology, prolonged

complicated journeys to cancer diagnosis, influences of place of care, inappropriate treatment protocols and lesser involvement in cancer clinical trials are all implicated [19–23]. The extent to which these factors contribute individually to the 'AYA survival gap' is not yet known. However, it is known that despite variations in healthcare provision, reports of inequalities in access to cancer care and research for AYAs appear to be universal, in the developed world at least [24–30]. It is likely that these inequalities exist and are indeed more pronounced in low- and middle-income countries that lack sophisticated healthcare infrastructure and the resources to investigate and report the problem.

As discussed previously in this chapter (Sect. 21.1.2), cancer clinical trials are necessary to test new treatments in a bid to improve survival and quality of life and to provide new information about the genetic and molecular drivers of malignancy in AYAs. Despite agreement amongst healthcare professionals about the importance of cancer clinical trials for all patients, under-represented patient groups, including ethnic minority populations, those of low socioeconomic status, elderly patients and AYAs [31], are well described. Poorer accrual of AYAs compared to children and older adults has been reported from the United States, Australia, Italy, Canada and the United Kingdom [25, 28, 32, 33].

21.2.2 Evidence to Support Under-representation in Cancer Clinical Trials for AYAs

In comparison to their younger and to a lesser extent older counterparts, AYAs with cancer are less likely to enrol on a clinical trial [21, 22, 34, 35]. The first report of under-representation of AYAs in cancer trials [36] demonstrated that recruitment of patients older than 15 years was less compared with children, regardless of the tumour type, and highlighted limited trial availability as a contributing factor [36]. Bleyer and colleagues hypothesised that lesser AYA involvement in trials was associated with relative deficits in mortality improvements compared with other age groups [22, 35, 37]. In the United States between 1989 and 1991, enrolment rates to Children's Cancer Group and Pediatric Oncology Group trials were in the region of 94 % for children compared to 21 % for those aged 15–19 years; the latter experienced lesser reduction in mortality rates over the same time period [37]. Analysis of accrual by region showed that the pattern of lesser accrual was universal and not related to race or ethnicity [37]. Deficits in recruitment to National Cancer Institute-sponsored bone and soft tissue sarcoma studies were linked with average improvements in 5-year survival by age [37]. Lesser improvements in survival for AYAs are likely part of a larger picture of complex interlinked factors.

Further to these initial reports from the United States, data then emerged from the United Kingdom, Italy and Australia, all reporting the same deficits in recruitment rates for AYAs aged generally beyond 15 years [28, 32, 38]. Despite over 20 years elapsing from the early reporting of under-representation of AYAs in trials, recruitment deficits persist. However, our understanding of the reasons has increased somewhat with a number of groups reporting a consequent increase in AYA accrual [39]. The most recent data from the United States and the United Kingdom are shown in Figs. 21.1 and 21.2, respectively. The former shows the recruitment of US cancer patients entered onto National Treatment Trials by 5-year age intervals and the typical nadir in recruitment to studies across the 15–29 years age group that has now been reported from many countries. Figure 21.2 illustrates the proportion of newly diagnosed patients recruited by age to 'selected trials' (those in commonly occurring cancers in 0–24-year-olds) across the United Kingdom. Although different in methodology, both figures show the same trend and, importantly, illustrate improvements in recruitment for the most recent reporting period. In the United States, improvements have been observed for patients aged 5–29 years, with the greatest increase in accrual being for patients aged 15–19 years. Similarly, in the United Kingdom, improvements have been observed up to age 29 years (for the cancer types studied), and again

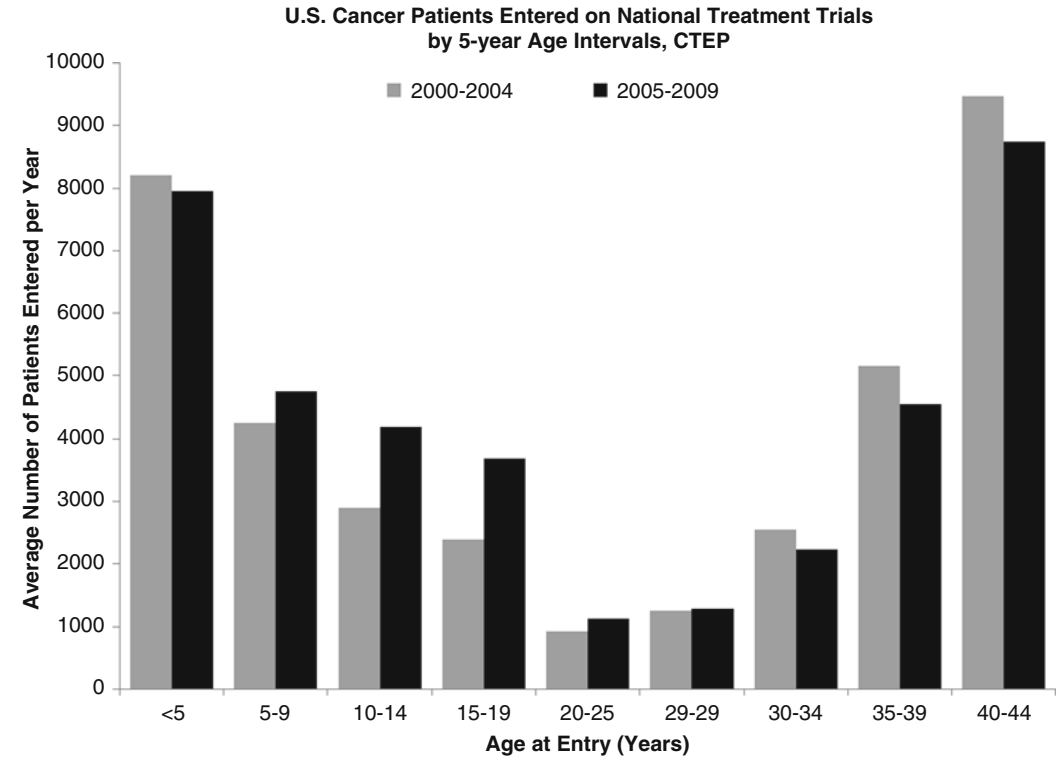

Fig. 21.1 Numbers of patients recruited to US cancer trials by 5-year intervals (Personal communication with author)

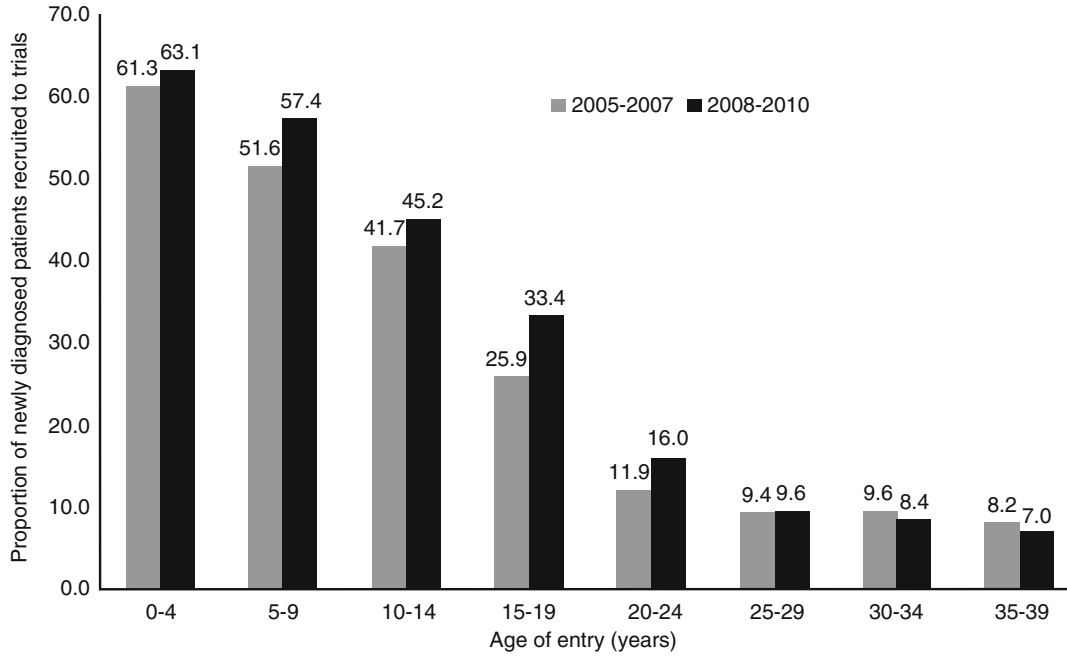

Fig. 21.2 Number of children, teenagers and young adults with newly diagnosed cancer entered onto selected clinical trials, 2005–2007 and 2008–2010, the United Kingdom

the greatest improvements were for those aged 15–19 years. Possible reasons for this will be explored later in this chapter.

Access to early-phase trials or new agents can be an issue also for AYAs. Although this is described less fully, it is recognised generally that age is a barrier to accessing early-phase studies, particularly for adolescents [40]. Currently, in North America, the adolescent patient's only access to new agents is through a paediatric phase 1 study. Since these studies are not initiated until the phase 2 dose for adults has been identified, there is a delay until the study is started, and then only a limited number of openings are available. Comparison of pharmacokinetic data between adults and adolescents suggests that there may be little difference between these groups, although these data should be evaluated on a case-by-case basis. In some cases, adolescent doses may be derived from the adult data and without the need for a dedicated pharmacokinetic study [41]. The current Children's Oncology Group study AOST 1322 (Phase II Study of Eribulin in Recurrent or Refractory Osteosarcoma) is an example of this, since patients 12 years of age and older are eligible despite the fact that the paediatric phase I study of eribulin was initiated later.

The design of clinical trials continues to evolve to accommodate new forms of hypotheses and novel additions to the therapeutic armamentarium. There are particular challenges in accruing AYAs to cancer clinical trials, not the least of which is the paucity of high-quality data on the relevant issues.

21.2.3 Limitations to International Comparisons of AYA Accrual

It is recognised that recruitment of AYA to cancer clinical trials is an international problem in developed countries, as detailed in Sect. 21.2. However, the reporting of recruitment to these trials is in itself problematic, and therefore a comparison between countries is difficult. To date, no country has developed a comprehensive national reporting system for AYA accrual in terms of complete geographical coverage, all available studies (including industry studies) and a denominator that defines the number of eligible incident cases (the number of patients with a disease profile suitable for the available studies). Further, information on recruitment to earlier phase studies for relapsed/recurrent disease is largely unknown. While the methodology of data reporting varies between countries, the common trend of lesser involvement of AYAs compared to children and some older adults is consistent. This calls for a uniform mechanism to be identified to allow direct comparisons to be made, not only to make fair comparisons but to allow for evaluation of initiatives put in place to improve accrual.

21.2.4 The Case to Improve Accrual

Despite limitations of existing accrual data and a lack of empirical evidence of absolute gains to individual patients participating in clinical trials, improving AYA recruitment to cancer clinical trials seems a worthwhile pursuit. Given the evidence of improvements in survival for children with cancer, there is no doubt that there is much to be gained by incremental survival improvements observed over time related to trial activity [42]. In addition, collection of biological tissue along with outcome and toxicity data will serve to further our currently limited understanding of the molecular basis of cancers in AYAs [18].

In the healthcare systems of high-income countries, the inclusion of patients of all ages in well-designed phase 3 trials is considered the gold standard of care. Consequently, as AYA cancer care emerges as a distinct speciality, many of the initiatives that are being implemented have a focus on healthcare policy directives to increase participation of young people in cancer clinical trials. Countries such as the United Kingdom, the United States and Italy are now reporting improvements in recruitment of AYAs to cancer clinical trials [39, 43]. Despite these improvements, recruitment of children to such trials remains superior to that of AYAs and efforts to improve recruitment of AYAs are ongoing.

The generalisability of the benefits of new drugs or interventions is limited if not tested in

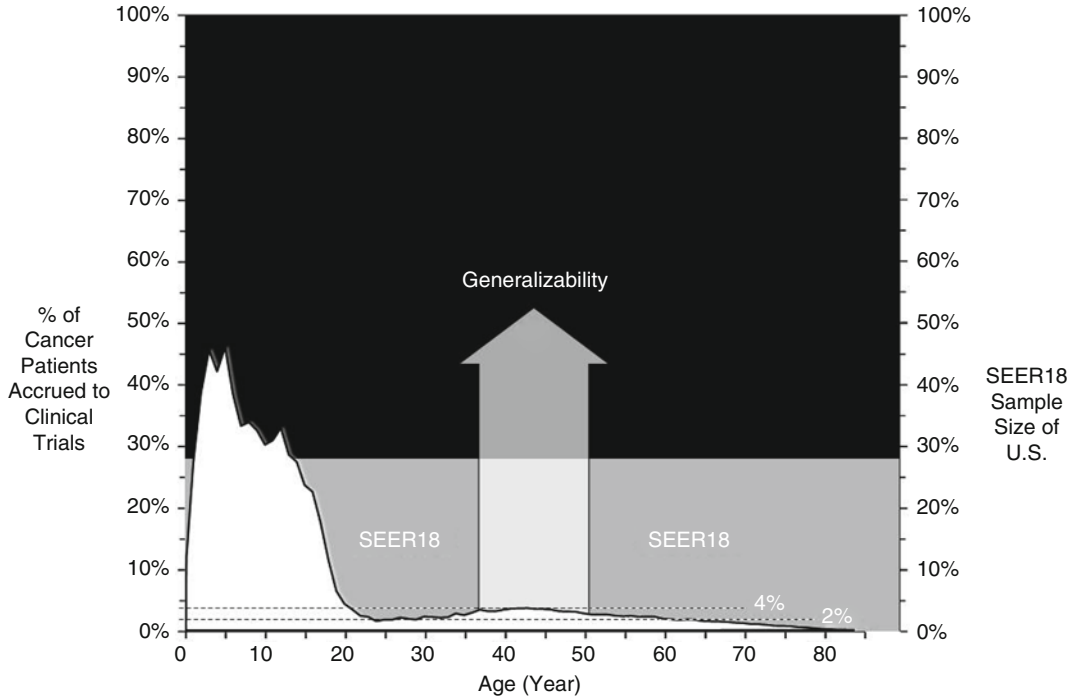

Fig. 21.3 Comparison of clinical trial accrual, registry data and the population for whom results are extrapolated. Estimated accrual to US National Cooperative Group clinical trials 2008–2010. SEER Surveillance, Epidemiology and End Results (Modified from JNCI 2015 courtesy of Archie Bleyer)

the patient age range in which a disease is most likely to occur. As demonstrated in Fig. 21.3, less than 4% of young adults with cancer in the United States were enrolled on national cooperative group trials between 2008 and 2010. Improving accrual would increase the generalisability of results, both in the AYA and older adult population. This phenomenon is well described for elderly patients, for trial participants tend to be younger than the mean age of patients with the disease and also free from co-morbidities common in the elderly population [44, 45]. In AYAs, the issues of co-morbidities are less; however, long-term toxic or late effects may not manifest in the remaining lifetime of an older population compared to young people who may survive for many decades beyond their treatment. In addition, the biology of disease in AYAs can be different from that in older adults and children [19], and therefore clinical response, particularly for new targeted therapies, may be altered or unpredictable. Issues related to fertility are also unlikely to be explored if the new agents are tested on a largely elderly population.

21.2.5 Challenges and Barriers to Accrual

There is no single reason for lesser involvement of AYAs in cancer clinical trials. The problem is multifaceted, and in an attempt to understand deficits in recruitment, researchers have turned historically to structural and organisational barriers for examination, for example, trial availability in centres where young people are treated and boundaries between paediatric and adult cancer care. More recently, the voice of the young person is being heard increasingly, and it is apparent that the reasons for lesser involvement of young people in cancer clinical trials may be more complicated than anticipated due to their unique psychosocial needs. The remainder of this section discusses some of the challenges and barriers to recruitment identified to date.

21.2.5.1 Appropriate Age Eligibility Criteria

Inclusion and exclusion criteria in clinical trials are important in defining a homogenous trial population. Medically and scientifically relevant parameters, such as disease and health status, restrict the study to those most likely to benefit safely from the intervention. However, the criteria that define the age of patients eligible for studies often have no medical or scientific rationale. Most commonly, age eligibility criteria reflect the source of the study, whether designed by paediatric or adult investigators, with adult studies typically having a lower age eligibility criterion of 18 years and paediatric studies having an upper age eligibility criterion ranging from 16 to 22 years. It is often these age eligibility criteria that deny young people access to research. Age eligibility criteria are applied to most studies despite statements in international healthcare documents that they should be avoided; see Box 21.1.

Box 21.1: International Statements Citing that Age Should Not Be Used as an Inclusion or Exclusion Criterion for Studies

- UK Cancer Reform Strategy: 'the use of age as an exclusion criterion in cancer clinical trials is avoided wherever possible' [50].
- Japanese Health Policy Bureau: 'it is inappropriate to establish an arbitrary age limitation in clinical trial protocols' [51].
- Guidance for industry E11 clinical investigation of medicinal products in the pediatric population.
- "The identification of which ages to study should be medicinal product – specific and justified" [52].
- The Lancet Oncology: 'especially problematic is the use of age as an exclusion criterion…widening patient eligibility criteria could lead to improved patient accrual, higher completion rates, and greater treatment equity' [53].

In the United Kingdom, monitoring of studies following amendment of age eligibility criteria has shown that this influences accrual of AYAs positively, with increased numbers of AYAs enrolling onto trials following age eligibility amendment. Consequently, all new investigators submitting proposals to the major funder of research are being asked to provide scientific justification for their use of age eligibility, and if a lower limit must exist, it should be set at 16 years rather than 18 years. This serves two purposes, namely, that new studies in the United Kingdom will have lower age eligibility and also that investigators will begin to think more carefully about the use and relevance of any age-related restrictions for trial entry. A model of text that could be applied to other international funders of research, to allow greater access for AYAs, is shown in Box 21.2. The impact of restrictive age eligibility criteria on patients is clear in the case study of Chloe Drury in Box 21.3.

21.2.5.2 Availability and Access

Whether a trial is available is a key determinant of recruitment. Cancers that effect young people are often rare and low in incidence compared to the more common types such as carcinomas of the breast, colon, lung and prostate. This can affect the availability of trials for young people at two levels. Low incident numbers, and therefore limited returns on investment, make trials of drugs for rarer cancers, such as those which occur

Box 21.2: Is Age to Be Included as an Inclusion/Exclusion Criterion?

If yes, please provide specific justification for both upper and lower age limits. Please note that if a lower age limit for studies involving adults is deemed essential, it should normally be set at 16 rather than 18 years. Low incidence of patients aged 16 and 17 is not sufficient reason for selecting a lower age criterion of 18 years.

Box 21.3: Case Study (Chloe)

The origins of age eligibility criteria are unclear, although the protection of paediatric patients is paramount and an obvious starting point. In the United Kingdom, the case of Chloe Drury, a 17-year-old patient unable to enter a new agent study until she was 18 and who later died from her disease, highlights the impact of exclusion by age for young people. Chloe was diagnosed with Ewing sarcoma in February 2010 aged 15 years, a true adolescent cancer with little improvement in outcomes over the past two decades. Three years later, having failed therapy, she was then denied access to a new agent being trialled at her local hospital. The study was open to patients aged 18 and over, typical for adult studies. Chloe was just short of her 18th birthday. Despite relentless campaigning by her mother, charitable bodies and healthcare professionals, Chloe had to wait until she turned 18 to enter the study. She died shortly afterwards.

> That drug offered us a last tiny bit of hope. I remain incredulous that we were blocked from accessing that drug because Chloe was considered "too young". She was 17 and nine months old. The lower age limit was 18. My daughter was denied a final shot at life because of a bureaucratic impediment. It is crazy and unbelievably cruel. We must do everything possible to stop this happening to another family. Please ask yourself what would you do if this was your child? Debbie Binner (Chloe's mum)

The impact of restrictive age eligibility criteria is clear in Chloe's case. Whether early access to the new agent would have prolonged Chloe's life is unknown; however, her family is left with a sense of frustration and injustice that the new agent was withheld based solely on age rather than clinical risk or exhaustion of alternatives. It is difficult to explain particularly to grieving parents, why, in this era of personalised medicine and in a country that boasts the highest rate of clinical trial participation in the world, young people are being denied access to new agents simply because they are not old enough. Further, there is a fundamental lack of knowledge of the host and cancer biology in young people upon which we can base targeted drug development reliably; excluding young people from studies of new agents augments this problem further.

In the United Kingdom, the major funder of cancer research is now asking investigators to justify the use of age eligibility criteria on new funding applications, and if a lower age eligibility is needed, it should be set at 16 years rather than 18 years. A great step forwards…*until the next Chloe is* 6 weeks *short of her 16th birthday*. Access to studies should be based on disease and physiological status rather than age. However, there is no 'quick win' solution. Change will require new ways of thinking to ensure that basic scientists, clinical triallists, governments and regulatory and research agencies achieve greater equality in access to studies that in turn will offer more generalisable results.

in AYAs, relatively unattractive to the pharmaceutical industry, and trials are often not available for the most common cancer types occurring in young people.

The availability of trials in treatment centres is also a barrier to recruitment. In most countries, young people will be referred generally to an adult or paediatric institution, depending on their referring physician. Even in countries with well-established AYA care programmes, not all young people reach specialised AYA care; in the United Kingdom, this is approximately half of all young people. Treatment within a paediatric setting tends to result in higher rates of accrual of AYAs to trials compared to treatment in an adult setting. For example, a US study examining trial accrual of AYAs in affiliated paediatric and adult cancer centres found around a quarter (26%) of all AYAs

treated in the paediatric setting were enrolled onto trials compared to just 4% of AYA, treated at adult centres [46]. This is related most likely to a greater availability of relevant trials and also to the ethos of recruitment to studies as the gold standard of care within paediatric oncology. Despite higher recruitment of AYAs to clinical trials in the paediatric setting, recruitment remains less than in children; a single-centre study, also in the United States, demonstrated that recruitment of patients less than 15 years of age was 38% of all new patients compared to 27% of new patients aged 15–22 years [30]. It is likely that lack of available trials is a contributing factor, as the spectrum of malignant disease changes with advancing age and trials available in children's centres will reflect common children's cancers that are different from those observed in adolescents and in particular young adults in whom carcinomas become more common [47]. In the aforementioned study, lack of trial availability was cited as a reason for non-recruitment in 41% of paediatric cases, 57% of those in the older age group [30]. For young adults with early-onset carcinomas, such as those of the breast or colon, the biology of their disease [19] may not be aligned with the availability of trials in adult centres where the majority of patients are older.

Access to available studies may be increased by appropriate referral to a treatment centre with available studies relevant to young people. When this is not possible, improved collaboration and crosstalk between adult and paediatric settings may facilitate access to studies. A causal relationship between the proportions of young people accessing specialist care and similar patterns of accrual has been cited in the United Kingdom [39], and further evidence of the impact of the formation of specialist AYA oncology programmes on recruitment was reported recently by Shaw and colleagues in the United States, including an increase in accrual rates of AYAs [43] from 4% to 33% in the adult centre, while recruitment in the paediatric centre remained consistently high.

21.2.5.3 Awareness

Awareness of several audiences on the necessity and gain of enrolling AYAs on cancer clinical trials will clearly influence accrual. At the outset of preclinical drug research and development, an awareness of the need to develop new agents for cancers that appear in young people has to be apparent to facilitate drug development and the availability of studies. As mentioned previously, low incidence numbers can make this unattractive to commercial companies. Within the clinical setting, the awareness of healthcare professionals of studies available within their institution, and of the importance of offering trial entry, influences accrual positively. An adult physician treating an AYA with a 'paediatric'-type cancer is unlikely to be aware of local paediatric studies available, further highlighting the need for crosstalk between adult and paediatric communities.

Amongst AYAs, lack of awareness of the importance of research may be a limitation of recruitment to studies. It is unlikely that shortly after diagnosis, given the complexity of conversations around treatment options, fertility preservation and the impact of cancer on life goals, young people would consider asking about available research studies, if indeed they are aware of clinical trials and their purpose. Further work is required to empower young people to ask about available research within their treatment centres, shifting the onus from a healthcare professional-orientated conversation to joint decision-making, thus further empowering young people in their cancer trajectory.

21.2.5.4 Acceptability

The acceptability of trials to both patients and healthcare professionals is a critical component of recruitment to cancer clinical trials for AYA. If the trial design or the trial question is not viewed as important or well addressed by healthcare professionals, they will be unlikely to recruit to the study. For AYAs who fall between paediatric and adult communities, early engagement during trial design may facilitate optimising the research question and delivery of the study, with further collaboration downstream to improve recruitment.

The acceptability of trial design is crucial for a patient of any age but for young people it requires additional considerations. A cancer diagnosis during AYA years poses unique challenges, and there are many aspects of trial design

that may jeopardise acceptability of the study. At the outset, the presentation of the study materials and understanding of increasingly complex study design may not be accessible to young people. There may be also a pressing need to prioritise fertility preservation, and study schedules that interfere with this may not be appealing or indeed acceptable to young people. Further along the cancer journey, the costs and inconvenience of additional clinic visits and/or additional inpatient stays may be too burdensome for young people. They may opt for conventional treatment rather than trial entry which may be perceived to interfere with transition back to 'normal life'. If the proposed study is perceived to interfere with the length of time to recover, so that return to work or education would be prolonged, young people may not be willing to delay these milestones. Referring back to Sect. 21.2.5.3, educating young people about the importance of research participation may help negate some of the aforementioned factors.

21.2.5.5 Affordability

The complexity of and the resources required to investigate rare cancers in a relatively small patient population, compared to adults with cancer, are substantial. Due to the rarity of cancers that appear in young people, clinical trial recruitment can be challenging, making international collaboration the only option for some cancers. This adds significantly to resources and the effort required. Small numbers make these diseases unattractive to the pharmaceutical industry even with the limited benefits that accompany orphan drug designation and patent protection. Variations in the interpretation of the Clinical Trials Directive in each country complicate collaboration further, stimulating consideration of the relaxation of clinical trial regulations. However, the role such regulations play in protecting patients and ensuring rigorous testing of new agents prior to implementation into clinical practice should not be undermined. A number of examples exist in which approval prior to full investigation has resulted in no efficacy or loss of life, such as targeted agents for lung cancer and stem cell transplantation for breast cancer.

21.2.5.6 Advocacy

The patient voice is now being heard with regard to access to research and clinical trials. Few studies have examined the attitudes and reasons for limited participation or explored the decision-making process of AYAs and their families regarding clinical trial enrolment. In one study, AYA's involvement in the phase 3 cancer clinical trial decision-making process was reported as limited despite caregivers and providers indicating that they had made efforts to involve the AYAs. Reasons the AYAs provided for this limited involvement were acute stress/distress, physical illness/reduced health-related quality of life and developmental immaturity. Suggestions for enhancing the engagement of AYAs in cancer clinical trial decision-making included structuring the diagnostic meeting in a manner that simplifies the presentation of information and confirms understanding. This may allow AYAs to become involved in the decision-making process while providing caregivers with the opportunity to process information about cancer, treatment and clinical trials. In addition, the use of decision support tools to address perceived barriers and benefits may facilitate increased AYA involvement [48].

21.3 Efforts to Improve Accrual

An international swell in interest from healthcare professionals in AYA oncology has resulted in a number of initiatives to improve access to cancer clinical trials for AYAs. A recent strategy for improving recruitment highlights that opportunities for increasing recruitment lie within the healthcare setting and involve consideration of the needs of AYAs by drug developers and regulators: available, accessible, aware, appropriate and acceptable – a strategy to improve participation of teenagers and young adults in cancer trials. Furthermore, the concept that clinical trial enrolment is not a one stop 'in or out' process but rather a continuum of steps, during which enrolment may be thwarted or facilitated, was presented recently [47]. By considering these frameworks, one could optimise trial design, delivery and recruitment processes in a bid to

Table 21.1 Examples of efforts underway to improve accrual of adolescents and young adults with cancer to clinical trials

Organisation	
US NCI Cancer Therapy Evaluation Program (CTEP) [47]	Newly formed National Clinical Trials Network (NCTN)
	Expanded collaboration between the Children's Oncology Group and adult NCTN Groups
	Identification of trial gaps
	Increased collaboration between groups
	Selected COG studies expanded to above 18 years and up to 49 years
AYA intergroup working group [49]	Increased collaboration crucial in uncommon diseases
UK National Cancer Research Network (NCRN)	Research group dedicated to increasing access to and promote research for young people in the United Kingdom
	Monitoring accrual
	New academic studies entering the portfolio have a lower age of 16 years
Italian Societa Italiana Adolescenti con Malattie Oncoematologiche (SIAMO) [48]	Newly formed comprehensive national programme for AYAs
	Multidisciplinary committee established to encourage collaborative working between adult and paediatric oncologists
	Platform to link with existing groups running clinical trials
	Eliminating restrictive age eligibility criteria

improve AYA accrual. Despite differing healthcare systems, many of the initiatives developed independently focus on the same principles of improving availability and access to studies for AYAs, ensuring appropriate age eligibility criteria, increasing awareness of AYA trial entry across paediatric and adult communities and engaging multiple stakeholders, including patients, in trial groups and study design. Table 21.1 shows examples of such initiatives. The creation of specific AYA groups responsible for improving recruitment also seems to be a key component of improving accrual [38, 42, 47].

The National Cancer Research Institute's Teenage and Young Adult Clinical Studies Group in the United Kingdom has demonstrated substantial improvements in participation rates of AYAs, particularly 15–19-year-olds, since 2006, framed within the five A's model [38]. Improvements in the United Kingdom have been related to increased trial availability of and access to studies relevant to young people, increased awareness of under-representation of AYAs amongst healthcare professionals and trials that have amended their age eligibility criteria to reflect disease biology. For example, UKALL2003 had an upper age limit of 18 years until the end of 2006 when it was increased to 20 years then again to 25 years in August 2007. These changes reflected emerging evidence that AYA patients appear to have improved outcomes on paediatric protocols rather than adult protocols for acute lymphoblastic leukaemia.

In Italy the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) Committee on Adolescents has seen increased accrual of AYAs through mechanisms described in the Access and Models of Care chapter in this book. From 1989 to 2006, the observed to expected ratio (O/E) for 15–19-year-olds enrolling on clinical trials compared to Italian incidence was 0.1 [27]. This figure rose to 0.28 for the 2007–2012 period (Ferrari A, submitted).

In the United States, the National Cancer Institute created the new National Clinical Trials Network (NCTN http://www.cancer.gov/clinicaltrials/nctn); a number of initiatives are anticipated to improve recruitment of AYAs to trials. The NCTN now consists of four US groups and one Canadian group allowing greater access to and availability of studies for AYAs as patients can enrol on studies sponsored by different cooperative groups. The newly formed NCTN AYA Working Group has a particular remit to advance AYA research in the NCTN through identification of trial gaps, facilitating collaborations for study development, monitoring accrual and increasing awareness of AYA accrual in NCTN groups.

21.4 Summary

There is an international consensus of the need to improve recruitment to trials for AYAs, but a comprehensive strategy with uniform reporting methods remains to be developed. Despite this, improvements in accrual are now reported from a number of countries, many targeting the same issues.

Appropriate age eligibility criteria appear to be a simplistic solution to improve access to cancer clinical trials for AYAs. However, this is just one factor in a complex picture of lesser involvement in cancer research by young people. Trial availability is limited due to lack of preclinical research, available tissue (further confounded by lesser involvement in clinical trials) and a lack of initiatives that incentivise the pharmaceutical industry to work with academia to ensure drug development for patient groups with the most clinical unmet need, particularly when the costs of both small- and large-scale clinical trials are high with international cooperation needed to accrue sufficient numbers for meaningful results. Specific AYA groups and collaboration between adult and paediatric communities are also key to improving recruitment.

Survival rates for many cancers in AYAs are high, particularly compared to some cancer types in older adults, such as pancreatic carcinoma, so ensuring that clinical trials for AYAs remain a priority area for future research will be challenging. Continued advocacy for trial availability and entry is required to ensure that as many young people as possible return to as healthy a life as possible with minimal long-term side effects. Ongoing trials examining new antineoplastic and supportive care agents are imperative to future progress.

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Adherence to Treatment Regimes in Adolescent and Young Adult Cancer Patients

22

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Abstract

Adherence, defined as the extent to which a patient's behavior coincides with medical or health advice, can have significant implications for AYA with cancer. Some of the facilitators of and barriers to adherence for the AYA population are similar to those confronting pediatric and adult populations, while others are distinct and unique to this age group. Best evaluated through a biopsychosocial model, unique barriers for AYAs include the impact of illness on physical well-being as physical development proceeds, the importance of "normality" in this age range, the impact of peer interaction, progressive evolution of the relationship with parents, and the distractibility that may mark adolescence. This evolution continues through young adulthood, a period of increasing and shifting behavioral, financial, social, and familial responsibilities.

A developmentally oriented framework for considering adherence among AYA with cancer is critical and encompasses specific approaches to enhancing patient engagement in the treatment process and the healthcare system, including the use of electronic gaming and monitoring; attention to the state of evolution of patient' cognitive and emotional functioning and psychological status; evaluation of patients' knowledge, belief framework around locus of control in health and illness; the AYA's perception of severity of illness and the related perception of vulnerability or invulnerability; and the dynamics of the relationship between healthcare providers

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and AYA patients, with particular emphasis on open and collaborative interaction.

When coupled with knowledge of potential tools to assess adherence, this framework can position providers to better address and support adherence among this population.

22.1 Introduction

Among the many factors that influence the course of illness and the success of a therapeutic intervention, a patient's level of engagement in and receptiveness to the treatment process can have significant implications for outcomes. This notion is often referred to as adherence: the extent to which a patient's behavior coincides with medical or health advice [1, 2]. There is an emerging body of literature examining this dynamic factor and recognizing its complexity, as it manifests in both acute and in chronic illnesses. Working with adolescents and young adults (AYAs) with cancer demands both an awareness of the importance of facilitating adherence and an understanding of unique developmental features that may influence how optimal adherence is achieved.

22.2 Definition

While the terms compliance and adherence are commonly used in the medical lexicon to describe the behavior of following prescribed advice or instructions [1, 2], the term adherence is now preferred. It is believed to better capture the nature of the treatment interaction, described in contemporary practice as an alliance between the patient and the healthcare providers [3].

In the medical context, adherence is considered most frequently in reference to a medication regimen but may also include adherence to diet, lifestyle, and other therapeutic modalities including medical follow-up. The World Health Organization (WHO) defines adherence as "the extent to which a person's behavior -taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [4]. Recognizing that adherence is a dynamic process, three phases of adherence to a regimen have been proposed: initiation, implementation, and persistence [5].

Nonadherence can be manifested as failure to fill a prescription, failure to take a medication as prescribed (e.g., incorrect frequency, timing, or dosage), failure to implement recommended behavioral changes (e.g., dietary restrictions), or ongoing lifestyle practices against which a patient has been advised (e.g., smoking cigarettes). Correctly defined, misunderstanding the instructions of the healthcare provider (e.g., confusing 6-mercaptopurine for methotrexate) does not constitute nonadherence. Likewise, while refusal of treatment might be considered nonadherence at its extreme, the total lack of agreement to accept any treatment is a different issue.

22.3 History and Evolution of Notion of Adherence

Historically, Hippocrates (470–410 BCE, Greece) expressed in his famous oath his concerns about patients' noncompliance: "Keep watch also on the fault of patients which often make them lie about the taking of things prescribed" [6, 7]. Research on adherence focused initially on "noncompliers" to medication regimens. The reasons given by patients for failure to adhere to instructions about medication

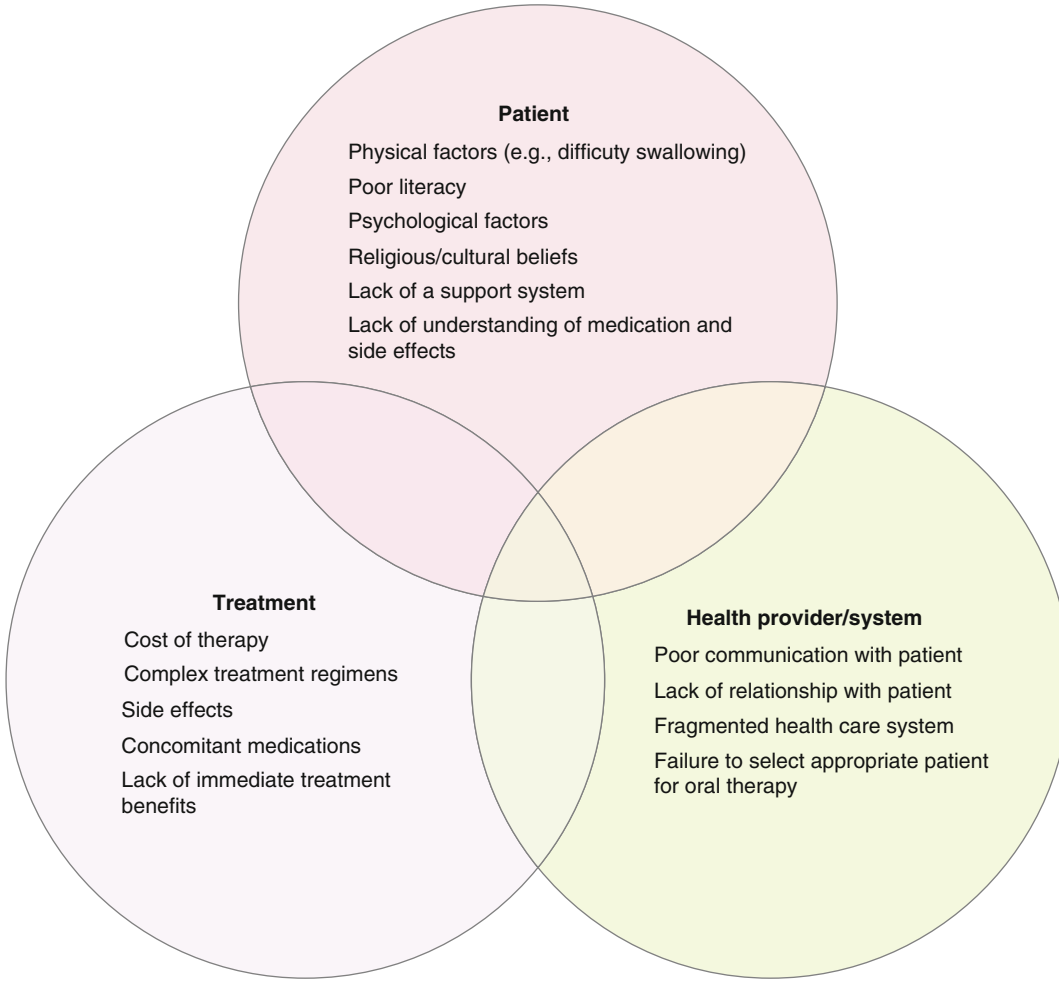

Fig. 22.1 Conceptual framework for understandig barriers to adherence (McCue et al. [9] with permission)

included the following: inadequate supply of medication, forgetfulness, misunderstanding of instructions, drug administration errors, discontinuation of treatment because of symptom resolution, resistance of the child patient, apparent ineffectiveness of medication, or side effects [8].

More recently, research has aimed to identify the risk factors and predictors of nonadherence by more objective measures. Social and legal changes pertaining to patient rights and autonomy have caused major changes in the patient–physician relationship as well as to the notion of adherence. The role of the patient and the definition of adherence also continue to evolve as a result of this therapeutic partnership.

22.4 Framework for Considering Barriers to Adherence

In 2003 the WHO developed a framework for understanding medication adherence across five key influences: patient related, therapy related, disease related, healthcare system, and socioeconomic factors [4]. A more recent concept simplifies the most influential factors into one of three categories: treatment related, patient related, and healthcare provider/system related [9]. Typically, multiple factors converge to manifest as lack of adherence, and any one factor may exacerbate or mitigate other potential influences. The complexity of the interplay of

Developmental tasks of adolescence

	Biological	Psychological	Social
Early adolescence	Early puberty (girls: breast bud and pubic hair development, start of growth spurt; boys: testicular enlargement, start of genital growth)	Concrete thinking but early moral concepts; progression of sexual identity development (sexual orientation); possible homosexual peer interest; reassessment of body image	Emotional separation from parents; start of strong peer identification; early exploratory behaviours (smoking, violence)
Mid-adolescence	Girls: mid-late puberty and end of growth spurt; menarche; development of female body shape with fat deposition Boys: mid-puberty, spermarche and nocturnal emissions; voice breaks; start of growth spurt	Abstract thinking, but self still as "bullet proof"; growing verbal abilities; identification of law with morality; start of fervent ideology (regilious, political)	Emotional separation from parents; strong peer identification; increased health risk (smoking, alcohol, etc); heterosexual peer interest; early vocational plans
Late adolescence	Boys: end of puberty; continued increase in muscle bulk and body hair	Complex abstract thinking; identification of difference between law and morality; increased impluse control; further development of personal identify; further development or rejection of religious and political ideology	Development of social autonomy; intimate relationships; development of voational capability and financial independence

Fig. 22.2 Developmental processes and tasks of adolescence (Christie and Viner [12]; Adapted from McIntosh et al. [13])

potential barriers to adherence is represented above in Fig. 22.1.

It is important to recognize that adherence is dynamic and must be viewed not only in the context of the interaction between patient and medical team but also as a personal cognitive-motivational process [10]. Furthermore, a more nuanced definition acknowledges adherence as a relative rather than an absolute outcome. Adherence, or lack thereof, thus becomes the facilitator of, or barrier to, relevant outcomes rather than an outcome in and of itself.

22.5 Adherence Among AYAs

Challenges associated with adherence transcend the boundaries of disease category and age group; however, there are unique considerations among the AYA population.

22.5.1 Adolescence

Adolescence is commonly defined as the age range between 11 and 19 years. It is a time of significant growth and development [11]. The successful transition from childhood to adulthood demands the achievement of a number of developmental tasks (Fig. 22.2). The accomplishment of these milestones allows the adolescent to individuate from the family and to gain progressively more control and independence. This progression, however, may not only involve tensions but also hinder medical adherence as the adolescent struggles with emerging autonomy. Responsibility for medical decision-making and management shifts from parent to patient, and the tasks of adolescent development may take precedence over other demands such as medication regimens, clinic visits, or lifestyle decisions. Research into chronic diseases such as inflammatory bowel disease, diabetes, HIV, and cystic fibrosis has found that adolescents are a group particularly at risk for poor adherence [14–17].

Recent literature advocates considering adolescence from a biopsychosocial approach, recognizing that adolescence involves all three of these components. Rather than considering adolescence from a discrete, progressive "stage" perspective, it is important to acknowledge that the adolescent exists within a dynamic system. This system is influenced by both internal (physical and psychological) and external (social) demands. Negotiation of any one developmental task of adolescence may influence and also be reliant on the accomplishment of other tasks at the appropriate time [12]. The introduction of a medical condition into the life of an adolescent may perturb this complex developmental system, with implications both for the adolescent's development and for the medical condition.

In studies of perceived barriers to adherence among adolescents with chronic illnesses, five

themes are identified most commonly. These are (1) implications for physical well-being, (2) forgetting due to distraction or lack of planning (e.g., missing doses due to engagement in another activity or not carrying medications when not at home), (3) striving for normality, (4) relationships with peers, and (5) relationships with parents [18]. Additional perceived barriers include treatment perceptions of patients (e.g., lack of belief in treatment effectiveness or usefulness), regime complexity (e.g., number of drugs, number of doses, timing of doses, clarity on medication administration instructions), challenges with organization (e.g., planning when to take medication), and financial costs [18]. Of these themes, the notion of a desire for normality, relationships with peers, and relationships with parents are issues specific to the adolescent population that have not been identified as challenges within the literature on adherence among adults.

22.5.2 Young Adulthood

New expectations and demands emerge as the adolescent transitions to adulthood. The definition of "young adult" varies in the literature; in North America, the term is traditionally applied to those between 18 and 29 years of age. This is a subpopulation which has been acknowledged only recently as distinct from the broader "adult" demographic and which is accordingly less well studied. Use of the term "emerging adult" may be helpful when considering adherence factors among this group. This terminology acknowledges that individuals in early adulthood continue to experience and participate in developmental changes through which an identity, worldview, and enduring approach to problem solving are shaped [19]. Tasks that are encountered during this life stage include adaptation to newly emerging intellectual abilities, balancing of peer and family influences, adjustment to society's behavioral expectations, transition away from parental involvement, increasing financial responsibilities, internalization of a personal value system, exploration of sexuality, and preparation for the workplace [10, 20]. For those with chronic conditions that persist from adolescence to young adulthood, such as cystic fibrosis and asthma, the time of transition from the pediatric to the adult healthcare system represents a window during which the risk of compromised adherence is particularly high [5, 20, 21].

22.6 Adherence Among AYAs with Cancer

Survival gains among AYAs with cancer lag behind those of children and older adults across shared malignancies [20, 22, 23]. For example, while children with acute lymphoblastic leukemia (ALL) have an approximately 80% 5-year event-free survival rate, the 5-year event-free survival in AYAs with ALL approaches 60% [24]. Among the multiple factors that may influence these differential outcomes, adherence is thought to be a significant contributor and remains relatively understudied in this population.

22.6.1 Significance of Adherence

With the advent of more successful treatment for cancers in childhood and adolescence, the role of adherence has gained greater importance because therapy is almost always given with curative rather than palliative intent. The emergence of more oral anticancer drugs similarly demands a greater attention to facilitating adherence as greater responsibility falls on the patient [25]. The clinical implications of poor drug adherence are enormous since strict adherence to chemotherapeutic protocols is essential to secure optimal outcome. Nonadherence with oral chemotherapy may play a role in the long-term prognosis of childhood leukemia [10, 14], in the relapse rate [15–17], and in graft survival after transplantation [12]. In chronic myeloid leukemia (CML), adherence to tyrosine kinase inhibitor (TKI) therapy has been associated directly with molecular response. As TKI therapy is a lifelong intervention in AYAs newly diagnosed with CML, poor adherence may have significant implications for survival [20]. In clinical trials,

Nonadherence	Consequence
Faliure to attend clinic appointments	Delayed identification of disease effects, complications, or secondary tumors
Nonadherence to chemotherapy	Reduced treatment efficacy and increased risk of relapse
Nonadherence in clinical research	Reduced capacity to assess treatment efficacy; compromised generalizability of results to AYA patients

Fig. 22.3 Consequences of nonadherence in AYA patients with cancer. Abbreviation: *AYA* adolescent and young adult (Butow et al. [10] with permission)

nonadherence can impact negatively on evaluation of trial aims and goals and may lead to an overestimation of required dosage and resultant significant toxicity and morbidity because of perceived lack of response.

Drug nonadherence may obscure the actual rate of adverse reactions and may lead to a waste of resources. The availability of venous access ports and easy-to-operate pumps makes the administration of parenteral chemotherapy at home ("home care") possible, but this introduces a new dimension to the issue of nonadherence. Examples of consequences of nonadherence in AYA patients with cancer are captured in Fig. 22.3.

22.6.2 Epidemiology of Adherence in AYAs with Cancer

The rate of nonadherence among AYA patients with cancer is not well known, due to a lack of large-scale, population-specific studies. Furthermore, interpretation of existing studies is complicated by variation in the definition of nonadherence [25]. Among studies in which the AYA group is either the entire sample or a part of the sample, nonadherence rates have ranged from 27 % to 63 % [5, 10, 26]. Adolescents are less adherent than younger or older patients with cancer, even when treated with similar protocols [10]. Adherence in clinical trials is inferior among the adolescent population, affecting the ability to research new interventions that may improve outcomes [22]. When examining rates of treatment refusal, findings vary quite broadly. A study with a large cohort of 576 Australian patients with various cancers, including both solid and hematologic malignancies, found only 1 % of AYAs failed to complete planned therapy due to nonadherence [11]. An older study found that 23 % of adolescent patients refused all or parts of treatment; of this group, 12 % refused all therapy, 35 % refused one treatment modality when multimodal treatment had been recommended, and 24 % started but failed to complete therapy [27].

22.6.3 Facilitators of Adherence

Approaching adherence from a strength-based orientation may prove beneficial since the focus is on promoting success rather than anticipating failure. Strength-based models have a strong evidence base in the adolescent medicine literature [28–30]. Factors that have been found to improve adherence among adolescents with cancer include a positive family relationship with open communication, good patient–provider communication, involvement of the adolescent in treatment decisions and illness management, and supporting continued participation of adolescents in usual activities, including social activities and "rite-of-passage" events such as school formals and graduations [10]. These factors are extrapolated commonly to be relevant to young adults as well.

22.6.4 Barriers to Adherence

Just as there are differences in the biology and characteristics of malignancies in the AYA population, so too do the behaviors and needs of this

demographic differ from other age groups confronting cancer. In order to understand the mechanisms leading to lack of adherence among adolescents, clinicians must recognize that adolescent brain development involves early predominance of the limbic system (i.e., the reward system) and only later the maturing of the prefrontal cortex (i.e., executive functioning and planning) to mitigate the impulses of the limbic system. Thus, the adolescent with cancer may prioritize immediate rather than future experiences disproportionately and may be more focused on the present and on surviving the current treatment than on future and long-term outcomes [31]. A review of general barriers to adherence has been addressed in a previous section. Factors that influence adherence specifically among AYAs with cancer are similar to those observed among AYAs with chronic illnesses in general. These include patient emotional functioning (depression and self-esteem), patient health beliefs (perceived illness severity and vulnerability), and family environment (parental support and parent–child concordance) [26]. While these barriers seem to associate more closely with characteristics and behaviors of the individual than the provider or the treatment, adherence challenges may also center around the healthcare system as it often is not oriented toward the unique needs of the AYA group [32]. Of note, while there is a body of literature exploring adherence among adolescents with cancer and among AYAs with other chronic illnesses, the relatively recent acknowledgment of young adults with cancer as a unique population leads to a dearth of significant literature examining the young adult population. Barriers to adherence among adolescents may be assumed to persist for young adults; however, the limitations of this assumption must be acknowledged.

22.6.4.1 AYA Barrier Dimension 1: Treatment Features and Engagement

There is an increased risk of nonadherence with oral rather than parenteral medications, used particularly in treatment protocols for ALL and Hodgkin lymphoma [10, 33, 34]. Among the general population with cancer or other chronic illnesses, adherence has been found to be related to the duration of treatment, the physical characteristics of the drugs such as the number of medications, the number of doses for each administration, and the mode of administration. For nonadherence in general, the cost and the appearance, color, and size of tablets have been found also to influence drug adherence. Interestingly, in studies focusing specifically on adolescents with cancer, these variables have not been identified as significant barriers. In fact, no clear relationship has been found between time since diagnosis, complexity of treatment regimen, or consistency of primary care provider and rates of adherence [5, 26, 35]. Studies indicate that adherence to one component of treatment does not always ensure adherence to other treatment-related demands; however, nonadherence to low-risk treatment demands (e.g., missing an outpatient appointment) has been found to be predictive of nonadherence to high-risk treatment demands (e.g., seeking medical attention when a fever develops) [26].

Adding to the challenge of understanding the impact of treatment characteristics on adherence in AYAs with cancer, there are conflicting findings with respect to treatment side effects. Some studies have found that adherence is better with drugs having less or milder side effects and among patients whose expectations about side effects were worse or about the same as what actually occurred. However, others have found no correlation between side effects and adherence [36].

Treatment in a pediatric rather than a nonpediatric setting has been found to influence outcomes positively among AYA patients with cancer, and improved adherence is one of the proposed mechanisms contributing to these differential outcomes. At present, though, improved adherence among those treated in pediatric settings remains a hypothesis rather than a proven factor in this complex and multifaceted dynamic. Clearly this is an area in which further research is required. What has been shown consistently is that treatment approaches in which the young person has no

role in decision-making or management have an adverse effect on adherence [10].

Thus, after synthesizing all of the varying findings on the role of treatment features on adherence, it may be that it is the patient's engagement in their treatment and relationship with the healthcare system, rather than the nature of the treatment itself, that impacts adherence.

22.6.4.2 AYA Barrier Dimension 2: Patient Emotional and Cognitive Functioning

The emotional functioning of adolescents with cancer is impacted by a strong desire for normalcy. This drive for normalcy may inform the adolescent's receptiveness and/or adherence to treatment [37].

There are limited studies examining the relationship between psychiatric comorbidities and adherence among AYAs with cancer. The few studies that do exist have indicated that depression and anxiety are both associated negatively with adherence. Depression need not be severe; even subclinical distress has been found to reduce adherence [18, 26]. Studies exploring the role of anxiety in more detail have found that poorer adherence may be manifested by those prone to anxiety in anticipation of potentially threatening situations ("trait anxiety") rather than those who experience more significant anxiety during an actual threatening situation ("state anxiety") [38]. Low self-esteem or self-image, while not a psychiatric diagnosis, has also been shown to be associated with decreased adherence [5, 39]. Finally, some adolescents report "forgetting by coincidence" to be a barrier as well [18]. This suggests that executive functioning and organizational skills may impact AYA patients' capacity to remain adherent to a treatment plan.

22.6.4.3 AYA Barrier Dimension 3: Knowledge, Beliefs, and Attitudes

Inadequate knowledge of the disease and treatment course can present barriers to successful adherence among AYAs with cancer. A lack of comprehension of the potential therapeutic benefits of an intervention may impede adherence further [5]. Beyond simple understanding of facts, how a patient interprets or appreciates the implications of treatment can have significant implications for adherence. Indeed, several studies have suggested that personal subjective beliefs may feature more prominently than factual knowledge in determining adherence [35, 39]. Which beliefs translate into poorer adherence is unclear; both an internal locus of control (i.e., sense that one can control events affecting health) and an external locus of control (i.e., belief that chance or fate has a role in outcomes) may present barriers to adherence [26]. One study found that those who believe that the physician or care team holds complete responsibility for outcomes are less likely to be adherent [39]. Lower perceived illness severity or personal vulnerability may translate into poorer adherence as well [26]. The tendency toward "compensatory beliefs," defined as "the conviction that negative disease-related behavior may be offset by a different positive behavior" (e.g., "smoking is okay because I eat healthily" or "I take my one medication consistently so missing another won't matter as much" [40]), is a consideration when examining adherence among AYAs with cancer [5].

22.6.4.4 AYA Barrier Dimension 4: Relationship Dynamics

Lack of parental involvement is consistently reported as a barrier to adherence [5, 10, 18, 26]. Lack of open communication, a controlling parent–child relationship, and family conflict are significant barriers to adherence among AYAs with cancer [5, 10, 41]. Open communication and a collaborative dynamic are similarly important within the patient–provider dynamic. Provider inconsistency, for example, with regard to following a treatment protocol, can erode the AYA patient–provider relationship and affect adherence negatively. Finally, a lack of attention to supporting AYAs in engaging in normative peer activities can undermine adherence, as this demographic

	Advantages	Disadvantages
Direct measures		
Observation	Direct monitoring of adherence	Impractical; time consuming; relation between adherence and health status not always clear
Bioassay—serum	Objective; confirms a drug has been taken	Invasive; inherent pharmacological variations in absorption, metabolism, and excretion complicates interpretation; not available for all medications; costly for routine practice
Bioassay—urine/saliva	Objective; non-invasive; establishes medication has been taken	Individual differences in pharmacokinetics still applies; not able to detect all drugs
Indirect measures		
Patient self-report	Easy to administer; high specificity; feasibility in all care settings	Vulnerable to overestimates or underestimates of non-adherence by patient; subject to recall bias
Health-professional ratings	Easy to implement; practical in all treatment environments	Prone to underestimations of non-adherence
Prescription monitoring	For use with large cohorts	Relies on completeness of pharmacy database; does not measure actual medication taken
Pill counts	Easy to implement	Provide no information about dosage schedule; does not confirm whether a pill has actually been taken; relies on patient returning pill container
Medication-event monitoring systems	Continuous assessment of adherence (in terms of timing and frequency)	Presumption that medication is consumed; reports of mechanical failure; costly
Therapeutic outcome	Objective	Outcomes might be confounded by other aspects of treatment; time consuming

Fig. 22.4 Methods of assessing adherence (Kondryn et al. [26])

places considerable emphasis on peer acceptance and the perception of "normalcy" [37].

22.6.4.5 Other Considerations

To our knowledge, there are no specific studies examining the implications of sociodemographic features for adherence specifically among AYAs with cancer. In studies of the pediatric oncology population and AYAs with other chronic illnesses, low socioeconomic status, linguistic features, ethnicity and race, culture, and immigration status all may impact adherence [5, 33].

22.7 Assessment of Nonadherence

Identification of nonadherence is important in explaining the absence of a therapeutic response, targeting individuals for intensive intervention, and the selection of appropriate adherence-improving strategies. Unfortunately, poor adherence is difficult to anticipate because of the lack of clear predictors. Without the use of tools to complete a formal adherence assessment, only 50% of providers will identify nonadherence successfully [42].

Both indirect and direct methods have been used to identify and monitor patients' adherence, with advantages and shortcomings for each technique (Fig. 22.4). Measurement of adherence over a short period of time may not reflect long-term patterns [43], and methods used for research purposes may not be practical for routine clinical use. An individualized approach should be chosen for each patient according to the conditions, personality of the patient, and the healthcare providers. A combination of different techniques, particularly direct and indirect methods, presents the most thorough means of assessment and may allow for the reliability of objective measurements complemented by the insight or context provided by subjective means.

22.7.1 Direct Methods

When nonadherence is suspected on clinical grounds, direct methods to assess adherence may be useful. These may include direct observation of therapy directly and bioassays.

Direct monitoring of adherence involves a healthcare provider observing a patient directly while taking a prescribed medication or engaging in a recommended activity. In addition to allowing for objective indication of adherence, this method may afford the opportunity to reinforce medication administration directions with the patient and to confirm the patient's understanding of medication dosing, preparation, and storage instructions. However, as an assessment approach, it provides only an indication of adherence at a specific time point and is difficult to sustain in the context of long-term therapy. A Cochrane Review examined the practice of directly observed therapy as an intervention to improve medication use in HIV and tuberculosis – two chronic diseases with the longest history of using this method as an intervention. Interestingly, the study concluded that directly observed therapy may not improve treatment completion, adherence, or clinical outcomes [44].

Bioassays may include measurement of drug or drug metabolite levels in the blood, erythrocytes, or urine [45] with specific tracers added to the drug for better monitoring [46]. The implications of these results will vary for each medication and patient, and conclusions regarding the relationship between drug ingestion, measured levels, and outcomes must be interpreted in light of these individual considerations [5]. Assays for drugs with short half-lives, for example, may be particularly problematic to measure or interpret accurately. In the setting of lymphoid malignancies, the presence of thiopurine metabolites of mercaptopurine may be influenced significantly by polymorphic gene expression affecting drug metabolism [47]. Furthermore, clinicians should be aware that this information typically reflects only recent ingestion of the drug and patients may alter their adherence just prior to the test [48].

22.7.2 Indirect Methods

Indirect methods of assessment of adherence can include both objective and subjective measures. Objective measures may include surrogate markers, pill counting, medicine returned, pharmacy refill data, and microelectronic monitoring. Subjective measures are typically self-report and include diaries, interviews, and questionnaires [5].

22.7.2.1 Objective Measures

Biologic response to medication therapy may serve as a surrogate marker to monitor for adherence. These monitoring endpoints may consist of either clinical or laboratory findings that reflect therapeutic or toxic effects of a drug. Unfortunately, a linear correlation does not exist necessarily between the amount of drug ingested and the surrogate marker. One common example in ALL treatment is the use of the absolute neutrophil count to indicate patient adherence to 6-mercaptopurine and guide dosing modifications throughout maintenance therapy [47]. As mentioned previously, however, drug pharmacokinetics may be influenced by genetic polymorphisms of drug metabolism, complicating the interpretation of patient adherence from surrogate marker findings.

Pill counts may document a discrepancy between the number prescribed and/or reported to be taken and the number of remaining pills. The value of this method may be limited in clinical practice, because patients may not always bring their medications to the clinic visit and drugs could have been vomited, spilled, or spit out [46]. In addition, patients may discard unused medications intentionally; this is known as the "parking-lot effect" or "pill dumping effect" [49]. Furthermore, having to bring pill bottles to appointments may be perceived by AYAs as yet another demand by the medical team and could in fact be a barrier to engaging in care or a deterrent from potentially beneficial activities such as enrollment in clinical trials. An alternative strategy that can provide information is to check prescription refill frequency with a patient's pharmacy or to develop a prescription monitoring program with collaborating pharmacies.

Recently, various microelectronic automated devices such as the Medication Event Monitoring System (MEMS, Aprex Corporation, Fremont, California) offer a major advantage in monitoring adherence [33, 50, 51], particularly in noncooperative patients [52]. Microprocessors in the cap of these standard drug containers record every bottle opening as a presumptive dose. MEMS can monitor adherence over a long period of time. For the individual patient, MEMS may help to determine the pattern of nonadherence and differentiate between true nonadherence and drug disposition (e.g., absorption or metabolism) problems [53]. Electronic measurement tools have been shown to have an intervention effect, which may be beneficial in the clinical population but confounding in research cohorts in which the true level of adherence is being studied. This intervention effect typically wanes over 5 weeks [5].

22.7.2.2 Subjective Measures

Reports from patients and family members as to whether drugs are being administered are a valuable and practical way to get a first impression in clinical practice. Research findings from studies assessing the level of correlation between self-report and objective measures are variable, with some studies revealing relatively high consistency [45] and others indicating that self-report measures may overestimate adherence as much as twofold [5]. Self-reports of nonadherence are often more accurate than self-reports of adherence [54]. The questions used in such investigations should be nonthreatening and nonjudgmental. Questioning patients per se tends to increase adherence by serving as a reminder to take the medication [46]. Therefore, interviews on drug adherence may serve as an effective intervention [36]. Written reports, diaries, and questionnaires, on which the patient records drug intake, may be helpful in obtaining more accurate data to monitor drug adherence. These modalities are often required tools incorporated into clinical trials evaluating an investigational agent that the patient must self-administer.

Physicians tend to overestimate drug adherence [55]. Nonadherence is often suspected with treatment failure, but clinical outcome or absence of side effects cannot be used as reliable indications of nonadherence, since the disease does not always respond to the treatment [56] and side effects do not always correlate with drug intake.

22.8 Adherence-Enhancing Interventions (AEIs)

It is critical that practitioners working with the AYA cancer population are aware of potential interventions to enhance adherence among this population. Knowledge of the risks associated with nonadherence and an appreciation of the potential barriers to adherence within this group should motivate providers to seek out strategies to facilitate optimal AYA understanding of the disease and treatment process, individual emotional functioning, healthy relationships, and ultimately treatment engagement. Again, current literature is very limited on strategies to improve adherence specifically among AYAs with cancer. Novel approaches with proven outcomes in studies of pediatric or adult patients with cancer or of AYAs with other chronic ill-

nesses may serve as a starting point to assist AYAs with cancer; however, rigorous research of interventions for this specific population is clearly warranted.

At present there is, to our knowledge, only a single large-scale randomized study examining an adherence-enhancing intervention (AEI) for AYAs with cancer [34]. This multicenter study examined the potential for improved adherence to self-administered oral medication with use of a video game designed specifically to address issues of cancer treatment and care among teenagers and young adults [34]. Three hundred and seventy-five patients aged 13–29 (87 % between ages 13 and 18) with an initial diagnosis or relapse of a malignancy were assigned randomly to either the intervention group (study video game) or control group (commercial video game). The intervention group was found to have greater adherence to prophylactic antibiotics and to 6-mercaptopurine, and the study concluded that this video-game intervention improved not only treatment adherence but also cancer-related self-efficacy and knowledge significantly [34]. A notable strength of this intervention is the relatively low volume of healthcare system resources required and the potential for easy distribution of the video game.

Alternative potential interventions have been studied in children and AYAs with other chronic conditions as well as in adults with cancer. The most appropriate intervention will depend on the nature of the barriers to adherence experienced by the individual patient, and thus a personalized assessment of such barriers should be the first step in implementing any intervention [5]. While AEIs are classified often according to the nature of the intervention, we have reframed this taxonomy to categorize AEIs by the barrier dimension they address most directly. Multicomponent interventions that employ multiple strategies have been shown to have particularly strong effect sizes in mitigating nonadherence, highlighting the importance of a holistic and thorough assessment of potential barriers to be addressed [5, 9, 57–59].

22.8.1 AEIs to Address Barrier Dimension 1: Treatment Features and Engagement

The video-game-based intervention noted above is an example of an effective intervention to address treatment engagement. Additional interventions that may hold promise in this regard include Internet- and mobile phone-based reminders and educational outreach programs. Internet- or text message-based interventions have been shown to facilitate individualized health promotion, peer support, and improved clinic attendance in AYA cancer survivors and AYAs with sickle cell disease [60–63]. Interventions focusing on effective transition from the pediatric to the adult healthcare system, such as transition clinics, transition readiness questionnaires, and transition summaries, may also support ongoing treatment engagement by preparing adolescents appropriately for the expectations of the adult healthcare system [21, 64]. Finally, electronically monitored medication systems provide individualized feedback on behaviors and have been shown to improve adherence among asthmatic children [65] and among adults with HIV [66] and other chronic illnesses [67].

22.8.2 AEIs to Address Barrier Dimension 2: Patient Emotional and Cognitive Functioning

Behavioral interventions, also referred to in the literature as cognitive-behavioral and problem solving oriented AEIs, have been shown to be effective tools in addressing emotional and cognitive barriers to adherence in children and adults with chronic illnesses in several meta-analyses and systematic reviews [58, 59, 68]. Behavioral AEIs focus on day-to-day functioning and employ applied behavioral strategies to enhance skills to manage anxiety, depression, and cognitive challenges. The goal of behavioral AEIs is to support patients in developing the skills to identify and

employ effective and adaptive solutions to specific problems encountered in everyday living [68]. This may include behavioral strategies to modify the environment to promote adherence, and interventions to provide positive or negative consequences for adherence-related behaviors [59]. Less intensive interventions that may help to address simple forgetfulness as a barrier to adherence include reminder systems such as adherence aids; mnemonic devices, using an alarm, medication scorecards, and preloaded medication cases [5]; or organizational skills training [69].

22.8.3 AEIs to Address Barrier Dimension 3: Knowledge, Beliefs, and Attitudes

Both targeted (i.e., based on identified deficits in patient's knowledge base) and generalized (i.e., non-individualized) educational interventions may promote adherence. Illness-related education can be achieved through direct interaction with an interventionist (e.g., a pharmacist), through written information (e.g., pamphlets), or through the use of technology-based platforms [5, 57, 58]. The Quality Oncology Practice Initiative provides a list of requisite educational components that should be addressed prior to initiation of oral chemotherapy in adults. These include information addressing the drug and indication, dose, dosing schedule, start date, route of administration, instructions for actions if a dose is missed, potential drug and food interactions, side effects and how to manage them, safe handling instructions, and clinic contact information [9]. The effect of purely educational AEIs has been found to be less durable than other intervention modalities, and thus these AEIs are best applied in combination with other AEIs, particularly those that are behaviorally oriented [67]. Beyond a patient's understanding of an illness and treatment plan, adherence requires patients to act on their knowledge. Motivational interviewing is a technique designed as "a client-centered, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence" [70]. In motivational interviewing, a trained clinician explores inconsistencies between a patient's values and behaviors with the aim of uncovering the patient's own motivation to act in a health-promoting manner. Motivational interviewing has been associated with improved outcomes in adolescents with chronic illnesses including HIV and diabetes [5].

22.8.4 AEIs to Address Barrier Dimension 4: Relationship Dynamics

Relationships are paramount for AYAs; promoting healthy peer, parent and provider relationships can have a significant positive influence on AYA functioning, including adherence. Appropriate social supports can scaffold AYA patients in such a manner as to bolster their ability to enact positive health-related behavior change. Peers can help adolescents to feel accepted, which in turn may help the adolescent accept their illness [69]. Interventions such as peer support groups have been found to improve coping among AYAs with cancer [5] and other chronic illnesses. Adult role models have also been shown to improve adherence in adolescents with diabetes [71]. Family therapy interventions are designed to teach effective family communication, including nonjudgmental interactions and open communication, and to improve parents' skills in effectual support, such as collaborative self-care, giving regular positive feedback, and providing incentives to promote adherence [69]. Care plans that acknowledge the patient as an active and important participant in care decisions improve patient–provider relationships and enhance rates of adherence. Consistent scheduled follow-up contact, either in person or by telephone, promotes communication and a sense of investment in patient outcomes on the part of the provider team, further cultivating positive patient–provider relationships [9]. Multidisciplinary teams may also foster a more secure and cohesive sense of relationship [5]; for example, pharmacist-led interventions have

been successful in improving adherence in adult chronic diseases [9].

Conclusions

Adherence is a complex and nuanced phenomenon with the potential to exert significant influence on an individual's illness course. Initially conceptualized as an issue of lack of patient conformity with prescribed medical instructions, in the contemporary landscape of patient-centered collaborative care, the notion of adherence should be regarded rather as an opportunity for partnership and shared agenda setting, with the objective being restoration, maintenance, or enhancement of health.

Achieving such an outcome demands an understanding of potential obstacles in this shared journey. This includes an awareness of patient, treatment, and healthcare provider/system components that converge in a unique manner for each patient. AYAs are a distinct subpopulation of individuals dealing with chronic illness, and supporting adherence in this group requires additional knowledge and sensitivities. AYAs are in the midst of an intricate developmental process that may be perturbed by illness. Such a disturbance may manifest as behaviors, considerations, needs, or apprehensions that are different from those of either the older adult or the pediatric population.

Adherence among AYAs with cancer is an area of growing interest, particularly given inferior survival gains as compared to other age groups with similar malignancies. There is a dearth of research on this critical issue; however, initial studies indicate nonadherence features prominently among AYAs with cancer. To date, our understanding of barriers to adherence for AYAs with cancer suggests that specific dimensions must be considered when working with this unique group. The best approach to promoting adherence in the AYA cancer population remains unclear since data on adherence-enhancing interventions is drawn almost exclusively from other populations.

As the field of AYA oncology continues to evolve, adherence will remain an important focus of inquiry and exploration. With the emergence of a greater number of targeted agents, many of which are delivered orally, the implications of treatment route (oral vs. parenteral) for adherence across all malignancies diagnosed in the AYA population will require consideration. Many lessons have been learned about the clinical impact of variations in adherence to oral, outpatient therapies from the pediatric ALL and adult CML experiences. These stories should serve as a cautionary tale as new and potentially effective treatments for cancer in the AYA population are developed.

AYAs are a population with tremendous potential. As we commit to advocating for improved attention to AYAs with cancer within the healthcare system, increased AYA representation in clinical trials, and ultimately superior AYA illness and quality-of-life outcomes, it is incumbent upon us to incorporate into all of these endeavors an orientation toward improving adherence. It will only be through focused and rigorous study of the issue of adherence among AYAs with cancer that advances in other domains of AYA cancer care will be able to reach their full promise and potential.

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Psychosocial Issues in Adolescent and Young Adult Patients and Survivors

23

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Abstract

This chapter focuses on the psychosocial impact of cancer on adolescents and young adults (AYAs) aged 15–39 years and provides an insight into therapeutic approaches. It examines unique developmental and psychosocial issues and subsequent needs of these young people as they occur throughout a continuum of survivorship, as well as approaches to address those needs. A diagnosis of cancer challenges young people's views about their invulnerability, threatens their self-esteem, and compromises all aspects of quality of life. Long-term educational and career goals can be seriously compromised by hospitalization and health complications. These obstacles and roadblocks may derail normal development, interfere with transition into adulthood, and significantly impact on family life and financial stability.

There has been substantial progress in the understanding of the psychosocial aspects of AYA cancer in the past 5–10 years. In the long run, the majority of young adult cancer survivors appear to be psychologically well adjusted, even when acknowledging visible and limiting physical effects of treatments. Overall, these young people experience emotions and behave in ways that are normative for this age population. However, a substantial minority experience post-traumatic stress, a form of emotional and psychosocial disability requiring psychological counseling of some form. An important minority appears to experience post-traumatic growth and are

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able to transform their lives in ways that represent more positive outlooks and competencies that one would have expected prior to their diagnosis and treatment. Given the full range of these responses, including the possibility that some teenagers and young adults surviving cancer can exhibit signs of greater emotional stability and security, intervention programs that historically have focused on alleviating stress and preventing negative outcomes (such as post-traumatic stress symptoms) must be complemented by programs focusing on promoting successful achievement of age-appropriate developmental tasks and positive psychological and emotional growth.

23.1 Introduction

This chapter focuses on the psychosocial impact of cancer on adolescents and young adults (AYA) aged 15–39 years and provides an insight into therapeutic approaches. It examines unique developmental and psychosocial issues and subsequent needs of these young people as they occur throughout a continuum of survivorship, as well as approaches to address those needs. In line with global trends, the upper age range for young adults has been increased from 29 to 39 years for this edition, so the AYA age group now includes a greater diversity of cancer types as well as representing people at vastly divergent developmental phases of life. The impact of cancer diagnosis on a young teenage scholar is bound to differ from that of a young adult with a family and teenage children. A diagnosis of cancer challenges young people's views about their invulnerability, threatens their self-esteem, and compromises all aspects of quality of life at all stages of young adulthood. Treatments are associated with major changes in physical appearance and physical energy. Long-term educational and career goals can be seriously compromised by hospitalization and health complications. These obstacles and roadblocks may derail normal development, interfere with transition into adulthood, and significantly impact on family life and financial stability.

This chapter includes on-treatment patients and survivors together because the experience of young adulthood stimulates responses to a personal history of childhood cancer that may differ from those evident in earlier developmental periods. Young adulthood is a time of increased vulnerability to stress and presents cancer survivors with major developmental challenges above and beyond those faced by other young people [1]. For example, gaining independence, establishing one's sense of identity, negotiating interpersonal relationships (including intimacy, forming families and caring for dependents), as well as making important decisions about education and employment, all require a focus, in most individuals for the first time, on the medical, cognitive, or psychosocial effects of cancer treatment.

23.2 The Cancer Trajectory

The cancer experience has been likened to a journey. The focus following diagnosis is on acquisition of information, acute care, and management. This is followed by an extended period from the end of intensive treatment through to a period of watchful waiting and fear of relapse, then a period of permanent survival with concern for adverse late effects, and finally an ultimate resolution. From diagnosis to long-term survivorship, psychosocial interventions should take into account the potential difficulties at each phase and the challenges transitioning from one to another. Ross emphasizes the need to be aware of the critical phases through which the AYA and family pass and determine the nature of the intervention based on a clear understanding of those phases [2].

23.2.1 Diagnosis

Any negative life event creates changes that can be stressful and that require adaptation on the part of

the individual. The initial period after such an event is critical, and the inability to cope during that period can be a precipitating factor in the development of long-term problems. Behavior patterns exhibited during this period are likely to become fixed and may shape behavior during subsequent phases [3], suggesting the benefits of an early and ongoing rehabilitation program [4]. Findings from a recent study emphasized the importance of early psychosocial intervention to reduce distress and manage treatment-related symptoms [5]. A study to evaluate a computer-based tool to explore symptom clusters experienced by AYAs found that it demonstrated potential to empower AYAs to communicate their symptom experience and partner with their healthcare providers, improve symptom management, and reduce distress [6].

Haase found that resilient adolescents frequently use the defensive coping strategy of denial in dealing with the cancer experience [7]. Baider and De-Nour found increased distress levels for young adults in active treatment that participated in a therapy group. They suggest that group therapy can be a factor in decreased denial in certain cancer patients and young people should be referred to group psychotherapy only when they are in a stable medical condition [8]. Maintaining a sense of hope and use of denial can be an important factor in the determination of when and what kind of therapy to offer AYAs with cancer.

23.2.2 End of Treatment

Given the frequent report of anxiety, fear, and feelings of vulnerability, MacLean et al. suggest psychological care to target patients as they transition from on-treatment to off-treatment [9]. Parents of adolescents with cancer report increased anxiety at end of treatment. A family systems approach is recommended to help both patient and family adjust to the off-treatment phase [10].

23.2.3 Follow-Up Care

Many survivors experience physical or psychological late effects depending on the treatment received. For many survivors, follow-up care needs to include psychological support [11]. Traditional health promotion advice is needed regarding the risks associated with smoking or sunbathing, for example. Problems that require some psychological intervention include those related to weight gain following treatment, infertility, or reduced cardiac function.

Chesler and Barbarin's [12] Stress-Coping model is useful for organizing psychosocial issues across five dimensions: intellectual, practical, interpersonal, emotional, and existential. The utility of this model comes from its organization of the cancer experience into observable categories of stress, coping responses and strategies, and sources of social support. It helps identify patient and survivor needs from perspectives incorporating quality of life, positive adaptation, and family systems, thereby informing the development of interventions that address psychopathologic disease prevention as well as health promotion.

Various forms of psychosocial support have been suggested in working with AYAs as they attempt to cope with cancer, including peer-based interventions [13–16], individual psychoeducational counseling [17, 18], and skill-based interventions [16, 19]. More recently, modern electronic applications created technology-based ways to deliver information and support have grown in popularity to satisfy AYA needs for information and support [16, 20]. Developmental age, diagnosis, individual challenges and needs, as well as phase of treatment along the continuum of care should be considered in choosing a psychosocial approach. Such support should be offered routinely rather than in a response to a crisis. While there is a need for crisis-initiated interventions, such programs are the last resort and tend to foster stigmatization, alter effective treatment, and discourage self-help [21].

23.3 Intellectual Issues

23.3.1 Information About Cancer Diagnosis, Prognosis and Treatment

Communicating information to AYA cancer patients can be a sensitive issue. How people com-

municate information, tasks and feelings to AYA patients and survivors affects how they experience their illness and think about themselves and their current and future situations. All parties – doctors, other medical providers, family members and friends – need to attend to the manner as well as content of their communications and interactions with AYAs and to the social and emotional context within which communication and interaction occurs [22]. Some patients prefer to be shielded from direct communication about their cancer; others may desire to assume a more prominent position in the information flow and management of their care. For instance, Young and colleagues [23] report that parents most often manage what and how their children are told about cancer and that young people vary in their preferences as to how much information should be disclosed to them. Last and Veldhuizen [24] found that while the majority of young people with cancer prefer to be fully informed about their disease, approximately one-third of the young adult patients surveyed preferred not to know. Nonetheless, in general, AYA patients' desire for information is a chief concern and the availability and communication of information is an important contributor to levels of satisfaction with care [25]. A sense of control plays a part in adolescent development and has implications for treatment adherence [26–28]. Giving adolescents options and choices is one way to regain a sense of control, often lost at diagnosis, for young patients. To enhance a patient's sense of mastery and sense of control, List et al. (1991) suggest simple and understandable information and explanations about the cancer experience [4], with written directions on treatment procedures and medical schedules also recognized as being important [27, 28]. Recognition of the cognitive capabilities and unique developmental challenges associated with adolescence and young adulthood is important [22]. They typically express preferences for face-to-face communication with health professionals that is open, honest, nonjudgmental, respectful and inclusive of them in the formulation of treatment plans [29, 30]. Within the AYA group, there also appears to be a discrepancy between self-reported unmet need with regard to cancer, treatment and nutrition information with AYAs aged 20–29 years more likely to report unmet need than either younger or older AYAs [31]. Researchers and clinicians alike have stressed the importance of AYA survivors receiving adequate and direct information about their cancer history and related risks (e.g., late effects, including reduced fertility, risks for second cancers, potential genetic effects to offspring) [32–34]. Survivors themselves often express desires for services related to diet and nutrition, supportive counseling, health insurance, assistance with career planning, guidelines for appropriate long-term medical follow-up and access to community physicians familiar with oncologic late effects and meeting other long-term survivors [35, 36].

23.3.2 Information Seeking

AYA survivors of childhood cancer often lack critical information regarding their cancer and its treatment, including information about types and dosages of treatment and in some cases even the type of cancer they had, along with knowledge about potential long-term late physical effects [37]. The active process of seeking and obtaining information about cancer appears to be related to improved self-confidence [34], and young survivors who preferred and received open communication about their diagnosis and prognosis at the initial stage of disease also showed significantly less anxiety and depression later [24]. Yet, AYAs' attitudes about information-seeking may change over time, depending on cultural backgrounds or beliefs about cancer, health, or illness. The extent to which survivors and their family members perceive risks of relapse or a "need to know" also may influence information-seeking.

As AYA cancer patients complete treatment, grow older, become geographically mobile (e.g., move away from their families of origin and from their source of medical/oncologic care), and become more solely responsible for their own health care, the process of seeking and accessing health care is often perceived to be stressful [38]. Selecting employer-offered or other group health insurance packages and finding a doctor are all

new experiences for cancer survivors to handle on their own. In these regards, survivors and health professionals alike have identified significant barriers or obstacles to obtaining appropriate follow-up care, including survivors' lack of knowledge about relevant and appropriate care, limitations with regard to health insurance and financial resources, as well as healthcare providers' lack of knowledge about relevant long-term survivorship issues [39].

The Internet is a useful resource for AYAs throughout the continuum of care for information, finding financial assistance, advocacy (returning to school, job searches, advocate for workplace accommodation), and fertility issues [40]. A study found patients who are newly diagnosed perceive the Internet as a powerful tool for acquiring information and for enhancing confidence to make informed decisions [41]. Other findings associated Internet use with increased self-efficacy, improvements in knowledge and treatment adherence, increased participation in their own care, and new modes of delivering cost-effective psychosocial support [16]. However, it is important that AYAs recognize that information on the Internet may be inaccurate and unbalanced and may cause unnecessary anxiety and concern.

Promising outcomes on the effects of telephone interventions and music video creation with AYAs suggest high levels of participation and satisfaction as well as improvement in symptom distress, self-efficacy, coping and quality of life [42, 43]. Kato et al. report that a video game for AYAs improved treatment adherence and knowledge [44].

23.4 Practical Issues

23.4.1 The Hospitalization Experience, Including Pain and Painful Procedures

As AYA patients undergo diagnostic procedures and subsequent treatment, they meet innumerable healthcare professionals and ancillary hospital staff who will be involved in their care for an extended period of time. Diagnostic tests, curative and palliative therapies, and subsequent side effects often bring discomfort, pain, nausea, vomiting, fevers and infections, fatigue, changes in appetite, altered bodily appearance, and sleep disturbances. While subject to these painful procedures and treatments, adolescent cancer patients have reported a lost sense of control over their lives [45, 46]. End-of-life care presents special difficulty as emotional stress increases, physical functioning deteriorates, and pain management becomes an issue.

23.4.2 School and Work

AYA patients and survivors confront myriad disruptions in the worlds of school and work as a direct result of cancer diagnosis and treatment. Returning to school represents the continuation of "normal" life, as junior high and high school attendance for all and college for some are vital social and developmental activities for this population. Regular school attendance is vital to foster normal development and to prevent isolation from peers and social regression [47]. Research suggests the importance of encouraging adolescents to participate in school activities as fully as possible, since positive school experiences can reduce teenagers' maladaptive emotional responses to the disease and its treatments by helping them feel academically accomplished and socially accepted [48]. It also helps reestablish normal life patterns and a renewed sense of control and stability as well as preventing educational disadvantage and decreased career/job opportunities for the future [49]. In young adult survivors of childhood brain tumors, in addition to positive affect, community integration and to a lesser extent vocational identity have been identified as important contributors to overall satisfaction with life [50]. Lower educational attainment and unemployment, among other variables, have also been identified as risk factors for psychological distress and poor health-related quality of life (HRQL) [51], highlighting the importance of attendance at school and work both early and later in the cancer survival trajectory.

In the United States and the United Kingdom, state and local school districts are required by law to provide a free, appropriate elementary and secondary education in the least restrictive environment for all young people needing special attention/education, including students with cancer or a cancer history whose medical problems might adversely affect their educational performance [52]. For those whose physical conditions place them at risk of further health problems, homebound or hospital-based education may be necessary. When possible, however, preference should be given to the regular school environment and, if this is not possible, the hospital-based school [49].

With regard to educational achievement, employment, and living situations, studies indicate that most patients and survivors are functioning well and leading normal lives [53–57]. Yet, many young adult cancer patients and survivors report having experienced restricted role function or problems at work and in daily activities, including social discrimination and rejection in employment and military opportunities [56, 58–63]. Some also experience difficulty maintaining or obtaining independent or family-based health insurance, encounter financial strain, and attain lower income levels when compared to other noncancer groups [32, 56, 58, 64, 65]. In the United States, lacking health insurance has been reported as a barrier to receiving any medical care among AYAs with cancer, as well as influencing educational and work outcomes [63, 66], further discriminating against a potentially vulnerable population.

Subsets of survivors also experience impaired achievement in education, employment, and social and family goals when compared to others [56, 62, 67–69]. Particularly, central nervous system (CNS) tumor patients/survivors and leukemia survivors treated with cranial radiation are much less likely to complete high school, attain an advanced graduate degree, or follow normal elementary or secondary school paths when compared to survivors of other cancer types and to healthy controls [62, 68, 70]. CNS tumor survivors also are more likely to be unemployed, have a health condition that affects their ability to work, and enroll in learning disabled programs [62, 71]. In the Childhood Cancer Survivor Study that monitors a multi-institutional epidemiologic cohort of over 16,000 survivors, comprised mainly of young adults, the use of special education services was reported by 23 % of survivors in comparison to only 8 % of siblings, with the greatest differences observed among female survivors who were diagnosed before age 6 years and most notably among survivors of CNS tumors, leukemia, and Hodgkin's disease [72]. In many areas, school reintegration programs provide advocacy training for parents of adolescents with cancer. However, there is a need to create similar programs for educational and vocational efforts for young adults [40].

23.5 Interpersonal Issues

23.5.1 Relationship with Parents

Literature suggests that seriously ill young people tend to become more dependent upon their parents, at least temporarily. For AYAs, this may involve regression from recently achieved independence into a prior dependent relationship. As young people with cancer try to deal with or discuss the illness with their parents, they sometimes discover that they have quite different coping strategies. Just as symmetry in coping strategies is an important factor in spousal interaction, it affects child-parent interaction as well. Parents may want to discuss issues with their children that the children do not wish to discuss, or vice versa, perhaps because doing so evokes issues or feelings that for so long have been buried in the past. Parents also may express or manifest emotional distress quite differently than their children. Some young people with cancer desire to protect their parents and not share their deepest worries with them, perhaps out of guilt for what their parents are going through or perhaps just because they can see how upset their parents are [12, 73].

23.5.2 Relationships with Peers

Normalcy and belonging to a peer group are paramount, yet the onset of illness and treatment side effects makes the AYA patient feel and look different. The loss of normalcy in terms of appearance, body integrity and daily activities may be of greater concern for the adolescent than the potential loss of life [74]. Opportunities for socialization with healthy peers and other AYA cancer survivors have been reported as helpful in coping with cancer [22, 75]. Problems with establishing close interpersonal relationships have been reported among long-term survivors and appear to be associated with longer duration of treatment and more recent illness [76]. Gray [77] reports that cancer survivors describe improvements in social relationships (as compared to controls) but also feel greater disappointment in those relationships, suggesting that this disappointment may be a result of having higher expectations of those relationships. Indeed, a common theme arising out of survivor meetings and present in the medical literature is the notion that prior social networks may fail to provide the type or kind of support that long-term survivors seek and may even cause additional stress [78].

The transition from dependent to committed, relationships that are reciprocal and mutually supportive, has been identified as an important component of the "emerging adulthood" life stage, defined as being between age 18 and 25 years [79, 80]. Satisfying intimate relationships are an important part of HRQL and require social interaction of one form or another to develop and thrive. Although adolescents with cancer may be thought of as being more socially isolated than their healthy peers, empirical evidence does not support this assertion. In general, adolescents with cancer have been shown to be similar to peers on numerous dimensions of psychological and social functioning [81]. However, AYAs with cancer commonly experience changes in friendships and a sense of isolation from friends due to lengthy time away from home, school, or work for treatments, and many friendships may fall by the wayside over time [82, 83]. Specifically, AYAs report feeling that some friends are no longer able to relate to their life situation and get uncomfortable continuously talking with the patient about cancer, resulting in feelings of being "different" and apprehensive about forming new friendships [82, 84]. Consequently, many of these young people form (or would like to form) new friendship circles, often with other cancer patients and survivors with whom they feel can relate to their current life situation and past experience with cancer.

According to Heiney [85], studies have found that there is a lack of knowledge about the anatomy and physiology of reproduction among adolescents generally. This comes at a time when most adolescents display heightened curiosity about sexuality, and some begin to experiment with intimacy and sex. Reviewing the impact of cancer treatment on sexuality, intimacy, and relationships, Thaler-DeMers [86] suggests that the issue of sharing one's cancer history with a new partner is particularly salient to a young adult survivor population, and Roberts et al. [15] report that relevant issues arising in a group intervention study among young adult survivors included concerns about fertility and raising children. With regard to family planning, Schover and colleagues [87] identify salient relationship-oriented concerns for young adults, including infertility, reproductive problems, desire for children in the future, sperm banking, concerns about offspring's' health and genetic risks, pregnancy concerns and complications, and attitudes about having children after cancer.

23.5.3 Relationship with Children

In the United States, approximately 1.5 million cancer survivors have almost 3 million children, and a third of these live with a parent who is beginning treatment for their cancer [88]. Parental cancer may pervade all aspects of family life with significant changes in living patterns, roles, and relationships [89], which may impact on parents' ability to attend to both emotional and physical

needs of their children [90, 91]. It is important to include child-centered interventions for AYAs to help families and children cope with the effects of parental cancer. "Yet to date, no studies have been published which evaluate child centered psychosocial interventions designed specifically for children dealing with parental cancer" (Wonders and Worries website). Children of a parent with cancer have been shown to be at risk of psychological and social difficulties [92, 93], which may in part be due to the perception of family dysfunction [94]. A recent literature review of the experience of parents with young children, following a diagnosis of cancer, identified three predominant themes, namely, being a good parent, informing their children of their own diagnosis, and maintaining routine at home [95]. Support and application of resources aimed at improving parents' perceived lack of confidence and communicating skills when talking to their children about cancer may promote family coping and facilitate improved family functioning [96].

A recent 5-year evaluation of a program for children with parents who have cancer has demonstrated that participation has had an impact on the children's anxiety, difficulty communicating about the illness, and disturbed sleep as well as family stress reduction (Wonders and Worries). Programs like Wonders and Worries and CLIMB Support program provide concurrent group-based programs as well as special events for parents, children, and teens. Wonders and Worries also provide bereavement support to families led by trained child life staff to help the child process their loss and express their emotions as needed.

23.6 Emotional Issues

23.6.1 Psychological Distress

Recent reports suggest that AYA's needs for psychosocial support to respond to the physical social and psychological challenges faced with diagnosis and treatment of cancer are not being met [31, 97, 98], with many AYAs unaware of what psychosocial services are available [99]. Significant distress among AYAs with cancer vary, ranging from 6 to 41 % in independent cross-sectional studies with varying sample sizes, age ranges, timing of data collection, and tools utilized [97, 100–103]. In a recent longitudinal study, clinical distress was present in 27 % of AYAs in the first year following diagnosis, and its presence did not appear to be related to cancer type or gender but may be related to pre-diagnosis mental health history [103]. This is significantly higher than in noncancer patients in whom the Centers for Disease Prevention and Control reported a 3.1–4.0 % prevalence of serious psychological distress and a 8.3–10.2 % prevalence of depression among young people aged 18–44 years in the United States in 2008 and 2009 [104].

AYAs may suffer from a wide range of psychosocial adjustment difficulties, such as delayed social maturation, altered body image, mood disturbances, academic difficulties, job and insurance discrimination, increased health concerns, relationship problems, and worries about having children [105]. Comparative studies have demonstrated significantly greater psychological distress in young adult survivors of childhood cancer than in various comparative groups when measured using standardized psychometric scaling techniques [64, 73, 106].

In contrast, a number of other investigators demonstrate that in the aggregate, AYA cancer survivors score in the normal range on standardized psychometric measures and live normal social lives with no evidence of significant mental or emotional distress, thereby being quite similar to peers without a history of cancer in terms of their psychosocial adjustment and quality of life [55, 107–112].

In some instances, psychological and quality of life outcomes among young adult survivors are the same as, if not better than, among comparison populations [57, 113–116]. In a study of young adult survivors of childhood leukemia and lymphoma, Gray and colleagues [107] indicate that, compared with peers, survivors reported significantly more positive emotional health status, less negative mood or affect, a higher motivation for intimacy (i.e., thinking about others, concern for others), more perceived personal control, and

greater satisfaction with control in life situations. Maggiolini and colleagues [117] showed that teenagers cured of leukemia showed a more positive and mature self-image when compared to student peers. In general, the psychosocial literature on survivors of pediatric cancer suggests that cancer universally alters the way survivors view themselves and that these alterations can be positive *or* negative and both positive *and* negative [105, 118, 119]. Salsman and colleagues [119] found that while AYAs with cancer reported poorer physical and emotional well-being than matched healthy controls, the same was not true for social well-being which was reported as higher in the AYA group. Adolescents, in particular, have reported a sense of relief upon completion of therapy but also ambivalence related to perceived loss of social ties (i.e., with other adolescents with cancer, with healthcare providers who have come to know them, with the healthcare system) and fears of life without the protective "crutch" of effective treatment [120].

Studies related to psychological distress in AYAs vary substantially in their theoretical frames, inquiry methods, and samples of informants. By examining them in the aggregate, a reasonable summary argues that some young adult and childhood cancer survivors have managed to grow in positive ways as a result of their cancer experience; most probably are relatively normal in psychosocial terms and on most psychosocial measures, and an important minority experience ongoing psychological and/or social adjustment problems. Moreover, most survivors, even those apparently doing quite well, continue to be concerned about the physical, psychological, and social quality of their current and future lives.

23.6.2 Post-traumatic Effects

The emerging literature on stress, threat, and trauma provides a different paradigm for examining and understanding emotional responses to life-threatening situations like cancer. The conceptualization of cancer as a psychological "trauma" has furthered our understanding of the long-term psychological effects of cancer and its treatment [121], with studies assessing symptoms of post-traumatic stress in AYAs with cancer or young adult survivors of childhood cancer indicating that anywhere from 10 to 30 % meet criteria for post-traumatic stress disorder (PTSD), and an additional proportion meet criteria for at least one trauma symptom [122–129]. Because of the unique characteristics of cancer, stressors may be both acute (e.g., diagnosis) and chronic (e.g., treatment, late effects); symptoms of post-traumatic stress may emerge differentially over the course of cancer [5]. Kwak et al. reported that a greater number of side effects were associated with higher levels of post-traumatic stress symptoms (PTSS) at 6 months while currently receiving treatment, having surgical treatment, diagnosis of a cancer type with a 90–100 % survival rate, remaining unemployed/not in school, and greater PTSS at 6 months were associated with higher levels of PTSS at 12 months after diagnosis, the latter suggesting early intervention may impact on later symptoms of PTSS [5].

For more long-term survivors, reporting symptoms of post-traumatic stress appear associated with survivors' retrospective subjective appraisal of life threat at the time of treatment and the degree to which the survivor experienced that treatment as "hard" or "scary," as well as with general anxiety, history of other stressful life experiences, less time since end of treatment, female gender, and lack of family or social support. There is compelling experience from a single-arm study that Internet-based cognitive behavior therapy may decrease PTSS and anxiety in AYA survivors of childhood cancer and that this decrease is maintained, at least in the short term. However, this efficacy requires confirmation in a randomized trial setting [130].

A relatively new trauma paradigm raises the possibility that some people may not just survive such stress and trauma, but that they may "thrive" or achieve "post-traumatic growth" (PTG) as a result, and they may create or experience a higher quality of life than prior to the stress [131–134]. As Folkman and Greer [135] argue, the focus on "psychiatric symptoms, such as anxiety and depression…obscures the struggle for psycho-

logical well-being and the coping processes that support it," and Paterson et al. [136] discuss how some people can transform their lives by responding to an illness in ways that enhance the quality and meaning of their lives. Some cancer survivors report positive growth as a function of how they and their families dealt with their illness and appear significantly better adjusted psychosocially, in comparison with population norms or healthy controls groups [113, 137, 138]. Even so, these young people still worry about their physical health status, their self-esteem and identity, their immediate family's welfare, relating with the social world and being "different," reintegrating with the school system, possibilities for the future (including access to life and health insurance, jobs and career options, and understanding genetic compromises stemming from treatment), and continued care from a skilled and attentive medical system [139–141].

23.6.3 Coping

AYAs have been described as utilizing an active behavioral coping style, in that they will actively seek and use information and support when needed [103, 142]. Research has addressed factors and variables associated with coping and adjustment among AYA cancer patients and survivors. For example, positive thinking or maintaining a positive outlook on the future is commonly reported as a coping strategy for AYA cancer patients and survivors [38]. In a quality of life assessment of 176 AYA survivors, Zebrack and Chesler [143] observed that having a sense of purpose in life and perceiving positive changes as a result of cancer were associated with good quality of life.

Some investigators have suggested that the above-described aspects of positive adaptation or meaning-making may in fact suggest that denial is a common coping style among AYA patients who maintain a positive outlook for the future [138, 144, 145]. However, AYAs with cancer can experience positive self-images and life outlooks without necessarily "denying" their true condition or fears [146]. Clearly, patients' and survivors' denial of their problems associated with cancer treatment (e.g., treatment refusal and noncompliance, ignoring signs of relapse or infections, engaging in health risk-taking behavior) is unproductive and maladaptive, but denial of some of the discomforting emotions associated with cancer (anxiety about recurrence, worry about peer acceptance, obsession about a healthy long-term future, feeling like a victim) may be very adaptive and productive. In these instances, denial may even lead to the adoption of disease-preventing and health-promoting behaviors or the assumption of a positive life future and possibility of long-term personal growth. Yet, gaining knowledge of one's cancer treatment and related effects also has been shown to be associated with positive adaptation and coping [34].

Skill-building interventions as a way to cope with cancer, treatment, and long-term effects appear to be a promising therapeutic approach [17]. Although few evidence-based interventions for AYAs have been implemented that teach new skills such as problem-solving [16], cognitive-behavioral therapies (CBT) [147], and stress management [148], this form of therapeutic intervention is likely to be instructive in addressing the unique needs of AYAs [16]. The efficiency of CBT in treatment for both anxiety and depression has been reported in adolescents without cancer [17]. Using a video-conferencing delivery method, Recapture Life is a new online skill-based intervention to help AYAs to transition to survivorship. These researchers found that AYAs respond positively to a CBT skilled-based intervention [147].

Preliminary outcomes of a pilot project on telephone-delivered coping skills training (CST) found HERO'S PLUS CST for AYA survivors of childhood cancer and their parents has clinical relevance for long-term follow-up and suggested that telephone-delivered psychosocial care is a practical means to deliver care to AYA [43].

23.6.4 The Importance of Social, Peer, and Family Support

During a period of time in which individuals increasingly experiment with and seek relationships and social support, a diagnosis of cancer

has the obvious potential to subvert normal AYA development. At the same time, a perception of high levels of social support can help teens and young adults with cancer cope with their illness and overcome the feeling that they are alone. Kyngas [34] found that social support was the major coping strategy used by adolescents to deal with cancer, with support coming from family, friends, and healthcare providers. Family and friends are most commonly reported as the major sources of social support by AYA patients [34, 149]. However, social support groups may also provide an important source of support for AYAs treated for cancer [150]. For some AYAs, meeting with others of the same age with cancer has been reported as being more helpful with coping than support from family and friends [151].

23.6.5 Family Support

Several studies identify family support and cohesiveness as the most important contributor to positive adjustment [152] and family functioning as the single best predictor of distress, with poorer family functioning predictive of greater distress [153]. There is also strong evidence that cancer is a dyadic illness shared between AYAs and their caregivers and that interventions should target this dyad rather than treat as independent individuals [154]. Whether caregivers are parents, spouse, or even siblings, psychosocial interventions for all family members should be integral in provision of supportive care services.

Research on patients with chronic illness found that interventions directed at changing illness perceptions can improve self-management behaviors. Efforts to provide such intervention should be routine not only for the patient but the caregiver. Thus, efficacious psychotherapy interventions may require consideration of both patients' and caregivers' perceptions of illness severity [154].

Given the relationship between maternal adjustment and the patient's, interventions to assist parents and families are highly recommended [149]. Parent support groups are important and may mitigate psychological distress in parents and subsequently their children [8]. Kazak's work on PTSD suggests that trauma-informed psychosocial interventions can be used to help patients and families, including normalizing the experience as potentially traumatic and using evidence-based interventions that are emerging to facilitate long-term well-being [155]. Maternal problem-solving therapy and other highly focused and educational therapies have been effective in decreasing distress and anxiety [10]. Other interventions designed for caregivers focus on developmentally specific stressors, such as how to talk with your teen about body image or how to empower your teen, which helps improve communication [10].

However, while young adults may share information about their condition with family members to allay their mutual concerns, they also may filter information that they felt would burden their family with excessive worry leaving some issues unexplored [156].

23.6.6 Peer Support Interventions and Support Programs

The experience of an illness like cancer is a profoundly social one [157]. Given the significance of peer relationships during adolescence and young adulthood and the reality that a cancer diagnosis may lead to physical and emotional isolation, peer-based interventions can play an important role in development and psychological adjustment [158] and decreased distress and anxiety [159].

Social interaction may take many forms including face-to-face weekly meetings, online groups, weekend retreats, conferences, and adventure therapy trips and is important in promoting the successful achievement of age-related developmental tasks [20]. Actively seeking support also has been demonstrated to be associated with positive adjustment [34, 160], and participation in social support groups may help to reduce stress and anxiety and promote an active lifestyle for AYAs with cancer [150, 159].

There are many benefits to peer group intervention. Group interaction in various peer support

programs allows members to feel that they give as well as receive, which can serve to enhance self-esteem, lessen feelings of powerlessness, and give meaning and purpose to the illness experience [161]. The opportunity to share with others provides a sense of community and reduces the sense of isolation so common among cancer patients [14, 16]. Modeling of coping skills and sharing information occur through interaction between young people at different stages of the cancer continuum [16]. Moreover, the use of groups for adolescents can give them an opportunity for peer reinforcement not otherwise available. This is particularly significant for adolescents given the fact that their mode of coping is often associated with support from a peer group [74].

Most studies on therapy groups for adolescents are qualitative and descriptive but in general show that group interventions can be effective [13–15, 74, 162]. Peer-based support groups foster normalcy and encourage independence. A support group had been found to broaden the range of coping strategies for members when compared with those who did not participate in the group [163]. Peer support programs help members feel more in control by providing an avenue to impart information, teach coping strategies, and encourage young people to take on more decision-making on their own [20]. This is particularly significant for adolescents. Byrne et al. found common themes in two adolescent groups that included fear of treatment and procedures, life controlled by illness, changes in physical appearance responsibility to be strong, and developing a life and death philosophy [13]. Ross observed that adolescents who are associated with others having similar medical conditions were more successful in developing positive self-images [2]. Given the fact that the adolescents' mode of coping is often associated with their support from a peer group, organized but informal groups can play an important role in this area.

From a developmental perspective, young adults may find that social ties with same-age peers with cancer may be more beneficial or different than the support from family and friends [151]. Support group intervention facilitates young adults' adjustment to cancer, and talking about their cancer experience helps them develop tools for promoting communication [15]. Despite this, there remains a lack of psychosocial interventions designed to assist young adult survivors in communication with their partner and learning new communication strategies [164].

Despite the many benefits, there exists a perception among oncologists and parents that attending support groups and revisiting the cancer experience may be maladaptive and prevent survivors from integrating with other so-called "normal" peers. Yet, there exists no empirical evidence to suggest this is the case. In contrast, Roberts et al. reported the results of support group intervention for young adults that led to improvements in well-being [15]. Topics covered included anxiety about health and physical well-being, worry about fertility and raising children, relationship problems, financial concerns, and body image. The authors noted that the group quickly developed a level of cohesion and suggested that the quickness and ease with which this happened were demonstrative of the need and desire for support among participants.

Although support and therapy groups are helpful for some, many AYAs have little or no interest in attending such groups [16]. Camps, retreats, adventure therapy programs, and annual events and activities organized through online communities formed by AYAs to meet other AYAs have an appeal for those who want to participate in experiences that make them feel normal.

A camp style format that provides informal activities rather than more formal discussion appeals to the younger range of this age group. Studies on effectiveness of camping programs suggest that this type of program can enhance a cancer patient's self-esteem as well as improve family communications [165]. This line of research was extended in two studies of adolescents with cancer who participated in a summer camp [166, 167]. These researchers found that camp participation improved adolescents' knowledge about cancer, even in the absence of formal educational programs. They also found that rela-

tionships formed at the camp were maintained after camp itself. Their key finding was valuable in bringing about better quality peer relationships and a higher degree of knowledge about the medical and psychological aspects of cancer.

Both adolescents and young adults can benefit from camp-like experiences with a conference format. In addition to developing important social ties and gaining knowledge and information about their illness and treatment, these camp-like experiences include educational, advocacy, and social skill building workshops that promote successful achievement of age-appropriate developmental tasks [168]. Throughout the year, 4-day conferences at Camp Mak-A-Dream are offered for young adult childhood cancer survivors and AYAs with cancer. Young adults who had been diagnosed with a brain tumor were found to benefit from a setting removed from parents, daily limitations, and time constraints. The importance of a playful setting was particularly evident for young adult brain tumor survivors [169].

Adventure therapy has been viewed as a positive experience with multiple benefits [170, 171]. It is a way to learn an extreme skill and to challenge one's self to push past perceived limitations and can be transferred to life beyond the adventure experience. These types of programs for young adult cancer survivors have been reported to decrease depressive symptoms [171] and increase self-efficacy, self-confidence, independence, self-esteem, and social contacts [172]. Trips serve as a catalyst for future group activities and group support [171].

Overnight retreats and workshops are another format that meets the AYA developmental need for normal peer interaction, independence, and opportunities to share meaningful explorations of the cancer experience such as coping with uncertainty, body image, sexuality, and fertility [161, 168]. Most stay connected and maintain a network of friends like themselves. Teen Impact, housed at Children's Hospital Los Angeles, has been providing 3-day retreats since 1989 for adolescents 13–19 years of age who are on or off cancer treatment. Retreats promote peer relationships through the integration of informal activities, structured self-expression workshops, and professionally led psychosocial discussions and activities. A unique feature of the model is involvement of young adult childhood cancer survivors as retreat counselors and co-counselors.

A relatively new model of group support manifested through social networking opportunities has become popular. These organizations formed online by AYAs offer age-relevant opportunities to meet face-to-face at events and regularly scheduled activities. These social networking events appeal to AYAs' sensibilities and have been successful in building a very large and growing community of AYA patients, survivors, and family members [16].

Online peer groups offer viable support options for AYAs with cancer [20, 173], yet little research has been completed on the use of groups on the Internet for this population [174].

There are many benefits to online group interventions that are not necessarily unique to this age group but part of its appeal. These include removal of physical distances [175], lower cost to support a potentially greater number of patients [176], ease of and lack of financial burden, maintaining anonymity while still offering support [175], and the argument that it can be less confronting and participants find they are less emotionally exposed [177]. In general, online groups offer more flexibility and convenience [20]. The potential of the web means it is possible to develop support groups for a specific age range, with a specific cancer and diagnosis.

Online groups however present many challenges that include technical problems, the limitations of communicating without nonverbal clues, discomfort with reading and writing and committing feelings to words, lack of established norms as a result of transient membership, risk of inaccurate information, and concerns about privacy. These challenges underscore the importance of the moderator's role in facilitating group process and managing potential conflict [20]. A study of the challenges faced by online facilitators found interpretation of tone and emotion and ebb and flow of membership affected the success of the group [178]. There is a fear that overuse of online groups may increase isolation for AYAs

and that the level of distress may increase when a member fails to log on for a long period of time [179].

23.7 Existential/Spiritual Issues

In the face of a life and death diagnosis which is rare and totally unexpected for people their age, AYA patients and survivors also experience a sense of existential crisis, a challenge to their sense of the normal order of things and the way they have assumed the world should work. Their faith in the continuity and predictability of life obviously is threatened. Especially because the precursors of adolescent and young adult cancers are largely unknown to the medical and scientific community, patients often experience a high level of uncertainty about their current and future place in the world.

23.7.1 Uncertainty

Uncertainty has been defined by young people with cancer as more than living with the unknown but also as not knowing what to expect [180]. Survivors in their teens and young adult years also suggest that while uncertainty can be a source of distress, it also can be a catalyst for personal growth, a deepened appreciation for life, greater awareness of life purpose, development of confidence and resilience, and optimism [181].

Having a positive life attitude, belief in one's own resources, belief in God, earlier positive life experiences, and willingness to fight against the disease also have been identified as important resources for coping with cancer [34]. Nichols [182] reports the use of spiritual support as a coping behavior for teenage patients, but waning in use as the length of illness increased. Many young people report their religious faith tested by the cancer experience; most who experience such a test report that their faith has been strengthened by their experience, if not by the fact that they survived. Others, with or without a strong religious orientation or commitment, report a greater sense of existential clarity, a form of psychospiritual adaptation and growth that takes the form of knowledge about the meaning and purpose of their life, a sense that God would not give them more than they could handle, and a willingness to accept the uncertainty of life [180, 181].

Reflecting the notion that "a positive future exists for oneself," the concept of hope has been investigated in AYA patients, with findings indicating a positive association between being hopeful and psychosocial adjustment [183]. In an investigation involving 8–18-year-old patients, increased hopefulness and decreased feelings of helplessness were the most important factors associated with positive coping and decreased anxiety [184], with hopefulness reflected in patients' comments about attending school, future careers, and marriage.

Conclusion

AYAs with cancer often report a desire for more information about their diagnosis, prognosis, treatment, and potential short- and long-term effects. These desires are often not expressed to the medical staff or parents and thus often go unmet. Moreover, young people with cancer often do not share with their parents the full extent of the pain and anxiety they experience during the treatment process. They observe and understand their parents' distress and often hide their own concerns in order not to further worry or add to their parents' strain.

In addition to anxiety about the future course of medical treatment, young adult survivors of childhood cancer report worry about body image, sexual identity, and fertility. Such issues are part of a normal developmental process in this age group but become more potent in the context of a serious and chronic illness. Moreover, these concerns may be further escalated in the case of unsettled peer relations, as absence from school during treatment often changes the young person's relationships with former friends and neighbors. For some, school absence results in educational disadvantage and delayed preparation for higher education or career progress. The same holds true for young adults in their work and

social worlds, where employment becomes disrupted, where they may be subject to prejudice and discrimination, and where young adults feel uncertain or burdened about how much to disclose about their cancer to employers, co-workers, and friends.

There has been substantial progress in the understanding of the psychosocial aspects of AYA cancer in the past 5–10 years. In the long run, the majority of young adult cancer survivors appear to be psychologically well adjusted even when acknowledging visible and limiting physical effects of treatments. Overall, these young people experience emotions and behave in ways that are normative for this age group. On the other hand, a substantial minority experience post-traumatic stress, a form of emotional and psychosocial disability requiring psychological counseling of some form. An important minority appears to experience post-traumatic growth and is able to transform their lives in ways that represent more positive outlooks and competencies that one would have expected prior to their diagnosis and treatment. Given the full range of these responses, including the possibility that some teenagers and young adults surviving cancer can exhibit signs of greater emotional stability and security, intervention programs that historically have focused on alleviating stress and preventing negative outcomes (such as post-traumatic stress symptoms) must be complemented by programs focusing on promoting successful achievement of age-appropriate developmental tasks and positive psychological and emotional growth.

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24 Sexual Consequences of Cancer and Its Treatment in Adolescents and Young Adults

Louise Soanes and Isabel D. White

Abstract

Sexual difficulties arising from cancer and its treatment remain a neglected aspect of survivorship within the adolescent and younger adult age group. This life stage is important in the development of sexual identity and orientation, sexual expression and function and intimate relationship formation. Hence, the impact of serious illness and treatment can be highly disruptive, leading to immediate- and longer-term/delayed physical, psychological, interpersonal and thus psychosexual consequences.

This chapter adopts a biopsychosocial model to address the aetiology, assessment and management of commonly encountered sexual difficulties in AYA oncology, including loss of sexual interest (desire), sexual pain, erectile dysfunction and ejaculatory and orgasmic changes.

The chapter concludes with recommendations for improved service provision within cancer centres and a greater focus on intervention research to raise the profile and standards of care for this aspect of people's recovery and lives after cancer.

24.1 Sexual Development from Childhood to Early Adulthood

24.1.1 Human Sexual Development

Human sexuality is a complex interaction of biology, sex, gender, culture and behaviour, and successful sexual development throughout childhood and adolescence is said to facilitate optimal life as an adult [1].

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Bancroft's [2] model of sexual development distinguishes three strands of sexual development, gender identity, sexual response and the capacity for close, dyadic relationships; however, cultural aspects also affect human sexuality [3]. These multiple factors combine to create the context when considering the development of human sexuality and provide a framework for understanding, not only the biological and behavioural attributes of human sexuality but also the cultural interplay.

24.1.2 Childhood Sexual Development

24.1.2.1 Childhood

Understanding sexual development in childhood and preadolescence is said to be increasingly important in order to understand 'normal' sexual development in adolescence and adulthood [4, 5]. This development starts before birth – babies in utero have been observed touching their genitals and within 24 h of birth vaginal lubrication and erections seen [6]. In the exploration of their own biological identity, infants touch their genitalia and as young children (2.5–3 years of age) openly fondle their genitalia as a natural form of sexual behaviour in the manner associated with adult masturbation [6]. Childhood play often explores gender identity through socialisation with others and in adult gendered roles but also allows freedom to experiment in cross-gender roles [1, 7]. As childhood progresses, sexual exploration and play continues but becomes more clandestine as children become more aware of the cultural norms attributed to sexual behaviour [8, 9].

24.1.2.2 Preadolescence

As children approach adolescence (8–10 years of age), they tend to organise themselves into homosocial (same-sex) groups [1]; therefore, sexual exploration and learning often involves peers of the same gender. Children at this life stage gain experience with masturbation; in their study, Bancroft et al. [10] identified that 38 % of men and 40 % of women recalled masturbating before the onset of puberty. At about 10–12 years of age, the first experience of sexual attraction occurs, followed by sexual fantasies approximately a year later [7, 10].

Behavioural changes, accompanied by the biological changes of puberty, e.g. group dating and mixed group parties, begin the process of forming and sustaining intimate relationships, a key task of adulthood [7]. At this time talking about sex, kissing and hugging and exposure of genitals are most common up to the age of 12 years [7, 11], and sexual experiences with oral-genital contact, vaginal or anal insertion with an object or finger and vaginal or anal intercourse are unusual [4].

24.1.2.3 Adolescence

During adolescence, increased testosterone and oestrogen levels and other biological factors and behaviours create opportunities for sexual interactions that facilitate or inhibit sexual expression [12]. Behaviours can reflect a key psychosocial task of adolescence – in the transition from role confusion to self-identity [13], both gender and sexuality are important. Achieving a sense of gender can occur for some adolescents; for others, the conflict remains into adulthood; sexual identity can also mirror confirmation or remain [14].

Sexual contact with partners may now include experimentation with foreplay behaviours such as erotic stimulation, touch and massage. Towards middle to late adolescence, a higher number of young people report having heterosexual intercourse [1]. Bancroft et al. [2] report that 2 % of adolescent males and 10 % of adolescent females report same-sex encounters during adolescence. As part of the increasing individualisation of identity formation, many in their late teens and 20s manage the emotional and intimate aspects of relationships through the media, social media and the Internet as the source of information on sex and intimacy rather than peers or parents [15, 16].

Although sexual experimentation and sexual activity are part of normal social and emotional development at this age [12, 14], the sexual experiences of adolescents are disproportion-

ately from the stance of the negative consequences of sexual activity [17, 18]. An example of this is sexting – the act of sending sexual messages, videos or photos via a cell phone or Internet [19]. One of the first and most commonly cited studies on sexting was conducted by the National Center for Injury Prevention and Control [20]. Using an online sample of 1,280 respondents (653 13–19-year-olds and 627 20–26-year-olds), 20 % of the 13–19-years-olds had sent or posted nude or semi-nude pictures or videos of themselves. The majority of these images were sent to partners, some were sent to someone the teenager wanted to date and 15 % to someone the sender only knew online. Sexting has received much media and academic attention as an example of adolescent risky [21, 22] and criminal sexual behaviour [23, 24]. Whilst the negative impact of exploitation, bullying and harassment mediated by sexting cannot be ignored, the meanings AYA apply to the practice in the context of their sexual development, experimentation and consensual use of technology require further attention [19, 23].

24.1.2.4 Young Adulthood and Adulthood

The process of sexual maturity continues in adulthood. In young adulthood the task of forming stable and intimate relationships [24] involves learning how to communicate with partners [25]. The development of self-identity in the context of sexuality and gender continue to be explored through different sexual encounters; these may be casual dating and sex or sexual activity limited to emotionally intimate, committed, monogamous relationships [26, 27]. Practical decisions are also made: the choice of contraception, the prevention of sexually transmitted diseases and when and if to become a parent [25, 26, 28]. Not all young adults choose or achieve a sex life; for some, celibacy is chosen or occurs; nonetheless, they retain their sexuality and a sexual identity [29].

For those in relationships or sexual partners, satisfaction with sexual relationships is an important component of sexual health. Couples experience fundamental changes in their sexual experience at least once in their relationship [29, 30]. Changes may result from developing greater understanding of self, others, communication difficulties, stressors external to the relationship, illness or accident [31]. Some relationships will grow through these events; others require professional help and some may not survive [1].

24.2 Gay, Lesbian, Bisexual, Transgender and Questioning

Individuals become aware of same-sex attraction very early in their life, even younger than puberty; however, they can acknowledge or act on this at any point in life [32]. However, since dating and relationships begin in adolescence, self-identification as being gay, lesbian, bisexual, transgender or questioning (GLBTQ) often occurs at this time [33]. Adolescent and young adults with cancer who are LGBTQ have similar health and sexuality concerns as their peers, however, coming-out at this time can be an additional challenge. This requires healthcare professionals to be aware of the potential discrimination and bias against sexual and gender minorities these young people may face during treatment [34].

24.3 Defining Sexuality and Sexual Function

Throughout this chapter, the terms sexuality and sexual function are used; these terms are defined as follows:

Sexuality has been defined in many different ways: the way in which individuals experience and express themselves as a sexual being, the awareness of gender, sex and the capacity for erotic experiences and responses [35]. Sexuality is an essential part of self, with or without sexual intercourse [36]. As an individual's view of themselves and others as a sexual being is influenced by their culture, ethnicity, society and religion, sexuality also encompasses peoples' relationships with others. The latter is sometimes spoken of as intimacy, a term often equated with privacy and closeness, but in the context of

human interactions, intimacy involves disclosure and responsiveness [37].

Sexual functioning can be seen as an individual's behavior as a sexual being and can be further deconstructed to the four phases of the human sexual response cycle (desire, arousal, orgasm, resolution) [38]. As sexual functioning relates to sexual behaviour, it may also be accompanied by sexual difficulties when behaviour does not or cannot follow its usual expression. [2]. The combination of sexual function and sexuality can be equated to sexual health [35].

24.4 Sexual Difficulties in Adolescents and Younger Adults

There are clearly significant global variations in sexual concerns and difficulties experienced and reported at the general population level. For countries fortunate enough to be able to offer comprehensive cancer treatment and aftercare, the prevalence and type of sexual difficulties commonly experienced by healthy young adults are important contexts for service provision regarding the sexual consequences of cancer and its treatment.

A recent UK-wide survey of 15,162 men and women aged 16–74 years (response rate 57.7 %) explored the nature and prevalence of self-reported sexual difficulties among age groups 16–24 and 25–34 years [39]. The study used computer-assisted face-to-face interviews in people's homes to deliver a validated outcome measure (Natsal-SF) specifically designed for this large public health survey. The Natsal-SF measured people's self-reported difficulties related to individual sexual response, sexual function within a relationship context, and self-assessment of sex life, resulting in data from 4,913 men and 6,777 women.

In the absence of prior measures of low sexual function for non-clinical populations, low sexual function was defined by researchers as the lowest quintile (20 %) of the distribution of scores obtained. *Low sexual function* ranged from 14.1 % in 16–24 years age group to 27 % in 65–74 years age group, with the highest rates of sexual difficulty found in the 55–64 years age group (27.8 %). This study found a strong association between low sexual function and age >55 years, menopause, depression, poor self-assessed general health and relationship dissatisfaction [39]. With the exception of age, many adolescents and young adults living with cancer will experience direct and indirect physical and mental health impacts of illness or treatment and are hence more vulnerable to sexual disruption than this age group in the general population [40, 41].

Table 24.1 outlines self-report survey data from young people (age groups 16–24 and 25–34 years) who were sexually active with at least one person in the past 12 months and had experienced a sexual concern or difficulty that had persisted for >3 months in the past year.

As can be seen from this summary, for men the most common sexual difficulties reported were:

- Rapid ejaculation (16.5 % and 19.1 %)
- Lack of sexual interest (11.5 % and 14.5 %)
- Difficulty in reaching climax (9.2 % and 9.8 %)

The prevalence of erectile difficulties reported by this younger age group was low at 7.8 % compared to a rate of 12.9 % in the overall adult male sample [39].

For women, the most common sexual difficulties reported were:

- Lack of sexual interest (24.8 % and 31.9 %)
- Difficulty reaching climax (21 % and 17.2 %)
- Lack of sexual enjoyment (11.3 % and 13.2 %)

The number of younger women reporting lack of sexual enjoyment may reflect those who experienced vaginal dryness (9.6 %) and sexual pain (8.8 %) or who lacked excitement or arousal associated with sexual contact (8.3 %). Table 24.1 also illustrates the fact that even in younger adult populations, it is not unusual to find more than one sexual difficulty affecting individuals at any given time. This finding highlights the

Table 24.1 Percentage of sexually active participants self-reporting problems with individual sexual response lasting 3 months or more in the last 12 months by gender and age group

Type of sexual difficulty	Men 16–24 years	Men 25–34 years	Women 16–24 years	Women 25–34 years
Lacked interest in having sex	11.5 %	14.5 %	**24.8** %	**31.9** %
Lacked enjoyment in sex	5.4 %	6.7 %	11.3 %	13.2 %
Felt anxious during sex	5.7 %	6.3 %	8.2 %	8.2 %
Felt no excitement/arousal during sex	3.3 %	4.3 %	8.6 %	8.0 %
Difficulty in reaching climax	9.2 %	9.8 %	**21.0** %	**17.2** %
Reached climax more quickly than preferred	**16.5** %	**19.1** %	3.8 %	2.5 %
Trouble getting/keeping an erection	7.6 %	7.9 %	**N/A**	**N/A**
Uncomfortable dry vagina	**N/A**	**N/A**	9.4 %	9.7 %
Felt physical pain as a result of sex	1.8 %	1.7 %	9.5 %	8.0 %
Experienced 1 or more of these problems	36.2 %	39.7 %	46.5 %	48.5 %
Experienced 2 or more of these problems	13.6 %	14.9 %	23.0 %	23.6 %

Natsal-3, adapted from Mitchell et al. [39]

interdependent relationship between sexual difficulties that affect different phases of the human sexual response simultaneously [38], hence the clinical importance of thorough assessment and integrated management.

As discussed previously, Fig. 24.1 illustrates the complex interplay of anatomical, physiological, psychological and relationship (interpersonal) mechanisms, any or all of which can be adversely affected by illness and treatment. Hence, the assessment and management of common treatment-induced sexual difficulties in this age group require integration of biomedical, psychological and psychosexual approaches in response to the multifactorial and multiphase impact of sexual changes encountered in clinical practice [42].

24.5 The Global Impact of a Cancer Diagnosis on Sexuality and Sexual Function

A diagnosis of cancer compounds the complexities of AYA development. Sexual health, function, interpersonal relationships and self-image (physical and psychological) are all factors that have an impact on the development of self-esteem during the transition periods into and throughout early adulthood [43, 44]. Adolescent and young adults with a cancer diagnosis report a substantially reduced quality of life compared to their peers without a cancer diagnosis [34], particularly in areas of emotional and social functioning [45, 46]. Recent studies have begun to reveal the complexity of the effects cancer and its treatment can have on AYA sexuality beyond sexual functioning. Young adults with cancer may have problems with body image and poorer sexual self-concept and adjustments compared with healthy peers [47]. Common cancer treatments (chemotherapy, radiotherapy and surgery) impinge on AYA physiological, emotional, psychological and sexual well-being [48, 49] and also heighten areas of distress like pain, fatigue, depression and anxiety [50]. In their study exploring the psychosocial impact of cancer on newly diagnosed AYA cancer patients, Bellizzi et al. [51] found 40.4 % 15–20 year olds reported cancer had a negative impact on sexual function/intimate relationships. Although the cancer experience may disrupt, delay and complicate the process of sexual development it does not always bring it to a halt; sexual identities, desires and practices continue, and relationships show resilience [52].

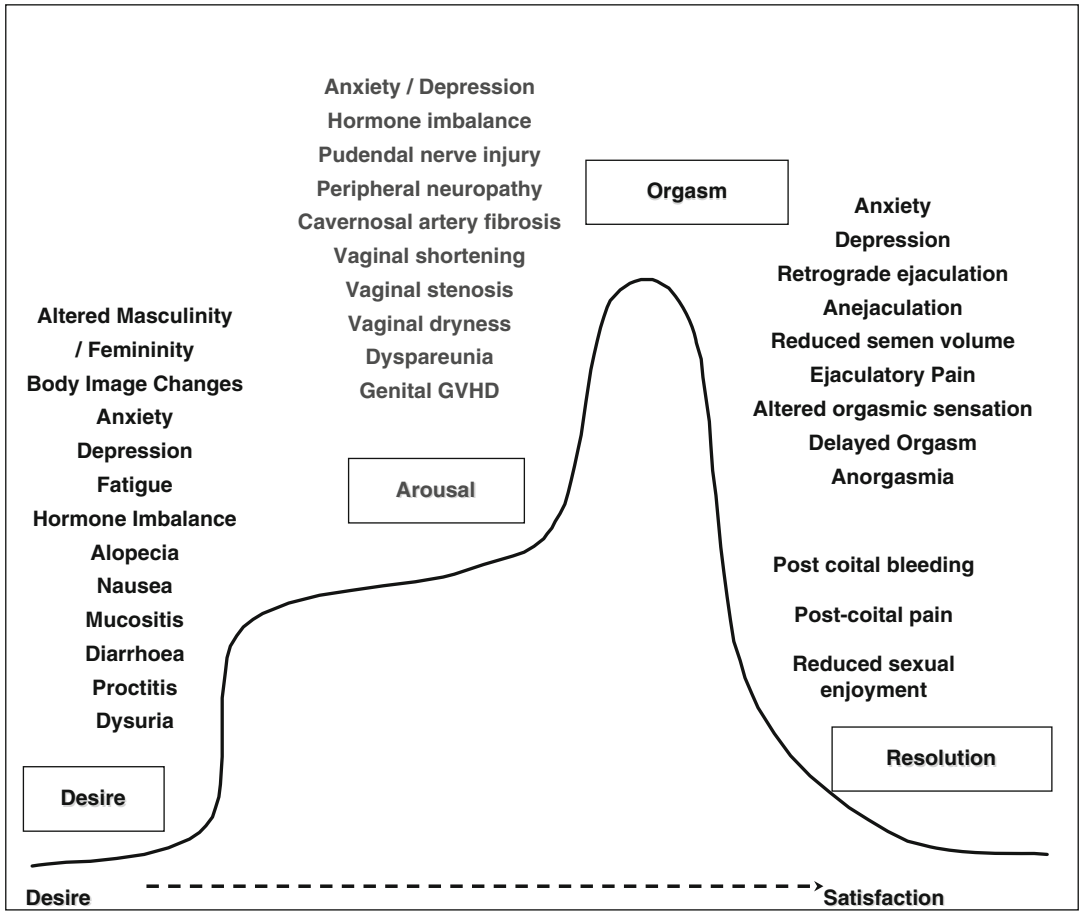

Fig. 24.1 Impact of cancer and its treatment on phases of the human sexual response

24.6 Promoting Sexual Health

Open and frank discussions about sexuality, sexual practices and intimacy are relevant and appropriate areas of psychosocial assessment when working with AYA cancer patients [53]. They are areas that should be revisited not only as the cancer pathway progresses (including palliative and end of life care) but also as the AYA matures during treatment and into survivorship; not all sexual behaviour during AYA is risky, but it is known to be a time of sexual experimentation. Adolescents and young adults need information and support to understand how their sexual behaviour (risky or otherwise) may need to be modified as a result of either their cancer or more likely its treatment.

Contraceptive and sexual health needs of AYA undergoing cancer therapy should be addressed as a separate issue from fertility preservation. The median age for first sexual intercourse is now 16 years in most industrialised countries, and over 50 % of young adults remain fertile after their cancer treatment [54, 55]. Provision of verbal, written, age-appropriate and relevant information should be freely available to AYA cancer patients in a variety of mediums and languages. Many younger patients may find it too confronting or personal to discuss this topic, so the response of professionals should be sensitive, non-judgemental and tailored to individual need of the patient. It is, however, important that professionals working in AYA cancer care receive adequate training on the potential legal, ethical, moral and

boundary management issues they may encounter when dealing with sexual health concerns.

Removal from the context of their normal social and peer network by hospitalisation and decline in physical ability may impact on developing sexuality [44]. The loss of independence, reduced autonomy and forced dependence on parents and others for care and social and financial support reduce self-esteem and self-confidence [56]. The physical side effects of cancer can compound these losses as AYA lose their physical image of self and an alteration in the perception of how others see them. These concepts may individually or in combination potentially impair relationship formation/function, decrease dating opportunities and alter sexual function. Global effects on functional role may also delay education/training, limit lifestyle options and compromise future goals, i.e. partnerships and parenthood. For older adolescents and early young adults, cancer may not only limit experimentation with different sexual partners but also the experience of positive, sexually arousing, intimate sexual relationships that are necessary in order to build sexual self-esteem and confidence [57–59]. Studies show that AYA with cancer differ significantly from peers by reporting lower sexual experience, lower self-esteem and how the fear of being rejected may delay sexual experimentation, dating and consequently the formation of meaningful couple and sexual relationships [57, 60, 61].

After cancer, dating and relationship formation may also be affected by reluctance or fear of disclosure regarding their cancer history [62], body image and sexual difficulties caused by cancer. These can be caused by a combination of the physical impact of cancer, the side effects of treatment and psychological issues raised by or distinct from cancer. Sexual dysfunction is one of the most common and distressing consequences of cancer treatment [63, 64]. Although some sexual-related adverse effects are short term, many survivors face long-term effects such as treatment-induced menopause, altered gonadal function and altered body image [60].

Both experienced and novice professionals may experience confusion and dilemmas when faced with certain sexual health issues; adequate supervision and support for staff should be considered when planning such services. One of the most challenging areas for professionals can be responding to concerns or disclosure of abuse during work with AYA and their sexual health. Adolescents and young adults may experience a broad range of neglect or abuse intentionally or by omission from parents/carers, other adults, organisations or their intimate partners. Healthy relationships (regardless of sexual orientation) require respect, trust, communication and responsiveness between those involved. Many young people have not been taught or witnessed these skills, especially if they have grown up in a home, community or society where violence and exploitation occurs. Intimate partner violence (IPV) may include psychological or emotional violence, stalking, physical violence and sexual violence such as non-consensual sexual contact and rape [65], all of which can have a negative effect on health throughout life [66]. Likewise non-partner sexual abuse/violence should be considered. In a world where the global movement of people across and within countries can no longer be simply described as ‘business or pleasure’ and local populations become increasingly diverse, professionals need to be alert to concepts such as human trafficking and female genital mutilation (FGM).

24.7 Recognising and Responding to Sexual Abuse

Human trafficking is the recruitment and movement (by coercion, deception or abuse of vulnerability) across and within borders for the purposes of exploitation through forced sex work, domestic servitude and low-paid labor and it affects an estimated 2.5 million people worldwide [67, 68]. As this chapter is about sexual health, it may be natural to focus on young people trafficked for sex work; however, those trafficked into domestic or other work often experience sexual abuse and violence [67]. Healthcare providers are one of the few professionals likely to interact with people who

have been trafficked [69]. All professionals working with AYA should receive training to recognise those who have been trafficked and on how to assess and respond to their social needs as well as their medical needs. The WHO defines FGM as procedures that involve partial or total removal of the external female genitalia or other injuries to the female genital organs for non-medical reasons. It is estimated that >125 million girls and women alive today have been cut in the 29 countries in Africa and Middle East where FGM is concentrated, most in childhood but some in adolescence or adulthood [70]. There is no medical benefit for FGM, and it is banned in many countries across the world; those working with young women with cancer should be aware of relevant processes and policies if they think young women are at risk of FGM or have had FGM and wish to seek psychological or medical support as a result.

24.8 The Impact of Cancer Treatments on Sexuality and Sexual Function

24.8.1 Altered Body Image

Physical reminders of cancer and its treatment can result in concerns regarding appearance and self-esteem, which in turn impact on self-confidence [57]. Changes in body image from cancer treatments constitute a major source of concern and distress for AYA [53, 54, 57]. These include hair loss, weight change and disfigurements such as scarring, stretch marks, stomas and the loss or alteration of a body part (e.g. breast or testicle) [57, 60]. Alopecia (body hair as well as cranial hair) can be the most distressing side effects of chemotherapy that may affect body image in both women and men [57]. Weight changes, striae, loss of fertility and other alterations to body image may impede sexual desire and arousal [71, 72]; the resulting loss of self-esteem and confidence may interfere with the normal tasks of sexual development.

Any visible physical changes, no matter how small, may significantly affect the development of sexual self-esteem, including delayed sexual maturation and formation of meaningful couple relationships [57, 58, 73]. Altered body/self-image has been shown to not only affect decision-making about dating but also AYA participation in social events, which provide opportunities to form relationships [62] including the ability to form intimate or romantic relationships as is the norm for this age group [59, 60]. One study [73] reported that 17% of testicular cancer survivors diagnosed as an AYA reported a negative change in body image following diagnosis and treatment for their cancer. These results were significantly correlated with other reported changes of sexual function, and similar findings were reported in more recent work looking at perceptions of masculinity and self-image in this group [61].

However, cancer treatment does not always have a negative impact on survivors, and a recent study of male survivors of bone cancer in childhood who had amputations demonstrated a higher level of sexual functioning than in the bone cancer survivors who had limb salvage surgery [74–76]. These findings demonstrate the resiliency reported for some, but not all, AYA with cancer [77, 78].

24.8.2 Surgery

24.8.2.1 Colorectal Cancer

Though still very rare, the global incidence of colorectal cancer in adults <40 years of age is rising [79, 80]. The nature of surgery and subsequent multimodal adjuvant treatments can give rise to significant short- and long-term effects on both sexual function and sexuality. The presence of a stoma or altered bowel function may not only lead to changes in body image but also can present challenges of disclosure to new partners or sexual adjustment/renegotiation with established sexual partners. Though no literature specifically relating to AYA with colorectal cancer could be found, problems related to the

following areas of sexual function have been reported in both sexes: reduced sexual desire and diminished orgasm, and in women, vaginal dryness and dyspareunia [81]. In men, although radiotherapy and chemotherapy contribute, surgical nerve damage is the main cause of sexual dysfunction, most often erectile and ejaculatory dysfunction [81, 82].

24.8.2.2 Pelvic Cancers (Women)

The sudden loss of oestrogen, progesterone and other androgens following bilateral oopherectomy brings about more severe and prolonged menopausal symptoms than seen in the natural menopause [83]. Little difference has been found in sexual function in research with age-matched cohorts experiencing natural or surgical menopause [84]. However for younger women, the sudden loss of sexual desire, vaginal dryness, dyspareunia and poor arousal and orgasm (and infertility) may lead to impaired sexual satisfaction, at a time normally equated with fertility, sexuality, partnerships and parenthood. Such a rapid change in reproductive and sexual health may have a significant effect on the sense of self as a sexual being beyond intercourse – women following gynae-oncological surgery report less kissing and sexual fantasy than their healthy peers [85].

Following such surgery, vaginal shortening may lead to dyspareunia. A qualitative study of the quality of life for women 1-10 years after radical trachelectomy for early stage cervical cancer [86] found sexual function was not a long-term problem for most women. However, some could feel the cerclage (stitch) during intercourse and although most developed techniques to manage this, younger single women felt particularly vulnerable [86].

24.8.2.3 Breast Cancer

Fewer than 5 % of all breast cancers diagnosed in the USA occur in women <40 years of age [87]. For many women, breast cancer surgery is the initial treatment; this may be breast-conserving surgery (lumpectomy) and axillary node dissection or a modified radical mastectomy (MRM) with or without immediate reconstruction. Though rare, some women in this age group may have a bilateral mastectomy; those who request this surgery are typically women with a strong familial history or those <45 years old when diagnosed [88]. Studies of the association between type of surgery, body image and sexual functioning have yielded inconsistent results, often due to the multimodal treatment used in this cohort. It is known that young women who receive chemotherapy following surgery report worse sexual functioning than women who do not [89, 90].

However, women may have different feelings about their breast and its changes following a cancer diagnosis and treatment; these may affect self- and body image before and following surgery. For example, some women may see surgery as a means of addressing cancer and the start of recovery [91], whilst for women in some cultures, a single breast can profoundly alter self and sexual identity [92]. Evidence shows that, overall, women with a better body image prior to diagnosis have higher sexual satisfaction scores than women with a worse pre-treatment body image; the health-related quality of life (HRQoL) impact of surgery also seems to be higher in the first year post-diagnosis, improving hereafter [90, 91].

In their work on sexuality and body image across surgical groups, Yurek et al. [93] found that women who had a mastectomy and breast reconstruction reported that their immediate post-surgery sexual behaviour and sexual responses were disrupted significantly more so than women receiving breast-conserving surgery or mastectomy without reconstruction. Moreover, their data suggested that reconstruction achieved no reduction in body change stress, at least in the early post-surgical period. Some women reported significant situational distress and avoidant behaviours, i.e. avoiding looking at their chest and changes in behaviour towards their sexual partner; Yurek et al.[93] suggested that those women with negative sexual self-views were more apt to engage in lower levels of sexual activity, have difficulties

with their sexual responsiveness and are vulnerable to heightened body change stress. Newer oncoplastic surgery techniques promise better overall cosmetic results [94] and further research into sexuality and self-identity is warranted.

24.8.3 Head and Neck Surgery

Traditionally oropharyngeal squamous cell carcinomas have been equated with older adults; however, largely due to HPV-related cancers, increasing numbers of younger patients who lack traditional risk factors are being diagnosed [95]. These patients require appropriate evaluation, counselling and treatment to ensure cure rates and lessen treatment-related side effects [95]. Potentially disfiguring surgery to the head and neck not only undermines a young adult's perception of themselves as a sexual being but may also alter their ability to communicate and express themselves to partners and others thus reducing relationship formation and relationship maintenance.

24.8.4 Neurosurgery

In a recent study of patients with diffuse low-grade glioma (DLGG), a tumour that often affects young adults [96], 50 % of participants reported lower sexual function and satisfaction following surgery in addition to issues related to cognition, balance, communication, body image, seizures and mood disturbance. Few patients spontaneously disclosed these issues to their healthcare team [96].

24.8.5 Bone Cancers

The nature of bone cancer treatment and its potential implications for physical disability, cancer treatment affects and the dual psychosocial impact make it unique in the context of sexuality and sexual function. The physicality of sex following amputation requires relearning how to have sex and may involve trying different positions and the use of supports, i.e. pillows to help with positioning and balance. Others find wearing prosthesis helps with position and balance. Pain was reported as distracting during sex and may reduce sexual desire [97]. For the sexual partners of adolescents and young adults, their partner's amputation can have an impact on their sexual life too. Verschuern [98] study of partners found that the patient's amputation changed their sexual functioning and sexual well-being (not always for the worst) and that most couples resolved issues themselves through communication, acceptance and practical adjustment.

Roberts [74] found that patients' quality of life was related to the functionality of the limb regardless of the type of surgery. Barrera et al. [75, 76] noted that patients with limb salvage surgery also had issues with sexual function as well as self-esteem, with young women and young adults being at particular risk.

24.8.6 Testicular Cancer

Cancer in a male organ that is highly associated with perceptions of masculinity, attractiveness, sexual function, fertility and romantic relationships [59] can have a significant effect on young men at a key point in their identity development. Impaired sexual function appears to vary by treatment regimen and histological subtype; survivors of testicular germ cell tumours report greater impairment and/or dysfunction compared with controls [99]. Sexual dysfunction varies by treatment modality too; chemotherapy and surgery show a greater risk of decreased libido or ejaculatory dysfunction; radiotherapy and surgery are more closely associated with erectile dysfunction. Additionally, those with a non-seminoma histological subtype note a greater risk of erectile dysfunction and ejaculatory dysfunction [59].

A single orchiectomy (if the remaining testicle is functional) does not alter physical sexual function and seldom interferes with fertility. However, surgery and the presence of a prosthesis

may alter body image and perceptions of masculinity. In rare cases where both testicles are removed, erectile dysfunction will occur due to lack of testosterone. Surgery to remove the retroperitoneal lymph nodes (RPLND) does not affect men's ability to have an erection or orgasm. However the consequences of surgery can cause infertility. In the past nerves controlling ejaculation were cut during surgery, without these the bladder neck does not close during ejaculation and sperm enters the bladder (retrograde ejaculation). Contemporary nerve-sparing RPLND techniques prevent this from happening, and fertility is often preserved and ejaculation normal.

Survivors reported that overall sexual interest, activity, enjoyment and function had changed very little or not at all [59]. Men in a committed relationship at the time of diagnosis describe improved physical and emotional adjustment to the cancer experience, often with increased closeness to their partner [58]. Those unpartnered at the time of diagnosis worry about how the testicular cancer may affect their future relationships [59]. Therefore being single at diagnosis appears to represent a vulnerability that remains even when survivors form a relationship after treatment completion.

24.8.7 Systematic Anticancer Drugs

24.8.7.1 Cytotoxic Drugs

Most of the information relating to the effects of cytotoxic drugs on sexuality and sexual function refer to women with breast or gynaecological cancer and men with prostate cancer or testicular cancer. Less is known about how the use of cytotoxic drugs in the treatment of other types of cancers affecting young adults effect sexuality. Systemic anticancer therapy impacts on sexuality and sexual functioning in different ways (Table 24.2). Treatment with cytotoxic drugs is often associated with loss of desire and decreased frequency of intercourse for both men and women [71] due to the psychological impact of body image as discussed earlier in this chapter.

The type, duration, cumulative dose and the combination of the cytotoxic drugs/modalities used influence the effect on sexuality and sexual function in both sexes. The acute physical side effects of cytotoxic drugs e.g. nausea, vomiting, fatigue, malaise can leave little energy for sex or relationships. Sexual desire most often returns as the acute impact of cytotoxic drugs lessens. However, the recovery period between cycles of treatment may be short; sexual interest might only just be returning as the next cycle of treatment starts. Once cytotoxic therapy is completed and the acute side effects diminish, sexual desire often returns to previous levels.

For women, one of the most significant factors affecting sexuality after chemotherapy is the loss of ovarian function [100, 101]. Women whose combination chemotherapy leads to permanent ovarian failure appear to be at higher risk of sexual problems than those who continue to menstruate or whose menses are temporarily interrupted [101]. The risk of permanent ovarian failure increases with the woman's age, especially for women over age

Table 24.2 Applying the side effects of systemic anticancer drugs to sexuality

Affect	Gender	Causative factors
Altered sexuality related to body image and sexual desire	Both	Alopecia
		Nausea/vomiting
		Fatigue
		Reduced libido
		Mood changes, anxiety, depression
		Weight change
		Acne
		Striae
		Bloating Peripheral neuropathy
Altered sexual arousal	Female	Dryness of mucosa (vagina)
		Atrophy (vagina)
		Inflammation of mucosa (vagina)
Altered sexual arousal & ejaculation	Male	Retrograde ejaculation
		Erectile dysfunction

35, and with alkylating drugs and higher total doses of chemotherapy [102]. In premenopausal women, chemotherapy-induced ovarian failure can cause vaginal dryness and thinning of the vaginal mucosa leading to dyspareunia and bleeding on penetration or withdrawal [100]. Peripheral neuropathy may cause vaginal pain, loss of sensation and numbness – altering arousal and decreasing the ability to reach orgasm [103]. Cytotoxic drugs that irritate mucous membranes in the body will do so to the mucosal lining of the vagina, causing dryness and inflammation.

For men, cytotoxic drugs rarely cause erectile dysfunction [102]; some drugs may cause nerve damage that affects erectile function, but this most often returns to pretreatment levels, unless function is affected by other treatment modalities. Hypogonadism and damage to pelvic nerves may lead to sexual dysfunction after intensive chemotherapy [102], so hormone replacement may be necessary to restore sexual function. More rarely, neurotoxic cytotoxic drugs may interfere with ejaculation, possibly due to damage to autonomic nerves involved in the contractions of the prostate, seminal vesicles and bladder neck [104].

All those who remain sexually active during treatment should be advised to take precautions to protect themselves from sexually transmitted infections if treatment lowers their immune system. Likewise advice for avoiding sexual behaviours that may cause trauma, i.e. anal penetration, should be avoided for those with platelet suppression. If using sex toys or other objects for penetrative stimulation, AYA should be advised regarding issues of hygiene to prevent infection and trauma which may necessitate changing practices, e.g. reducing the size of vibrators, avoiding vaginal or anal penetration with other objects, considering condom use on sex toys that may be shared between partners and taking precautions when having oral sex. Lastly due to a lowered immune system, young women need to be aware that they may be prone to vaginal candida infections and both sexes with a history of anogenital warts aware they may have a recurrence [105].

24.8.8 Biological Targeted Therapies

Small molecule inhibitors or monoclonal antibodies are increasingly used in the treatment of AYA cancer. A key difference between cytotoxic drugs and biological targeted therapies is that the former are designed to kill all cancer cells during intense courses of treatment, whereas the latter are often cytostatic and must be given continuously for months or years [106]. Studies of the effects of these agents on sexuality and sexual function could not be found, and work investigating the effects these agents have on fertility is limited. The broader side effects of therapy, e.g. flu-like symptoms, dizziness, nausea, vomiting, muscle or joint aches, fatigue, skin changes and altered mood, should be noted as these are likely to affect AYA's sexuality. The longevity of treatment may result in a prolonged effect that as yet is unreported in the literature.

24.8.9 Radiotherapy

The effect of radiotherapy on AYA sexuality is dependent on the site, dose and volume of the treated area. Acute effects relate to damage to tissues with rapidly dividing cells notably the skin, hair follicles and mucosa – applying how these relate to sexuality and sexual function requires an individual assessment and approach to intervention [81, 82]. The effects of radiotherapy can be long lasting and significant [34, 82, 102].

Young adults may receive pelvic irradiation as adjuvant treatment for their cancer. Complications affecting sexuality may be acute, i.e. fatigue, malaise, diarrhoea, skin changes or long term and permanent organ, blood vessel and nerve-related, and the source for potential psychosexual late effects both in males and females.

The accumulated radiation dose to the pelvic organs is critical for acute bowel, bladder and genital toxicity [106]. Fibrotic changes and small-vessel injury in and around the prostate gland may cause ejaculatory dysfunction and

erectile dysfunction [102]. However, the aetiology of erectile dysfunction, for example, in colorectal cancer patients, is believed to be similar to that of patients treated for prostate cancer [107]. Radiotherapy for testicular cancer has been reported to be associated with decreased testosterone production and vascular damage, decreasing sperm counts and possibly causing erectile dysfunction [99].

In women, sexual dysfunction following pelvic radiation is suggested to be associated with both multiple organic changes and psychological issues [107]. Women report a feeling of lack of femininity, sexual attractiveness and confidence besides being distressed by vaginal bleeding, vaginal pain, vaginal dryness and decreased vaginal elasticity, resulting in fear of sex and less sexual enjoyment [100]. The rapid cell turnover of the vaginal and vulva epithelium makes it very sensitive to the effects of radiation [100, 104]. Severe acute mucosal erythema and desquamation are often present but are normally resolved within 2–3 months after radiotherapy. In the longer term, vaginal wall thinning, adhesions, atrophy and fibrosis may occur and followed by decreased vaginal elasticity, vaginal lubrication, narrowing, shortening leading to dyspareunia and delayed or reduced orgasm [100]. Both sexes may experience loss of or reduced libido.

24.8.10 Human Stem Cell Transplantation (HSCT)

Conditioning regimes prior to HSCT often include alkylating agents and/or total body irradiation (TBI). Total body irradiation is toxic to gonadal function and can damage the function of the hypothalamic-pituitary-gonadal axis, cause genital sensitivity and atrophy, impair testosterone production for men (at least for the first year) and induce ovarian failure in woman [108].

Sexual problems in men may also be a result of gonadal and cavernosal arterial insufficiency resulting in lower sexual desire, arousal and penile vessel scarring and adhesions may lead to erectile dysfunction.

If the transplant is allogeneic, AYA are at risk of graft versus host disease (GVHD). Chronic GVHD may manifest anywhere in the body; for women, vaginal mucosal tissues are particularly susceptible to vulvovaginal GVHD, and it has been reported in 25–49 % of stem cell transplant survivors [109]. Vulvar symptoms can occur first: median 7–10 months post-transplant with vaginal disease occurring possibly years later. Vulvovaginal GVHD causes pain, vulva and/or vaginal dryness, burning, pruritus and long-term vaginal fibrosis, all of which can affect intimacy, sexual function and quality of life and may be compounded by concurrent disruption to ovarian function. Therefore, vulva/vaginal GVHD is often delayed or misdiagnosed ovarian failure [109].

Genital manifestations of chronic GVHD are less reported in men. However, penile lichen sclerosis [110], chronic GVHD of the penis [111] and Peyronie's disease [111, 112] have all been reported.

24.9 Clinical Assessment of Sexual Consequences of Cancer and Its Treatment

Health professionals and patients alike continue to experience embarrassment in talking about the sexual consequences of treatment, resulting in a tendency to avoid such discussions in medical follow-up consultations [53, 101, 102, 113–115]. The ability to establish a discussion about how treatment may impact on the sexual function and confidence of a teenager or young adult may prove more challenging than discussions with older adults due to the developmental stage of the young person where they may not have established their sense of sexual identity, sexual self-esteem or confidence within the context of what are often transient/evolving relationships [25, 53].

Aubin and Perez [116] propose that clinical assessment of treatment-induced sexual concerns in this age group benefits from inclusion of information from the clinical interview, medical

records and self-report questionnaires (PROMS), suggesting that a comprehensive assessment should address the following domains:

- Socio-demographic details
- Medical history (physical and emotional health)
- Fertility, contraception and sexual health
- Sexual function
- Sexual coping style
- Body and self-image
- Sexual and relationship history

These authors also raise the importance of creating a direct and open communication style, similar to a life-coaching or mentorship approach, to work in partnership with AYAs to explore sexual concerns and deliver psycho-education whilst ensuring maintenance of clear and mutually agreed boundaries of privacy and confidentiality [116].

Many health professionals avoid discussions about sexual difficulties associated with cancer treatment because they fear embarrassing themselves or patients, feel they do not have the skills and knowledge about how to assess and manage these difficulties or know about the most appropriate specialist services to which they can refer [113, 115, 117]. A useful vehicle for both initiating and structuring, what can be, challenging consultations is the use of self-report screening or measurement instruments (usually questionnaires) validated for clinical use. Whilst the majority of sexual morbidity measures have not been specifically validated within adolescents, some have been evaluated for use in heterogeneous adult samples that have included younger adults.

A recent study from the US National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) initiative [118] tested three single-item screener instruments for sexual problems or concerns in a probability-based sample of the adult population ($n = 3515$) that included 750 men and women in the 18–29 year (21.3 %) and 882 (25.1 %) in the 30–44 year age groups. Whilst these screeners were developed for use in a general adult population, instrument development was informed by self-report items used in oncology, gynaecology and sexual medicine clinics by clinician and researcher members of the scientific network on Female Sexual Health and Cancer. The instrument that appeared most effective in eliciting sexual problems/concerns was the checklist screener (see Table 24.3). This brief checklist offers clinicians and patient's rapid completion and adequate detail of the specific sexual problem or concern and is therefore likely to improve identification, management or onward referral [118].

The specific patient reported outcome measures (PROMS) most commonly used in sexual morbidity research and clinical practice are the Female Sexual Function Index (FSFI) and the International Index of Erectile Function (IIEF) [119]. The **FSFI** was evaluated in two diagnostic groups of women ($n = 217$) aged 18–50 years, one group treated for gynaecological cancer and the other post-bone marrow/stem cell transplant for haematological malignancies [120].

The questionnaire demonstrated sound psychometric properties in these groups of women and offers a useful framework of questions (19 items) that address difficulties with sexual desire, arousal, orgasm, sexual satisfaction and sexual pain. The FSFI takes approximately 15 mins to complete, and validation studies have established

Table 24.3 Clinical screener for sexual problems/concerns

In the past 12 months, has there ever been a period of 3 months or more when you had any of the following problems or concerns?
(Please tick/indicate all that apply)
You wanted to feel more interest in sexual activity
You had difficulty with erections (penis getting hard or staying hard) – *Men only*
Your vagina felt too dry – *Women only*
You had pain during or after sexual activity
You had difficulty having an orgasm
You felt anxious about sexual activity
You did not enjoy sexual activity
Some other sexual problem or concern
No sexual problems or concerns

Adapted from Flynn et al. [118]

a clinical cut-off score of <_26 as the threshold for indicating the presence of female sexual dysfunction (FSD) [119].

The main limitation of this measurement instrument, in common with the majority of validated self-report measures for sexual dysfunction, is that the FSFI may not provide valid assessment of sexual function among women who have not had recent sexual activity [120].

For male patients experiencing treatment-induced sexual difficulties, the International Index of Erectile Function (IIEF) appears to be the most useful PROM for clinical use. The **IIEF** (15 items) addresses the domains of sexual desire, sexual arousal (the confidence to get and maintain an erection sufficient for penetrative intercourse), orgasm, ejaculation and sexual satisfaction and takes an average of only 10–15 mins to complete. Furthermore, the IIEF is also available in a short (five-item) version, the Sexual Health Inventory for Men (SHIM), which is also commonly used for screening purposes in clinical practice [121].

Ideally, the use of any PROM should complement a clinical discussion that includes recording an appropriate sexual history to ascertain the young person's sexual experience and relationship context together with the nature and scope of sexual difficulties experienced. Good clinical assessment is more likely to lead to selection of the most appropriate management, including any need for further investigations and/or onward referral to specialist services. However, for some clinicians and patients, a PROM also offers a more objective, structured and systematic method to discuss what can be, for many, a sensitive topic whilst providing a common language to record changes in sexual function, expression and well-being.

Whilst the DSM-V [122] offers a classification system used by mental health services and many healthcare payment systems, it may have limitations in defining the predominantly organic (vascular, neurological, endocrine or anatomical) sexual disorders encountered in oncology. However, DSM-V does offer diagnostic criteria that assist clinicians in reaching a decision as to whether or not a sexual difficulty or concern warrants further investigation and treatment.

An identified sexual difficulty/concern should normally:

- Have been present for a minimum duration of 6 months
- Be present in association with sexual encounters at a frequency of 75–100 % of the time
- Be deemed to have caused 'significant distress' to the individual/couple

Furthermore, in assessing any person experiencing sexual difficulties, it is important to take account of contributory factors that influence the relative importance of sexual difficulties to the individual or couple and may have a bearing on management and referral decisions. These include:

- Partner and relationship factors (sexual coercion/violence, absence of/multiple partners)
- Individual vulnerability factors (mental health, substance misuse, social support, past history of sexual abuse/violence, sexual risk taking behaviour)
- Cultural or religious factors (religiosity, female genital mutilation, cultural/religious restrictions on sexual expression, early marriage/childbearing)
- Medical factors (current treatment/medication, no. of acute problems, disease stage/status, disease or treatment-related risks, concurrent STIs, HIV-/HPV-related malignancy, co-morbid mental/physical health concerns)

24.10 Clinical Management of Sexual Difficulties Arising from Cancer and Its Treatment

The mixed aetiology of difficulties commonly encountered in adolescents and younger adults after cancer treatment emphasises sexual medicine's dominant biopsychosocial practice

model that integrates biomedical, psychological and psychosexual approaches [123, 124]. Psychological strategies with individuals or couples that have been used alone or in conjunction with pharmacological or device interventions include psycho-educational, brief cognitive behavioural therapy (CBT), mindfulness and sex therapy approaches [125–128].

It is clearly important for cancer services to offer pharmacological and biomedical management for sexual difficulties of dominant organic aetiology, such as neurogenic or vasculogenic erectile dysfunction (ED) or vaginal pain arising from oestrogen deprivation or genital graft vs. host disease. For difficulties arising from adverse impacts on emotional well-being, sexual identity, relationship formation or limited sexual experience, services should enable access to psycho-educational, psychological and psychosexual interventions across different levels of clinical complexity; from the integrated management of ED to the more complex sexual rehabilitation after pelvic exenteration and vaginal reconstruction.

A recent meta-analysis of psycho-educational intervention studies ($n=15$) in cancer and sexuality found evidence of medium to large effect sizes post-intervention with a mean difference of 0.75 [128]. Study outcomes included **physical** (sexual activity, sexual function, comfort during sexual activity, physical function and physical symptom level), **psychological** (anxiety, depression, mental health and stress), **cognitive** (body image, concern about sex life, knowledge, sexual need and sexual satisfaction) and **social** (relationships, intimacy, couple adjustment, sexual role and social support).

This meta-analysis concluded that greater effect sizes were found when the intervention-targeted individuals (0.85) in preference to groups (0.50) was delivered by a psychologist/qualified nurse combination (2.38) or nurse alone (2.22) compared to psychologist (0.60) or peer alone (0.27) and used methods of face-to-face/telephone ± Internet combined (1.04) compared to face-to-face (0.62) or telephone (0.58) alone.

The majority of study participants (breast, gynaecological, prostate and colorectal) were in the mid-older adult age range, and subgroup analysis found a lower effect size for the adolescent and young adults study (0.74) compared to women with gynaecological cancer (1.04) but equivalent to women after breast cancer (0.74) and higher than studies in colorectal (0.59) or prostate (0.31) cancer [128].

Psychosexual or sex therapy can be offered as a first-line treatment for sexual difficulties with a dominant psychogenic component or as a useful adjunct to biomedical strategies [2, 123, 124, 129].

The mainstay of psychosexual therapy since its inception in the 1970s [130, 131] is the use of a behavioural framework often referred to as sensate focus (see Table 24.4). Psychosexual therapy addresses the predisposing, precipitating and maintaining factors for sexual difficulties [132] through three key components:

- Stepwise framework of structured sensual touch and behaviours to encourage improved couple communication and mutual nondemand sensual/sexual pleasuring
- Addressing blocks to progress that occur as a consequence of undertaking sensate focus at home ('homework' exercises)
- Psycho-educational interventions individualised for the patient/couple and specific sexual difficulty

Brotto et al.'s [127] review of psychological interventions for the sexual sequelae of cancer identified 27 empirical studies, 19 of which offered level 1b evidence in moderate support of the effectiveness and feasibility of such interventions for sexual dysfunction after cancer. There is evidence of acceptability and efficacy for sex therapy techniques, sensate focus and sexual communication approaches for adult couples [133], and in a small ($n=31$) sample of women with desire and arousal difficulties after gynaecological cancer, Brotto et al. [134] demonstrated improvement in all domains of female sexual response after brief mindfulness-based CBT. However, small sample sizes, methodological limitations and con-

flicting findings undermine confidence in the efficacy of these interventions, and questions remain regarding maintenance of improvement over time and their suitability for different genders and for adolescents and younger adults [127, 133].

Clinically, psychosexual therapy is useful for individuals with performance anxiety, low sexual confidence and limited sexual knowledge/experience. It can also improve sexual difficulties that have a limited response or are not amenable to biomedical management such as low desire, lack of subjective arousal, orgasmic changes and sexual fear or avoidance. Specific work with couples can improve couple communication and relationship adjustment, develop shared strategies for supporting sexual recovery and negotiate revised sexual behaviours such as sexual frequency, coital/noncoital sexual expression, use of lubricants and safer sex practices [126]. Table 24.5 offers a summary of the strategies most often used for the management of treatment-induced sexual difficulties encountered in this age group and addressed by this chapter:

- Reduced sexual interest or desire
- Reduced sexual responsiveness (erectile dysfunction and sexual pain difficulties)
- Orgasmic and Ejaculatory Changes

24.11 Reduced Sexual Interest or Desire

A reduction in or total loss of desire or interest in sex is not uncommon throughout different stages of the lifespan, being associated with periods of stress or low mood and significant life change such as leaving home, starting/changes in employment, pregnancy and childbirth and experiencing loss [129, 135, 136]. In the context of cancer and its treatment, loss of desire following diagnosis and during/immediately following treatment is common and in many individuals will spontaneously resolve when the psychological and physical stressors associated with treatment have improved.

Most clinicians would, however, agree that when absent or low, desire is present for over 3 months, is accompanied by individual or couple distress, or disrupts normal relationship formation or maintenance; then this may warrant further discussion and possible intervention [122]. A recent postal survey of young adult (18–45 years) cancer survivors ($n=99$) found that whilst 75 % of the sample were happy with their relationships, 64 % reported having sex less frequently post-diagnosis. There was an association between greater sexuality needs and higher levels of fatigue, and women surveyed had greater sexuality needs than male participants, with 38 %

Table 24.4 Stages of sensate focus

Sensate focus stage	Adaptation to accommodate illness/treatment-induced changes
Stage 1: non-genital touch	Avoid breasts after surgery/reconstruction; avoid areas of pain or altered sensation; avoid site of IV access/stoma devices; use body stockings, lingerie, underwear/nightwear to manage altered body image impacts
Stage 2: genital touch	Erotic/sensual touch/massage to alternative erogenous zones and negotiate stimulation to areas of the body not accessed in stage 1 as appropriate and with aim of inducing comfortable sexual arousal
Stage 3: vaginal containment	Amend for anal intercourse; consider graduated digital, vaginal or anal dilators; vibrators; ensure adequate lubricant use; precoital use of aids to erectile function; use of constriction loops/rings (cock rings); sexual positions advice
Stage 4: vaginal containment with movement	As above; precoital analgesia (topical/systemic)/vaginal/anal lubrication
Stage 5: vaginal intercourse	As above and alternative sexual positions advice (female superior; side-lying; pelvic tilting; pillows/support for balance/prosthetics)

Adapted from Masters and Johnson [130] and Kaplan [131]

Table 24.5 Integrated management of treatment-induced sexual difficulties

Sexual difficulty	Management (male)	Management (female)
Loss of sexual desire	Testosterone supplementation	Systemic/topical (vaginal) HRT
	Psychoeducation: barriers and enablers of sexual interest	Testosterone supplementation
	Psychological therapy (anxiety/depression/ body image/masculinity concerns)	*Psychoeducation*: barriers and enablers of sexual interest
	Psychosexual therapy: sensate focus, mindfulness	*Psychological therapy* (anxiety/depression/ body image/femininity concerns)
		Psychosexual therapy: sensate focus, mindfulness
Erectile dysfunction (male arousal disorder)	*Oral pd5 inhibitor drugs*: sildenafil, tadalafil, vardenafil, avanafil	
	Alprostadil (intra-urethral pellet or ointment/intracavernosal injection (ICI)	
	Vacuum erection device (VED)	
	Penile constriction rings/loops	
	Psychoeducation: subjective/objective (erection) arousal, barriers/enablers to arousal, Zilbergeld's Myths (1999)	
	Psychosexual therapy: wax and wane masturbatory exercises, erotic fantasy, sensate focus re-additional sources of arousal	
	Surgically placed penile implants (inflatable)	
Sexual pain difficulties	Genital pain uncommon:	*Women's/vaginal health*: HRT/vaginal oestrogen
	Genital desensitisation through sensate focus/structured massage	Nonhormonal vaginal moisturisers Vaginal lubricants (water, oil, silicone based)
	Pain clinic: topical/systemic analgesia	Vaginal desensitisation: digital exploration, vaginal dilators, vibrators
	Psychological therapy: mindfulness, relaxation techniques	Kegel exercises
		Psychoeducation: subjective/objective arousal, barriers/enablers to arousal
		Psychosexual therapy: masturbatory exercises, vibratory stimulation, erotic fantasy, sensate focus re-additional sources of arousal
		Pain clinic: topical/systemic analgesia
		Psychological therapy: mindfulness, relaxation techniques
Orgasmic and ejaculatory changes	*Psychoeducation*: orgasm/ejaculation differentiation; causes of ejaculatory pain, retrograde ejaculation	*Psychoeducation*: barriers/enablers to adequate arousal/orgasm
	Barriers/enablers to adequate arousal/ orgasm	Relaxation exercises
	Relaxation exercises	*Psychological therapy*: anxiety management; review antidepressant medication effects
	Psychological therapy: anxiety management; review antidepressant medication effects	*Psychosexual therapy*: sensate focus, fantasy, erotic images/literature, masturbation, vibrator therapy
	Psychosexual therapy: sensate focus, fantasy, erotic images/literature, masturbation, vibratory stimulation/therapy	
	Analgesia (ejaculatory pain)	

expressing a need for support in relation to changes in sexual feelings [137].

24.11.1 Clinical Management

When the underlying mechanism for loss of desire is associated with reduced testosterone levels (serum testosterone <_10 nmol/l), particularly when accompanied by other signs of testosterone deficiency such as reduced body hair, fatigue, muscle weakness/loss of muscle definition and strength, erectile difficulties and absence of waking erections, then testosterone replacement therapy or supplementation should be considered [52]. Furthermore, in mild to moderate erectile dysfunction or loss of desire (accompanied by distress), it may be appropriate to offer testosterone supplementation even when the level of free testosterone is within the low normal range [52].

In young female patients, low oestrogen levels or complete ovarian failure may indicate a need for hormone replacement therapy. When HRT results in normal oestrogen levels, but absent sexual desire persists, it may be appropriate to consider testosterone supplementation although the level required to increase sexual desire in women is both variable and lower than that required for male patients [138, 139].

Loss of desire is commonly associated with psychological adjustment difficulties such as altered body image, high anxiety or low mood/depression and is sometimes a side effect of both anxiolytic and antidepressant therapies [140, 141]. In situations where low or absent desire is thought to arise as a consequence of psychological issues, then referral for psychological or psychosexual therapy may be helpful [142]. Psychological therapy often addresses the underlying emotional adjustment difficulty, and, through its improvement or resolution, sexual interest frequently improves.

Psychosexual therapy can be used to improve low sexual desire through the use of sensate focus (see Table 24.4). The aim of sensate focus is to improve couple communication, encourage greater emotional and sexual intimacy and offer individualised behavioural strategies to enhance sexual interest and arousal [130, 131, 143]. Psychosexual therapy can enable young men and women to focus on erotic and sensual behaviours that reduce anxiety, improve sexual self-confidence and offer coping and adjustment strategies that address altered femininity or masculinity and other treatment consequences.

24.12 Sexual Pain Associated with Treatment-Induced Changes

Sexual arousal in women comprises **subjective** feelings/thoughts and bodily sensations (genitals/breasts) associated with being sexually responsive "turned on" or "horny" together with **objective** physical signs in the body including the breasts and genitalia. The vagina manifests specific changes that are necessary to facilitate anticipated (penile) penetration such as vaginal lubrication and vaginal tenting plus rising of the uterus within the pelvis [2].

After treatment-induced ovarian failure, vaginal changes associated with radiotherapy (shortening, stenosis, fibrosis, telangiectasia), radical pelvic surgery (shortening/vascular changes) or genital graft versus host disease (bleeding, fragile mucosa) may mean that the vagina no longer lubricates adequately during sexual arousal resulting in greater friction during intercourse, sexual pain and post-coital bleeding [139, 144, 145]. Sexual pain is usually either *superficial* (vulval, introital, perianal and/or associated with secondary vaginismus) or *deep* (pelvic fibrosis/altered organ/vaginal anatomy) associated with deeper penetration.

Anal (superficial) or rectal (deep) pain may occur where anal play or intercourse is attempted in the presence of acute radiation inflammation, anal stenosis, anorectal fibrosis, lower GI ulceration or GVHD [109, 146, 147].

Penile pain can be a manifestation of peripheral neuropathy or genital GVHD, and painful oral sex may be associated with radiation or chemotherapy-induced mucositis.

It is important to identify exacerbating and relieving factors for sexual pain and to offer specific biomedical, psycho-education and practical advice to reduce/ameliorate this problem to enable comfortable and enjoyable sexual activity to be re-established [126].

24.12.1 Clinical Management

In addition to the timely provision of systemic and topical HRT to prevent/ameliorate the development of vulvovaginal atrophy associated with treatment-induced menopause, it is important to offer young women advice about how to maintain vaginal health when changes interfere with sexual activity [139, 148, 149]. Women should be given self-management advice regarding how to spot the early signs of viral, bacterial and fungal infections in the vagina and vulva as their systemic and pelvic treatments place them at greater risk of developing such infections in the context of evolving relationships and changes in sexual partners.

Women should also be given information about the use of vaginal lubricants to reduce friction associated with intercourse and, except during the acute post-RT inflammatory phase, can select from water-, oil- or silicone-based intimate lubricants [150]. In general, greater friction reduction can be achieved through the use of oil- or silicone-based lubricants as long as they do not induce repeated *Candida albicans* infection or tissue irritation.

Topical HRT is often effective in improving vaginal lubrication and reducing pruritus even where the woman receives an adequate dose of systemic HRT [148]. If the woman has an oestrogen receptor-positive malignancy, where systemic HRT is contraindicated, then a nonhormonal vaginal moisturiser such as Replens or Hyalofemme can be used regularly, irrespective of sexual activity, to improve vaginal moisture and restore acidic Ph [151–153].

Vaginal dilators are normally advocated to assist in the breakdown of vaginal adhesions associated with pelvic RT to prevent the development of vaginal shortening and stenosis [154, 155]. They can also be used for women who have had radical pelvic surgery affecting the vagina (excision of anterior or posterior vaginal wall) or after exenteration and vaginal reconstruction to assist in maintaining vaginal patency and dimensions and to prevent introital narrowing. However, it should be noted that women experience considerable difficulty in adhering to the recommendation of regular dilation, particularly in the absence of precise guidance regarding overall duration of use and empirical data on efficacy [144, 155, 156].

Oil- or silicone-based lubricants are also useful to reduce discomfort associated with anorectal pain, and steroid treatment may be helpful for oral, anal, vaginal or penile GVHD [157, 158]. Persistent neuropathic pain affecting genital sensation may benefit from referral to a chronic pain team where, in addition to mindfulness or CBT techniques that modify cognitive interpretation of pain and desensitisation techniques, medication for chronic pain such as gabapentin or pregabalin may be useful.

Psychosexual therapy offers a behavioural framework to broaden sexual expression in a series of stages (see Tables 24.4 and 24.5) that initially may include a ban on penetrative sexual activities associated with pain to prevent cyclical reinforcement of this distressing symptom [159]. Once anticipatory tension/sexual avoidance is reduced through CBT or mindfulness techniques and noncoital sexual behaviours restored, the patient may be taught desensitisation and graduated instrumentation with fingers, dilators or vibrators prior to vaginal (or anal) containment and progress to full intercourse as altered genital anatomy permits [134, 142, 159].

24.13 Erection Difficulties

Erectile dysfunction (ED) is defined as the persistent inability to achieve and/or maintain a penile erection that is sufficient to complete sexual activity. In a recent UK national survey (Natsal-3) the prevalence of erectile difficulties in the general population demonstrated an age-related prevalence, predominantly accounted for

by the development of cardiovascular risk factors associated with diabetes and lifestyle factors such as smoking [39].

However, a recent study in younger adult survivors of lymphoma ($n=59$, age range 18–55 years) found that 61 % of men had ED post-treatment as measured by the IIEF [160] and no association was found between the presence of ED and these traditional risk factors.

In considering the management of ED in younger men after cancer treatment, it is important to consider the psychosocial factors that may influence erectile function such as an evolving sexual identity, transient relationship contexts, variable sexual experience and levels of sexual knowledge [161]. Given the multifactorial aetiology (vascular, neurogenic, hormonal and psychogenic) of erection difficulties in this age group, it is therefore likely that integration of pharmacological and psychosexual or psychological strategies will yield the best outcomes [123, 124, 162].

As in the management of older adults with treatment-induced erectile difficulties (ED), the underlying or dominant aetiological mechanism(s) often dictate selection of pharmacological treatment for ED [162]. It is important to note that adequate testosterone levels are important not only for sexual motivation, penile erection and orgasm but also for response to oral pde5-I medications such as sildenafil, tadalafil, vardenafil or avanafil [163–165].

Where cancer treatment (pelvic surgery or radiotherapy) has had an adverse impact on vascular or neural components of erection, the early initiation of a suitable oral pde5-I drug is usually considered first-line treatment either alone or in combination with sexual counselling/psychosexual therapy, particularly where significant psychogenic issues or performance anxiety is identified [124, 162]. Young men who require support of erectile function with oral medication may need to try the drug on up to six to eight occasions under optimal conditions (with adequate sexual stimulation) before consideration of dose or drug amendment in order to avoid prematurely abandoning treatment [162].

For gay men or couples who engage in anal intercourse, reduced erectile rigidity that is adequate for vaginal penetration can prove problematic as greater erectile rigidity is normally required for anal penetration. Furthermore, pelvic radiotherapy can cause acute and longer-term changes in the rectal mucosa, leading to pain and bleeding if anal intercourse is attempted. Compliance with safer sex practices, including condom use, can also be problematic when erectile rigidity is unreliable [166].

Where oral medication fails to offer an adequate erectile response, it is usual in older adults to consider the use of topical (injection, intra-urethral pellet or ointment) alprostadil and/or the use of vacuum erection devices (VEDs). However, clinical experience suggests there is a heightened reluctance among younger men with severe treatment-induced ED to use biomedical management strategies that reduce spontaneity and require greater partner cooperation/visibility. Hence, assuming an adequate trial of suitable oral medication proves ineffective, there may be an argument for earlier consideration of surgical penile implants where aetiology of the ED is largely organic (neurogenic or vasculogenic) and considered unlikely to improve.

24.14 Ejaculatory and Orgasmic Difficulties

Changes in orgasmic or ejaculatory function, whilst a common sexual consequence of pelvic surgery or radiotherapy, are rarely discussed pre- or post-treatment unless raised by patients themselves [102, 115, 167].

Young men who experience either retrograde ejaculation after retroperitoneal lymphadenectomy or a total loss or reduction in semen production (anejaculation or dry orgasm) after pelvic surgery or radiotherapy sometimes experience orgasmic sensation as less intense or satisfying [71, 107].

For many gay men, viewing and handling ejaculate is an important aspect of the couple's sexual enjoyment which can be adversely affected [168].

Some clinicians have used off-licence medications such as alpha blockers to improve bladder neck closure, thus reducing surgically induced retrograde ejaculation, but unfortunately empirical evidence of efficacy is not available.

For young men and women, difficulty in achieving orgasm or climax can also be associated with inadequate sexual arousal, sexual pain, increased anxiety or a tendency to "split" mind and body whereby the person experiences self as a "spectator" during sexual encounters [169, 170]. During traumatic experiences, including intrusive and unpleasant cancer treatments, it is not uncommon to find that disassociation or creating a mind-body split is a useful coping strategy to tolerate such events and reduce emotional distress. However, once the threat is past, this mind-body split can be maintained, resulting in an inability to receive/connect with the multiplicity of sensations and stimuli associated with sexual encounters and/or an inability to relax and 'let go' to experience climax. Furthermore, as illustrated in Fig. 24.1, if the person has little or no desire for sex and cannot become subjectively aroused, then the necessary level of sexual tension does not occur, and again orgasm (and thus ejaculation) remains elusive [169].

Sensate focus and psycho-education combined with vibratory devices (clitoral or vaginal vibrators, cock rings) and intimate lubricants that enhance or create genital sensation (warming/cooling/tingling) are often used to enable greater sensual awareness and promote relaxation during sensual erotic and sexual contact. Furthermore, psychological techniques such as CBT, mindfulness and relaxation exercises may be used to reduce generalised anxiety and negative tension thus allowing the person to remain *in the moment* and become more aware and aroused by multiple sensual inputs from self and partner [142, 171].

24.15 Implications for Health Professionals Working in AYA Oncology

Within oncology, even in patient groups considered high risk for sexual morbidity, patients and health professionals continue to demonstrate reluctance to discuss the sexual consequences of treatment [102, 114, 115].

A recent UK survey of younger adults (18–45 years, 66.2% response rate) sought participant's views of medical follow-up after treatment for breast, germ cell or haematological malignancies. Participants completed questionnaires prior to and following their scheduled follow-up appointments regarding the topics they intended to (T1) and subsequently discussed (T2) with their medical team [172]. At a mean of 8 years post-treatment completion, only 19 participants (12.4% / mean age 37.9) stated an intention to discuss sexual difficulties at follow-up, with only 8 (5.2%) subsequently reporting they had actually done so. Perhaps unsurprisingly, survey participants stated that they preferred a hospital-based model of follow-up, with a focus on disease surveillance and obtaining reassurance regarding remission/disease control remaining their service priority [172].

However, despite this narrow focus on disease recurrence, young adult survivors were in favour of improved access to supportive care services such as dietetics advice and psychological counselling. It therefore remains important for AYA cancer services to explore alternative models of follow-up (AHP/nurse/GP-led) that can be more inclusive and responsive to the broad range of treatment consequences experienced by younger adults living with and beyond cancer.

Schover et al. [102] recently argued that all large cancer centres should, ideally, have multidisciplinary sexual rehabilitation clinics with outreach services both within and beyond the centre to address site-specific and more complex sexual consequences of treatment.

It may be necessary to consider a service provision model that is "multilevel" in terms of complexity (Fig. 24.2) with oncology professionals that can offer Level 1-supported self-management strategies to all patients [173, 174]. Specific oncology professionals could be trained in sexual morbidity and rehabilitation to offer initial screening and proactive psycho-education on sexual recovery to all higher-risk patient groups (Level 2

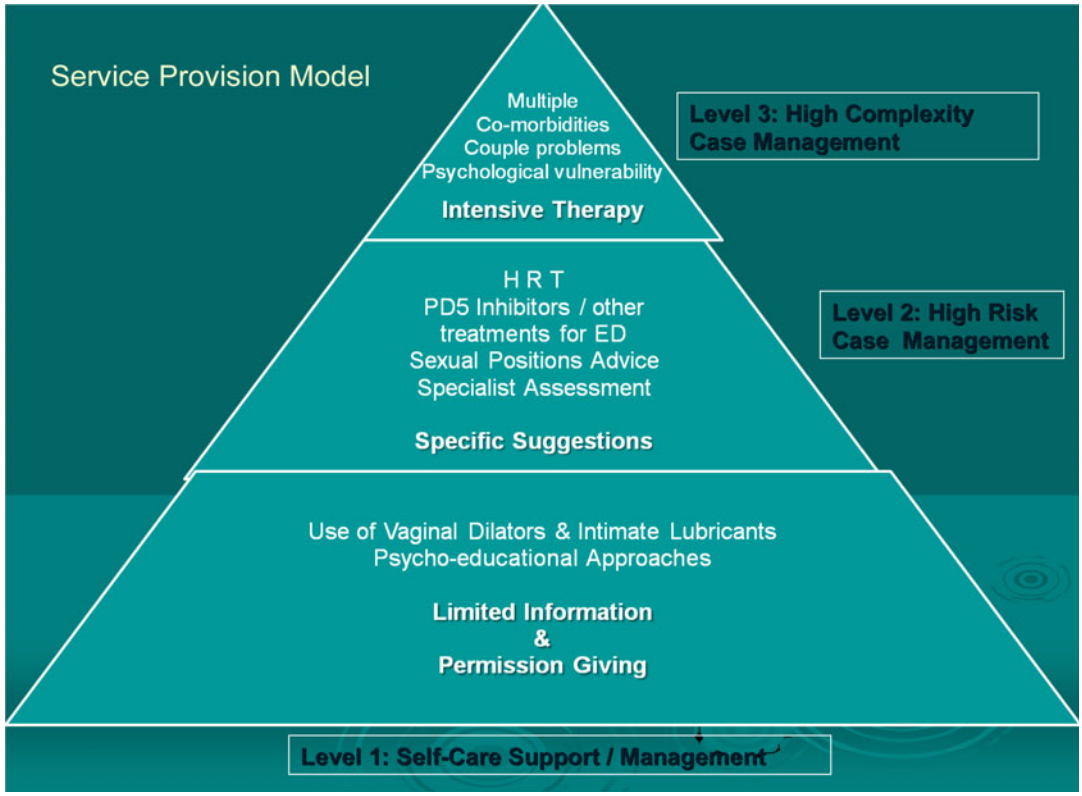

Fig. 24.2 Service provision model for sexual rehabilitation after cancer treatment (Adapted from Annon [173])

high-risk case management). And finally the Level 3 specialist management of smaller numbers of individuals or couples with more complex and enduring difficulties can be better managed by those with specialist training and clinical research expertise in the assessment and management of treatment-induced sexual dysfunction.

Furthermore, in order to ensure patients and partners receive optimal management of their sexual concerns and difficulties, we need to address the paucity of intervention studies in this neglected aspect of cancer survivorship. Whilst there is adequate understanding of the prevalence and type of sexual difficulties that most commonly affect adult patients [102], the evidence base remains scarce in the adolescent and younger adult age group. What is urgently needed for all ages and diagnostic groups, however, is the design of methodologically robust intervention studies regarding the most effective biomedical, psychological and psychosexual management of treatment-induced sexual difficulties. This research is essential for clinicians and those responsible for the funding and provision of services, to begin to offer high-quality, systematic management for the common sexual difficulties that continue to adversely affect the lives of adolescents and young adults affected by cancer.

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Fertility Preservation in the Pediatric Setting

25

Yasmin Gosiengfiao and Teresa K. Woodruff

Long-term effects of cancer therapy have gained significance with advances in childhood cancer treatment and rise in survival rates. Of the myriad of late effects, infertility is among the top concerns of survivors of childhood cancer. Surveys show that a majority of survivors of pediatric cancers express the desire to have children in the future [1–4]. Although many patients and their parents are focused on survival at the time of diagnosis, for majority, fertility became an issue after treatment, especially as they became adults and their peers married and began families [4, 5].

Sterility is defined as the inability to conceive a pregnancy naturally in the absence of clinical interventions [6]. Infertility is the inability to conceive after 1 year or more of unprotected sexual intercourse with the same partner during the fertile phase of the menstrual cycle [7]. Impaired fecundity is the physical difficulty in either getting pregnant or carrying a pregnancy to live birth [8]. In the general population, the baseline incidence of sterility is about 1 %. This does not change with age during the reproductive period [9]. In the 2006–2010 National Survey of Family Growth [8], it was noted that 6 % of married women aged 15–44 were infertile while 11 % of all women in that age group had impaired fecundity. About 9.4 % of men aged 15–44 reported some form of infertility.

In the Childhood Cancer Survivor Study, about 13 % of female childhood cancer survivors have been reported to have clinical infertility [10]. Male childhood cancer survivors were half as likely to sire a pregnancy compared to a sibling cohort, with a 46 % prevalence of infertility [11, 12]. The Childhood Cancer Registry of Piedmont reported a fertility deficit of 41 % among female childhood cancer survivors treated from 1967 to 2000 [13]. The Fertility after Chemotherapy and Radiotherapy in Childhood and Adolescence (FeCt) survey in Germany reported that 31 % of 83 female and 29 % of 117 male survivors have infertility based on previous fertility tests [14]. Based on each of these studies, it is clear that there is an impact of treatment on long-term reproductive tract function – both fertility and endocrine activity. That said, the treatment effect on reproductive health and fertility depends largely on the age and gender of the patient, type of surgery performed, dose and site of radiation, and type and cumulative dose of chemotherapy, so providing precise information to an individual patient remains a challenge in our field [15–18].

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25.1 Impact of Cancer Therapy on Reproductive Health and Fertility

25.1.1 Male

Surgery, chemotherapy, and radiation can affect a male's reproductive function by impairing the normal functioning of any of the components of male reproductive health, from the hypothalamic-pituitary-gonadal axis to the testes and genitourinary organs. Infertility can result from the spinal/pelvic surgery- or radiation-induced functional abnormalities of the genitourinary organ, gonadotropin deficiency from therapy directed at the central nervous system, or gonadotoxic effect of chemotherapy.

Adult male childhood cancer survivors are less likely to sire a pregnancy compared to their siblings (Hazard ratio of 0.56) [11], with the prevalence of infertility in survivors of 46 % compared to 17.5 % in siblings [12]. Up to half of these survivors are found to be azoospermic or oligospermic [11, 19].

A primary risk factor for oligo- or azoospermia is alkylating agent-induced gonadotoxicity. Patients receiving high doses of cyclophosphamide or procarbazine [20–25] are at particularly high risk. Other alkylating agents often associated with oligo-/azoospermia include mechlorethamine, ifosfamide, busulfan, melphalan, and cisplatin. The degree of gonadotoxicity is related to the cumulative dose of alkylating agents administered. Cumulative doses reportedly associated with a high risk of azoospermia are listed in Table 25.1. In a small group of cancer survivors, exposure to bleomycin was also found to be a risk factor for infertility [12], although this has not been demonstrated in other studies involving patients who received bleomycin. Chemotherapy which appears to not have deleterious effects on spermatogenesis includes actinomycin, vinblastine, and vincristine [22].

More recently, in order to be able to better assess alkylating agent exposure and risk of gonadotoxicity, two methods, the summed alkylating agent dose (AAD) score (Table 25.2) and cyclophosphamide equivalent dose (CED) (see Table 25.3), have been used.

Table 25.1 Cumulative alkylating agent doses associated with azoospermia [2, 11, 20, 22, 26–30]

Agent	Cumulative dose associated with azoospermia
Cyclophosphamide	>5–7.5 g/m^2 associated with abnormal semen parameters, >19 g/m^2 consistently result in azoospermia
Ifosfamide	>60 g/m^2
Procarbazine	>4 g/m^2
Busulfan	>600 mg/m^2
Melphalan	>140 mg/m^2
Cisplatin	>600 mg/m^2

Table 25.2 Summed alkylating agent dose score

	Tertile score		
Alkylating agent	1	2	3
BCNU (carmustine)	1–300	301–529	530–5370
Busulfan	1–317	318–509	510–6845
CCNU (lomustine)	1–361	362–610	611–3139
Chlorambucil	1–165	166–634	635–3349
Parenteral cyclophosphamide	1–3704	3705–9200	9201–58,648
Oral cyclophosphamide	1–4722	4723–10,636	10,637–143,802
Ifosfamide	1–16,771	16,772–55,758	55,759–192,391
Melphalan	1–39	40–137	138–574
Nitrogen mustard	1–44	45–64	65–336
Procarbazine	1–4200	4201–7000	7001–58,680
Intrathecal thiotepa, mg	1–80	81–320	321–914
Thiotepa	1–77	78–220	221–3749
	Cumulative doses in mg/m^2 except where noted		

Adapted from Green et al. JCO, 2009 [31]
Add tertile score for each of the alkylating agents given to the patient

Table 25.3 Cyclophosphamide equivalent dose

CED (mg/m^2) =	1.0 × cumulative cyclophosphamide dose (mg/m^2)
	+0.244 × cumulative ifosfamide dose (mg/m^2)
	+0.857 × cumulative procarbazine dose (mg/m^2)
	+14.286 × cumulative chlorambucil dose (mg/m^2)
	+15.0 × cumulative BCNU dose (mg/m^2)
	+16.0 × cumulative CCNU dose (mg/m^2)
	+40 × cumulative melphalan dose (mg/m^2)
	+50 × cumulative thiotepa dose (mg/m^2)
	+100 × cumulative nitrogen mustard dose (mg/m^2)
	+8.823 × cumulative busulfan dose (mg/m^2)

Adapted from Green et al. [32]

In a large CCSS study [11], the summed AAD score was found to be inversely correlated with the likelihood of siring a pregnancy with those with higher AAD scores having a lower likelihood of siring a pregnancy: summed AAD score of 2 (HR, 0.67), 3(HR, 0.48), 4 (HR, 0.34), 5 (HR, 0.38), or 6–11 (HR, 0.16). In addition, those who received a higher cumulative dose of cyclophosphamide (third tertile HR 0.42) or procarbazine (second tertile HR 0.48, third tertile HR 0.17) were also less likely to sire a pregnancy. The summed AAD score or 3 or higher was also found to be a risk factor for infertility on multivariate analysis in another CCSS study of 938 male childhood cancer survivors and 174 siblings who had tried to become pregnant [12].

Similarly, the CED was inversely correlated with the likelihood of siring a pregnancy, with a statistically significantly decreased likelihood of siring a pregnancy in those who received a CED≥4000 mg/m^2 (4000–<8000 HR 0.72; 8000–<12,000 HR 0.49; 12,000–<16,000 HR 0.37; 16,000–<20,000 HR 0.53; ≥20,000 HR 0.17) [32]. The CED was also found to be negatively correlated with sperm concentration in 214 adult male long-term childhood cancer survivors on the St. Jude Life Cohort [33], with a mean CED of 10,830 mg/m^2 in those who were azoospermic, 8480 mg/m^2 in the oligospermic, and 6626 mg/m^2 in the normospermic. Those with a CED <4000 mg/m^2 were very likely to be normospermic. However, there was a substantial overlap of CED with normospermia, oligospermia, and azoospermia. It is thus postulated that genetics, pharmacogenomics, and other factors may play a role.

Younger age or prepubertal state does not seem to be gonadoprotective [11, 21, 22]. They exhibit similar rates of azoospermia or oligospermia as postpubertal males. Despite this, prepubertal males who received gonadotoxic chemotherapy still seem to be just as likely to be able to undergo puberty after chemotherapy [22].

Radiation has significant gonadotoxic effects as well. Patients treated for tumors in the pituitary-hypothalamic region or with testicular radiation have severe gonadal and sexual dysfunction [23]. In a CCSS study, partners of male survivors whose testes were in or near the radiation field or whose testes were shielded had very few live births [34].

The testicular germinal epithelium is sensitive to the gonadotoxic effects of radiation. Testicular radiation doses as low as 0.1–1.2 Gy can cause oligo- or azoospermia by damaging dividing spermatogonia and disrupting cell morphology [35, 36]. Permanent azoospermia has also been reported following a single fraction of testicular radiation with 4 Gy or 1.2 Gy fractionated [35, 36].

Leydig cells are more resistant to damage from radiation, and despite severe impairment of spermatogenesis, survivors are frequently noted to have normal pubertal progression and normal potency. The extent of damage may be related to the dose and age at which radiation is delivered [36]. Testicular radiation dose >20 Gy in prepubertal males and >30 Gy in sexually mature males is associated with Leydig cell dysfunction [37].

25.1.1.1 Pregnancy Outcome

Many male childhood cancer survivors are able to sire pregnancies. In a Childhood Cancer Survivor Study (CCSS) [24], 1227 out of 4106 sexually active male childhood cancer survivors reported siring 2323 pregnancies. Of these, 69 % resulted in live births, 1 % stillbirths, 13 % miscarriages, 13 % abortions, and 5 % had unknown outcomes or were in gestation. The proportion of live births was lower for partners of childhood

cancer survivors compared to partners of male siblings of cancer survivors. Pregnancy outcome did not seem to be affected by the type of chemotherapy the survivors received. However, the rate of miscarriage was higher for partners of male survivors treated with >5000 mg/m^2 procarbazine compared to those who received less or no procarbazine. Even among survivors who met the definition for infertility, a little over a third reported at least one pregnancy with a female partner that resulted in a live birth, suggesting there may be periods of fertility and infertility [12]. Although sperm concentration is reduced after cancer therapy, studies have shown that the sperm produced seems to carry as much healthy DNA as sperm from the healthy population [13]. This suggests that assisted reproduction may be considered in these patients.

25.1.2 Female

After cancer treatment, females can develop acute ovarian failure which may or may not recover, premature menopause, and varying degrees of sub- or infertility [3]. Acute ovarian failure occurred in 6.3 % and premature nonsurgical menopause in 8 % of childhood cancer survivors in the CCSS [38]. Adult female childhood cancer survivors are less likely to have ever been pregnant [31] with an increased risk of clinical infertility compared to siblings, most pronounced in the early reproductive ages, and an increased time to first pregnancy [10]. Particularly at risk are those who are of or approaching reproductive age at the time of cancer treatment, those who have received high doses of alkylating agents (particularly cyclophosphamide, lomustine, and procarbazine), and those diagnosed with Hodgkin lymphoma [31, 38–43].

Those who had a summed AAD score (Table 25.2) ≥3 were less likely to have ever been pregnant and to develop nonsurgical premature menopause [31, 44]. Similarly, increasing CED (Table 25.3) was associated with a higher likelihood of developing nonsurgical premature menopause (CED 4000–<8000 mg/m^2 HR 0.72; 8000–<12,000 HR 0.49; 12,000–<16,000 HR 0.37; 16,000–<20,000 HR 0.53; ≥20,000 HR 0.17) [32].

Direct or scatter radiation to the female reproductive organs (either by total body irradiation TBI), spinal, abdominal and/or pelvic radiation) may also cause ovarian and/or uterine damage.

The human oocyte is sensitive to radiation with an estimated lethal dose (LD_{50}) <2 Gy [45]. Abdominal radiation results in severely damaged ovaries with follicle growth inhibited in most cases, and the number of small, nongrowing follicles markedly reduced in most [46]. Increasing doses of radiation to the ovaries (especially >10 Gy) result in increased likelihood of developing acute ovarian failure or nonsurgical premature menopause [38]. Predictions to estimate the age of menopause after radiation may be made using an adaptation of the Faddy-Gosden model by Wallace et al. [45].

Uterine radiation in childhood increases the incidence of nulliparity, spontaneous miscarriage, and intrauterine growth retardation. Although the mechanism is unknown, it is believed to be due to reduced elasticity of uterine musculature and uterine vascular damage [47, 48].

Female childhood cancer survivors who received hypothalamic/pituitary radiation ≥30 Gy (RR 0.61) or ovarian/uterine radiation dose >5 Gy (RR0 0.56 for 5–10 Gy, RR 0.18 for >10 Gy) were less likely to have ever been pregnant [10, 31].

25.1.2.1 Pregnancy Outcomes

Pregnancy outcomes may be affected by cancer treatment in females as well. Female childhood cancer survivors are less likely to have a live birth. In the CCSS study [49] of 4029 pregnancies in 1915 survivors, 63 % resulted in live births, 1 % stillbirths, 15 % miscarriages, and 17 % abortions and 3 % had unknown status or were in gestation. The type of treatment did not have a significant impact on pregnancy outcome although there was a trend toward a higher risk of miscarriage if the ovaries were irradiated or near the radiation field and there was a higher risk of miscarriage with spinal radiation. No adverse pregnancy outcomes were noted with most chemotherapy agents.

Children born to female childhood cancer survivors were more likely to be born preterm and small for gestational age, especially those

born to women who received uterine radiation doses >5 Gy [38, 50]. The effect of uterine radiation may be greater and the threshold lower for girls treated prior to menarche. Differences in gender ratio and increases in simple malformations, cytogenetic syndromes, or single-gene defects have not been noted in offspring of female survivors [49].

25.2 Surrogate Markers of Fertility

Pregnancy or siring a pregnancy is the best measure of fertility. However, the use of pregnancies as a measure of fertility is limited by the need to wait until adulthood and attempts for pregnancy. Surrogate measures of fertility are therefore necessary to assess the effect of cancer treatment on fertility. Several markers have been used to assess ovarian and testicular reserve as surrogate measures of fertility (Table 25.4). Of note, most of the research regarding these markers has been performed in adults seeking treatment for infertility [51]. These markers can be affected by a variety of factors, including age at the time of testing, age at the time of chemotherapy and/or radiation therapy and/or gonadal surgery, type and cumulative dose of chemotherapy received, dose and target site of radiation received, genetic factors, other illnesses, and history of infertility.

Table 25.4 Measures of ovarian and testicular reserve

(A) Measures of ovarian reserve
(a) Menstrual cycles
(b) Antral follicle counts
(c) Endocrine hormones
(i) Follicle-stimulating hormone (FSH)
(ii) Luteinizing hormone (LH)
(iii) Estradiol (E2)
(iv) Inhibin B
(v) Anti-Mullerian hormone (AMH)
(B) Measures of testicular reserve
(a) Semen analysis
(b) Endocrine hormones
(i) Follicle-stimulating hormone (FSH)
(ii) Luteinizing hormone (LH)
(iii) Testosterone
(iv) Inhibin B

The differences in male and female reproductive systems influence the available methods for assessing ovarian and testicular reserve as well as options for fertility preservation. In females, it is generally accepted that oocyte production ceases in fetal life and a female is born with a finite number of follicles (ovarian reserve) which diminishes throughout life until menopause [52]. At 5-month gestation, the initial number of follicles in humans is approximately ten million primordial follicles. By the time a girl reaches menarche, this number has declined to nearly 500,000 and continues to decline thereafter until menopause through the release of a few oocytes during the menstrual cycle, with the majority being lost as a result of atresia. There is limited evidence that ovarian regeneration may occur from stem cells of a variety of sources, including bone marrow [53–55].

In males, spermatogenesis begins in the prepubertal stage. Spermarche (release of spermatozoa) occurs in early to mid-puberty with age-appropriate gonadotropin production, preceding the ability to produce an ejaculate.

25.2.1 Assessing Ovarian Reserve

25.2.1.1 Menstrual Cycles

The presence or absence of menses has traditionally been used as the primary measure of fertility. In the United States, menarche (onset of menstruation) occurs at a median age of 12.43 years [56]. Menopause is the absence of menstrual cycles for 12 consecutive months, with the average age of menopause in the United States being 51 years. Menopause before the age of 40 years is called premature menopause.

Survivors of childhood cancer in the United States had a cumulative incidence of nonsurgical premature menopause of 8 % compared to 0.8 % in their siblings (RR = 13.21, 95 % CI = 3.26–53.51; $P < 0.001$) [40]. In contrast, in Europe (Euro2K cohort), the median age at menopause among childhood cancer survivors was noted to be 44 years old, with only 2.1 % having

nonsurgical premature menopause [43]. Survivors who received both alkylating agents and abdominal-pelvic radiation were more likely to be postmenopausal than were those who underwent surgery alone, and there was a dose correlation of both radiation and alkylating agent and the risks of menopause and infertility [42].

In the perimenopausal period, despite a decreased ovarian reserve or fertility, women may continue to menstruate, suggesting that the presence of regular menstrual cycles does not correlate with intact fertility or ovarian reserve. Adult childhood cancer survivors with regular menstrual cycles and basal FSH <10 IU/l have been noted to have diminished ovarian reserve with smaller ovarian volume, lower number of small antral follicles per ovary, and lower total number of follicles per ovary [41]. Bath et al. found subtle ovulatory disorders in adult female childhood leukemia survivors who had normal menstrual cycles [57]. In addition, 22 % of survivors who suffered chemotherapy-induced amenorrhea were able to have children [58].

25.2.1.2 Antral Follicle Counts (AFC) and Total Ovarian Volume

Antral follicle counts (AFC) and total ovarian volume (TOV) can be measured in adult women through transvaginal ultrasonography. In normal women, AFC, TOV, and chronological age are individually predictive of menopausal status [59] with an age-related decline in both AFC and TOV [60].

In adults, the mean premenopausal ovarian volume is 4.9 ± 0.03 cm^3, while the postmenopausal volume is 2.2 ± 0.01 cm^3. An evaluation of the ovarian reserve and reproductive lifespan could be assessed using ovarian volume in correlation with the Faddy-Gosden model [61]. In adult survivors of childhood cancer, ovarian volume is reduced compared to controls [41, 62].

The mean AFC declines from 15 in normal women aged 25–34 years to 4 in those aged 41–46 years [63]. In assisted reproduction, AFC predicts ovarian response and pregnancy results with no pregnancy occurring when the AFC is <3 [64]. Adult childhood cancer survivors with normal menstrual cycles have been noted to have fewer small antral follicles and total number of follicles per ovary [41].

In children, AFC and TOV could be performed transabdominally. However, this has not been well studied. No normative values exist and there are very few radiologists skilled in this technique.

25.2.1.3 Endocrine Hormones (FSH, LH, Estradiol [E2])

During the menopausal transition and menopause, decreased ovarian function results in increase in FSH levels, decrease in E2 and inhibin B, and a marked decline in primordial follicle numbers in the ovaries [65–68]. Several studies demonstrate the same findings in select groups of female childhood cancer survivors.

However, the use of FSH, LH, and estradiol in assessing fertility potential of cancer patients is limited by variation with the menstrual cycles and low to undetectable levels in prepubertal children, making it difficult to detect changes with or after cancer therapy.

25.2.1.4 Endocrine Hormone: Inhibin B

Inhibin B is a hormone secreted by granulosa cells of the preantral and early antral follicles in females, which has been investigated as a possible surrogate marker of ovarian reserve in childhood cancer survivors. Crofton et al. [69] showed inhibin B to be suppressed with chemotherapy, though usually transient, in nine prepubertal females. Lower inhibin B levels have also been noted in childhood cancer survivors compared to controls (median, 94 vs. 111 pg/ml; $P = 0.03$) [70]. Although inhibin B levels decrease with age and during premature ovarian failure, it does not predict the onset of ovarian failure and is a fairly late marker of a reduced follicle pool [71–74]. Its use as a marker is also hampered by variation during the menstrual cycle [75].

25.2.1.5 Endocrine Hormone: Anti-Mullerian Hormone (AMH)

AMH is a hormone produced by the granulosa cells of the secondary, preantral, and early antral follicles. It acts as a follicular gatekeeper, limiting follicle growth and estradiol production from small antral follicles prior to selection [76, 77].

At birth, the serum AMH level is barely detectable and then rises in childhood and adolescence, peaking in a woman's early 1920s before declining to menopause, correlating positively with nongrowing follicle recruitment [72, 78, 79].

AMH has been increasingly used as a measure of ovarian reserve to assess the gonadotoxic effect of chemotherapy/radiotherapy, especially in children in whom FSH and inhibin B are not useful [80–84]. Compared with other ovarian reserve markers, AMH appears to be the best hormonal marker for ovarian reserve as it has several advantages. AMH levels reflect changes in ovarian function earlier, there is no significant fluctuation during the menstrual cycle, and it is highly predictive for timing of menopause [73, 85, 86]. Serum AMH levels are detectable in healthy females from birth to menopause [87, 88], making it suitable as a marker even in prepubertal girls. However, AMH assays continually evolve and there are no international standards established. In addition, there is limited data correlating AMH and natural fertility at different stages of reproductive life, especially in children and adolescents.

Several studies looking at AMH as a measure of ovarian reserve in cancer survivors have shown promise. In women treated with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) chemotherapy for Hodgkin lymphoma during childhood, AMH was noted to be lower compared with healthy women and women treated without MOPP [89]. Although the mean AMH concentration in a cohort of childhood cancer survivors was no different from controls, the AMH levels were lower than the 10th percentile of normal values in 27 %, identifying subgroups at risk for decreased fertility or premature ovarian failure [90]. AMH declined in adult women with cancer during treatment followed by recovery in some patients, with the rate of recovery determined by the pretreatment AMH level [83]. Similarly, in two small cohorts of female childhood cancer patients 0–18 years old, AMH was detectable across the age range with note of a progressive decline during chemotherapy, regardless of AMH at diagnosis, age, menarche, or treatment given. The degree of recovery depended on the gonadotoxicity of the treatment given [91, 92]. Although promising, more long-term data is needed to ascertain the use of AMH to predict long-term ovarian function after cancer therapy as well as evaluate fertility preservation strategies.

25.2.2 Assessing Testicular Reserve

25.2.2.1 Semen Analysis

Semen analysis is the gold standard for assessing fertility status in the male. It is an easy, cost-effective, and noninvasive test to determine fertility potential in the male at any stage following puberty. Although useful, it is an imperfect tool. It cannot be used in prepubertal males. Controversy remains on what constitutes as "normal" spermatozoa in semen. Current analysis is guided by the 5th edition of the World Health Organization manual [93]. Routine semen analysis includes semen volume and viscosity, sperm concentration, sperm motility, and morphology.

Varying chemotherapeutic regimens can cause temporary (with recovery within 24 months) or permanent oligo- or azoospermia [20, 22, 23, 27, 33, 94]. Of the chemotherapeutic agents, the effect of alkylators (especially cyclophosphamide) on semen has been the most extensively studied. Similarly, radiation effects may also recover within 24 months, depending on dose and site of radiation.

Other sperm function tests (such as sperm-cervical mucus interaction, tests of sperm capacitation, tests of hemizona and zona pellucida binding, sperm penetration assay, tests of sperm DNA damage, assessment of reactive oxygen species, and sperm proteomics) are available but not routinely used clinically [95–97].

25.2.2.2 Endocrine Markers: FSH, LH, Testosterone, and Inhibin B

Levels of FSH have been shown to be inversely correlated to testicular spermatogenic function. Azoospermic patients are found to have an elevated basal FSH [98]. Male childhood cancer survivors have higher FSH and LH and lower testosterone levels than controls [19, 21, 27]. Testosterone can be normal prepubertally and

drop postpubertally [13, 14]. Although an elevated basal FSH level gives a good indication of testicular damage, normal levels do not rule out azoospermia [15].

Inhibin B is a hormone secreted by the Sertoli cells. More recently, inhibin B has been used and found to be low in male childhood cancer survivors compared to sibling controls [18]. Lower levels of inhibin B have been noted in males after chemotherapy and radiotherapy, such as after treatment with MOPP (mechlorethamine, vincristine, procarbazine, prednisone) chemotherapy for Hodgkin lymphoma [99], with inhibin B showing an independent correlation with sperm concentration. However, others show that inhibin B alone does not reflect spermatogenesis as well as inhibin B in combination with FSH in childhood cancer survivors [100]. More conflicting results have recently surfaced. In the St. Jude Lifetime Cohort Study, it was noted that although serum inhibin B is directly correlated with sperm concentration, neither inhibin B nor FSH nor their ratio is adequate for distinguishing between azoospermic and nonazoospermic long-term survivors of childhood cancer [101].

25.2.2.3 Guidelines for Assessing Ovarian and Testicular Reserve

The Children's Oncology Group (COG) has put together the only available guideline regarding the assessment of ovarian and testicular reserve in long-term survivors of childhood, adolescent, and young adult cancer (http://www.survivorshipguidelines.org/).

In females, the recommendations include checking pubertal (onset and tempo), menstrual, and pregnancy history annually as well as Tanner staging annually until a patient is sexually mature. Baseline FSH, LH, and estradiol are checked at age 13 and as clinically indicated in patients with delayed or arrested puberty, irregular menses, primary or secondary amenorrhea, and/or clinical signs and symptoms of estrogen deficiency [Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers, version 4.0. October 2013]. There are currently no guidelines available on the use of AFC, TOV, and AMH.

In males, the recommendations include annual pubertal (onset, tempo), sexual function (erections, nocturnal emissions, libido) history, annual history of medication use impacting sexual function, as well as Tanner staging and measurement of testicular volume by Prader orchidometry yearly until sexually mature. Baseline FSH, LH, and testosterone are recommended at age 14 and as clinically indicated in patients with delayed puberty and/or clinical signs and symptoms of testosterone deficiency. Semen analysis is not routinely recommended and is to be done as requested by the patient and for evaluation of infertility. Periodic evaluation over time is recommended as resumption of spermatogenesis can occur up to 10 years post therapy [Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers, version 4.0. October 2013].

25.3 Fertility Preservation

In 2006, the American Society of Clinical Oncology released its recommendations on fertility preservation for patients with cancer [28]. These recommendations were updated in 2013 [102]. Several organizations since have followed suit, including the American Society for Reproductive Medicine [103, 104], the American Academy of Pediatrics [105], and the Center for International Blood and Marrow Transplant Research [106]. Key recommendations from these guidelines include discussion with patient and/or parent of the risk of infertility with treatment and available (standard and experimental) options for fertility preservation and referral to a fertility specialist, if interested in fertility preservation. A summary of all professional society guidelines can be found at http://oncofertility.northwestern.edu/ODT-web-portal.

Several fertility preservation options are currently available, the use of which are dictated by gender, age, and sexual maturity, actual or perceived urgency to start cancer therapy, availability of options, and cost (Table 25.5).

Table 25.5 Fertility preservation options

Females
Ovarian shielding during radiation
Ovarian transposition/oophoropexy
Embryo cryopreservation
Oocyte cryopreservation
Ovarian tissue cryopreservation (experimental)
Gonadotropin analogues (experimental)
Males
Testicular shielding during radiation
Testicular transposition/orchiopexy
Sperm cryopreservation
Masturbation
Testicular sperm aspiration (TESA)/extraction (TESE)
Testicular tissue cryopreservation (experimental)

25.3.1 Female Options

25.3.1.1 Ovarian Shielding During Radiation

Females who undergo pelvic radiation may be offered ovarian shielding to protect the ovaries from the harmful effects of radiation. The efficacy of this method has not been studied extensively and it does not protect the ovaries from the effects of chemotherapy. In one report, five of ten patients had evidence of ovarian function after treatment, four of whom achieved pregnancies. Of the other five who developed ovarian failure, four had received multiple courses of highly gonadotoxic chemotherapy and one had a pelvic primary and received radiation to the femoral lymph nodes and pelvis with little central shielding [107].

25.3.1.2 Ovarian Transposition/ Oophoropexy

Another option for females about to receive pelvic radiation is to have the ovaries surgically moved out of the radiation field. Depending on the type of tumor, the ovaries are moved to the paracolic gutters, contralateral to the tumor, or in line with the iliac crests. Ovarian transposition is usually done by minimally invasive surgery although it can also be done by open surgery in case of concomitant resection of the abdominal tumor. In 10–14 % of cases, the procedure can fail to protect the ovaries [108]. A few long-term results in adults have shown mixed efficacy, with earlier reports showing poor outcomes, although this may have been due to coadministration of highly gonadotoxic chemotherapy [109]. Recent data appears to demonstrate more favorable results with 12 live births in 11 women who underwent oophoropexy as part of their Hodgkin lymphoma treatment during adolescence [110]. In another series, girls who underwent oophoropexy had a lower rate of ovarian dysfunction compared to girls who did not have oophorexy [111].

25.3.1.3 Embryo Cryopreservation

One of the available options for fertility preservation in women is embryo cryopreservation. This method involves induction of ovulation with gonadotropins followed by oocyte harvest and in vitro fertilization using partner or donor sperm followed by cryopreservation of the resulting embryos. This option has generally been limited to adult women with known partners or those willing to use donor sperm. Also, this option is limited to those who have ample time to wait prior to starting their cancer therapy. Traditionally, it required a 3–6-week delay for ovulation induction, but with current random start protocols, this delay has been cut down to about 2–3 weeks.

25.3.1.4 Oocyte Cryopreservation

Oocyte cryopreservation involves the same process as embryo cryopreservation with the exception of in vitro fertilization. This obviates the need for a partner or the use of donor sperm. Oocytes are fragile because of their large size, water content, and spindle chromosomal architecture. This process was considered experimental for a period of time due to low success rates, with poor survival rates of cryopreserved oocytes (33.3 %) [112]. Significant improvement in success rates for this procedure prompted the American Society for Reproductive Medicine in 2013 to update their committee opinion on fertility preservation in patients facing gonadotoxic therapies and deemed oocyte cryopreservation to no longer be considered experimental [113].

25.3.1.5 Ovarian Tissue Cryopreservation (OTC)

Ovarian tissue cryopreservation (OTC) is an experimental method of preserving fertility, which should only be performed under an IRB-approved protocol [114]. This technique is an option for patients who require immediate gonadotoxic treatment of an aggressive malignancy when there is insufficient time to undergo the necessary ovulation induction and oocyte retrieval for oocyte and/or embryo cryopreservation. It is also the only available option for prepubertal girls.

Whenever possible, ovarian tissue should be obtained prior to any chemotherapy or radiotherapy. The procedure is usually performed via laparoscopic technique, although a minilaparotomy has also been described. Most oocytes are located in primordial follicles in the cortex of the ovary and some consider a biopsy of a small piece of cortical tissue to be sufficient as it potentially enables cryopreservation of large numbers of oocytes. Nevertheless, many institutions opt for an oophorectomy, with the ovarian cortex being cut into and frozen as cortical strips. In postpubertal girls and adult women, cryopreservation of ovarian tissue may be combined with removal, via puncture, of small antral follicles, making it possible to freeze both ovarian tissue and isolated immature oocytes [115].

When desired for ovarian function resumption and/or for pregnancy purposes, the ovarian tissue can be reimplanted orthotopically (to the original site) or heterotopically (to a site other than its original site). Ovarian function has been shown to be similar for both heterotopic and orthotopically transplanted fresh and frozen ovarian cortex [116]. The first live birth after orthotopic autotransplantation of cryopreserved ovarian tissue in the human was reported by Donnez et al. in 2004 [117]. In 2005, Meirow reported the first live birth after in vitro fertilization following transplantation of thawed cryopreserved ovarian cortical tissue [118]. Since then, over 40 live births have been reported in the literature [115, 119–123], some occurring as late as 5 years posttransplantation.

Despite these successes, concern remains that malignancy may be reintroduced when transplanting tissue that is potentially involved [124]. Tumor contamination is especially concerning in patients with leukemia, in whom obtaining ovarian tissue after first attaining clinical remission may be preferred to reduce the risk of transmission [125–129]. Tumor contamination has also been reported in one patient with Ewing sarcoma [125] but not in other sarcomas [127]. The use of eight-color flow cytometry to detect minimal residual disease in leukemia patients' ovarian tissue has been suggested either prior to cryopreservation or transplantation [126]. This issue of potentially reimplanting tumor-contaminated tissue may be circumvented by harvesting oocytes from the cryopreserved ovarian tissue, then performing in vitro in follicle or oocyte maturation followed by assisted reproduction. Several murine models for in vitro oocyte maturation have been reported with limited success [130, 131]. The use of a three-dimensional alginate hydrogel matrix to mimic the in vivo follicle architecture has been shown to successfully mature immature follicles in mice, resulting in improved in vitro fertilization and embryo implantation birth rates [132–137].

In children, ovarian tissue cryopreservation has been performed since 1998. The procedure has been noted to be feasible and safe without significant postoperative or long-term complications, even in prepubertal girls, and can be safely combined with other medically indicated procedures to minimize the potential inconvenience, additional anesthetic risks, and costs [138, 139]. A higher mean number of primordial follicles per mm^3 have been noted in younger girls [119, 139–141]. Although concerns have been raised about the potential utility of ovarian tissue cryopreserved from prepubertal girls, recent data has shown promise. Cryopreserved ovarian tissue from prepubertal patients that was xenografted into mice survived the transplant with very high number of surviving follicles, a large pool of dormant primordial follicles and note of growth of follicles in response to gonadotropins [142]. Two cases of puberty induction have recently been reported with autograft of cryopreserved ovarian tissue [143, 144]. In addition, in 2015, Demeestere

et al. [145] reported the first live birth after autograft of ovarian tissue cryopreserved before menarche. This was in a woman with primary ovarian failure after a myeloablative conditioning regimen as part of a hematopoietic stem cell transplantation performed for homozygous sickle-cell anemia at age 14 years. Although this patient was premenarchal at the time of ovarian tissue cryopreservation, she already had breast development which began at 10 years of age. Nevertheless, the case offers reassuring evidence for the feasibility of the ovarian tissue cryopreservation procedure when performed during childhood.

25.3.1.6 Gonadotropin-Releasing Hormone (GnRH) Analogues

GnRH analogue administration during chemotherapy is hypothesized to protect the ovaries from the gonadotoxic effects of chemotherapy by suppressing the pituitary-gonadal axis. In rhesus macaques [146] and mice [147, 148], GnRH analogue administration was shown to result in reduction in primordial follicle loss following chemotherapy. However, conflicting results have been noted in adult women [149–154], with this inconsistency being attributed to different chemotherapy protocols being used and different outcome measures employed. Despite its use for fertility preservation purposes being considered experimental, because it is commercially available, many providers recommend and prescribe GnRH analogues to patients undergoing chemotherapy.

25.3.2 Male Options

25.3.2.1 Testicular Shielding During Radiation

For males undergoing radiation involving the testes, the use of radiation shields may protect the testes from the harmful effects of radiation. Although this method of fertility preservation has been available for a long time, its efficacy has not been studied extensively. One report showed that this was effective in protecting testicular growth and function, but attainment of fertility may be difficult to achieve [155].

25.3.2.2 Testicular Transposition

Just as in females, the testes can also be temporarily relocated outside of the radiation field, to either the thigh or anterior abdominal wall [156, 157].

25.3.2.3 Sperm Cryopreservation (SCP)

Sperm cryopreservation after masturbation is the most established and effective method of fertility preservation in adult and pubertal males. Mature spermatozoa can be found at Tanner stage III with testis volume >5 mL. However, spermatozoa production is generally effective in those 13–14 years or older [158–161]. Semen collection in adolescents may be hampered by technical or psychologic considerations. For example, accompanied males were much less likely to produce a semen sample compared to unaccompanied males [162]. Majority of adolescent males are able to produce a semen sample, and in majority, the quality of the sperm is considered potentially useful for assisted conception; hence SCP should be offered to this group of patients [159, 161].

Alternative methods of sperm collection include the use of external vibratory stimulation, electroejaculation under sedation or anesthesia, testicular sperm aspiration or extraction or postmasturbation, or early morning urine sample.

Ideally, sperm should be collected prior to any chemotherapy or radiation. Posttreatment, there is concern of risk of damage to its DNA integrity or compromise to the sample quality. However, a recent study showed that in childhood cancer survivors, the sperm produced do not appear to carry a greater burden of damaged DNA. The DNA fragmentation index was significantly higher only in those treated with radiation or surgery alone, suggesting that the DNA impairment may be associated with the disease rather than due to treatment [163].

25.3.2.4 Testicular Tissue Cryopreservation

For prepubertal boys who cannot bank sperm, the only available option for fertility preservation is to cryopreserve testicular tissue obtained surgically, either by biopsy, wedge resection, or an orchiectomy. This is an experimental method of fertility preservation which should only be done

under an IRB-approved protocol. In various species of mammals of all ages, the spermatogonial stem cells (SSC) in the tissue can be cryopreserved, retain spermatogenic function on thawing, and regenerate spermatogenesis when transplanted [164]. Unlike ovarian tissue cryopreservation, no human pregnancy or live birth has been reported as a result of this fertility preservation method. Meanwhile, the same concern regarding autotransplantation of tumor-contaminated tissue exists. Cell-sorting strategies have been shown to be feasible to isolate germ cells and remove malignant contamination from testicular cell suspension, but concern remains regarding the sensitivity of these methods. Technology to culture and expand SSCs in vitro and then differentiate them to postmeiotic germ cells, including morphologically normal sperm, is underway [164, 165].

25.3.2.5 Costs of Fertility Preservation

Fertility preservation can be a costly endeavor. These costs could include the procedure itself (oocyte harvest, oophorectomy or ovarian biopsy, testicular biopsy, or orchiectomy), infectious disease testing mandated by the Food and Drug Administration (FDA), medications (such as hormones for ovarian stimulation or GnRH analogues), tissue processing and freezing, shipping to a storage facility, and annual storage. In many cases, the patient and his/her family will shoulder a portion of or the entire cost of fertility preservation as insurance has limited, if any, coverage in many states [166–169]. In Illinois, many insurances will cover some of these costs, although tissue processing and freezing, shipping, and annual storage are never covered (personal experience). Financial assistance in the form of negotiated discounts is provided by some organizations such as LIVESTRONG Fertility (formerly Fertile Hope) and Verna's Purse, while some institutions will provide some of their services for free. In addition, patients should also consider the future cost to use the gonadal cells or tissue. Assisted reproduction may or may not be covered by insurance and the cost may run into the tens of thousands. It is important to counsel patients and families regarding these costs and available financial assistance to aid them in decision-making regarding fertility preservation.

25.3.3 Options for Patients Who Have Been Rendered Infertile

Infertility after cancer treatment is devastating to many cancer survivors. However, there are options available for parenthood even for these individuals. Third-party reproduction may be an option for some cancer survivors wherein a third party could donate sperm, eggs, or embryos or "lend" a uterus (surrogacy). Traditional surrogacy refers to when a woman carries the pregnancy after intrauterine insemination (IUI) with the intended father's sperm, while gestational surrogacy is when the implanted embryo is genetically unrelated to the birth mother. Alternatively, infertile cancer survivors could choose to adopt. Just as in fertility preservation, cost could be a potential barrier to these family-building options.

25.3.3.1 Pediatric and Adolescent Oncofertility Practice

Need for Pediatric Oncofertility Practice

Despite recommendations from physician organizations and availability of fertility preservation options, there remains a need for better integration of fertility preservation information and referral into oncology practice. A survey of 879 young adult cancer survivors showed that 68.7 % felt a need for infertility information and 42.5 % felt this need was unmet; 38.2 % said they felt a need for information on infertility treatment and services, and 62.2 % felt this need was unmet [2]. A survey of pediatric oncologists in 2011 [170] showed that while majority acknowledged fertility as a concern and that postpubertal patients should be offered fertility consultation, only 46 % reported that they referred postpubertal male patients to fertility specialists >50 % of time prior to cancer therapy. Even worse, only 12 % reported referring their postpubertal female patients to a fertility specialist prior to cancer treatment.

Among National Cancer Institute (NCI)-designated comprehensive cancer centers (CCCs), 20 of the 30 sites interviewed had some fertility preservation services on-site or had referral programs, but only 13 had experimental services, such as ovarian tissue cryopreservation, and only 8 (27 %) had staff with time dedicated to fertility preservation [171].

Establishment of oncofertility programs or standardized processes addressing patients' fertility preservation needs has been demonstrated to decrease barriers to fertility preservation and increase access to fertility preservation services [172–174]. Despite some progress, there continues to be a need for decisive changes in hospital and public health policies to facilitate the access of young cancer patients to reproductive health care.

25.4 Fertility Resources for Patients and Healthcare Professionals

American Fertility Association
http://www.theafa.org
American Society of Clinical Oncology
http://www.asco.org/guideline/fertility
American Society of Reproductive Medicine
http://www.reproductivefacts.org
Cancer.Net
http://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations--patients/fertility-preservation
Fertile Action
http://www.fertileaction.org/
Fertility Within Reach
http://www.fertilitywithinreach.org/
International Council on Infertility Information Dissemination
http://www.inciid.org
LIVESTRONG Fertility (formerly Fertile Hope)
www.livestrong.org/we-can-help/fertility-services/
MyOncofertility
Patient education resource provided by the Oncofertility Consortium.
www.myoncofertility.org
Oncofertility Consortium
https://oncofertility.northwestern.edu
Repropedia
http://www.repropedia.org/
RESOLVE: the National Infertility Association
http://www.resolve.org
Verna's purse
http://www.reprotech.com/financial-assistance.html

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Rehabilitation and Exercise

26

Marilyn J. Wright and Kirsten Ness

Abstract

Rehabilitation and exercise are essential components of comprehensive cancer care as the disease and its treatments present many challenges to functional independence, health, and quality of life. For adolescent and young adult (AYA) these challenges are compounded by the complex developmental transitions that take place during this time of life. Therefore, cancer rehabilitation practices must be linked with an understanding of the potential interruptions to the typical physical and psychosocial trajectories inherent to adolescence and young adulthood.

Rehabilitation focuses on the prevention or alleviation of physiological and psychosocial impairments, the maximization of function, the promotion of participation in age-appropriate activities, and addressing environmental barriers. Clinical practice is informed by a growing body of research evidence which is integrated with general principles of rehabilitation and theory-based knowledge regarding physiology, psychology, and development. The overall goal of a rehabilitation program is the achievement of an independently functioning and self-sufficient individual who has a satisfying social and emotional life and is a contributing member of society within the limits of their disease and environment.

26.1 Introduction

Rehabilitation and exercise are essential components of comprehensive cancer care as the disease and its treatments present many challenges to functional independence, health, and quality of life. For AYA these challenges are compounded by the complex developmental transitions that take place during this time of life. These include

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autonomy from parents; development of identity in regard to appearance, values, and sexuality; and consideration of the future in regard to education, vocation, relationships, and family planning. Therefore cancer rehabilitation practices must be linked with an understanding of the potential interruptions to the typical physical and psychosocial trajectories inherent to adolescence and young adulthood.

Rehabilitation focuses on the prevention or alleviation of physiological and psychosocial impairments, the maximization of function, the promotion of participation in age-appropriate activities, and addressing environmental barriers. Clinical practice is informed by a growing body of research evidence which is integrated with general principles of rehabilitation and theory-based knowledge regarding physiology, psychology, and development. The overall goal of a rehabilitation program is the achievement of an independently functioning and self-sufficient individual who has a satisfying social and emotional life and is a contributing member of society within the limits of their disease and environment. Rehabilitation goals among AYA may simply be focused on getting back to normal life activities.

The International Classification of Functioning, Disability and Health [66] provides a standard language and framework for the description of health and health-related states to classify and address rehabilitation assessment, treatments, service delivery models, outcomes, and research that is conducive to the field of oncology [26]. The tool recognizes the interactions among the dimensions of *body function and structure*, physiological function and anatomic structure; *activity*, the performance of a task or action by an individual (capacity); and *participation*, an individual's involvement in life situations (performance). Problems within these dimensions are termed, respectively, impairments, activity limitations, and participation restrictions. The model also considers the impact, as either facilitators or barriers, of contextual environmental and personal factors on functioning.

The potential issues encountered by those receiving treatment for or surviving cancer within these dimensions are outlined in Fig. 26.1. They encompass a diverse and complex spectrum. Morbidity varies greatly within the course of treatment and among patients, even in those receiving the same treatment. Many of the impairments have bidirectional associations with components of activity and participation such as mobility, activities of daily living, and involvement in sports, recreation, education, social life, and employment which can impact overall quality of life and the transitions that take place typically through adolescence and young adulthood.

26.2 Body Structure and Function

Impairments of body structure and function are not uncommon among AYA treated for cancer. Documented problems related to rehabilitation include fatigue, disordered sleep, pain, sensory loss, cardiovascular or pulmonary dysfunction, and neuromusculoskeletal or movement disorders.

Fatigue is a common, pervasive, and distressing complication of cancer treatment, which may persist after treatment is completed [87]. It can be described as physical, emotional, or cognitive tiredness not proportional to recent activity (National Comprehensive Cancer Network 2015) with a significant impact on activities, participation, and quality of life [75, 111]. The underlying etiology is likely multifactorial: initial onset is thought to be associated with reduced oxygen delivery to cells, and persistent fatigue may be associated with an inflammatory process as positive correlations between cytokine levels (IL-6, IL1ra) have been reported [110]. Davies et al. [21] categorized fatigue in children and adolescents receiving treatment for cancer as typical tiredness (normal tiredness from regular activities or circumstances), treatment fatigue (energy lost greater than energy replenished resulting from hospitalization, disrupted sleep, pain, chemotherapy, radiation therapy, anemia, psychological or emotional stress), or shutdown fatigue (sustained or profound loss of energy resulting in disengagement with surroundings). Impairments such as chronic pain and fatigue can contribute to social isolation from peers [48, 112].

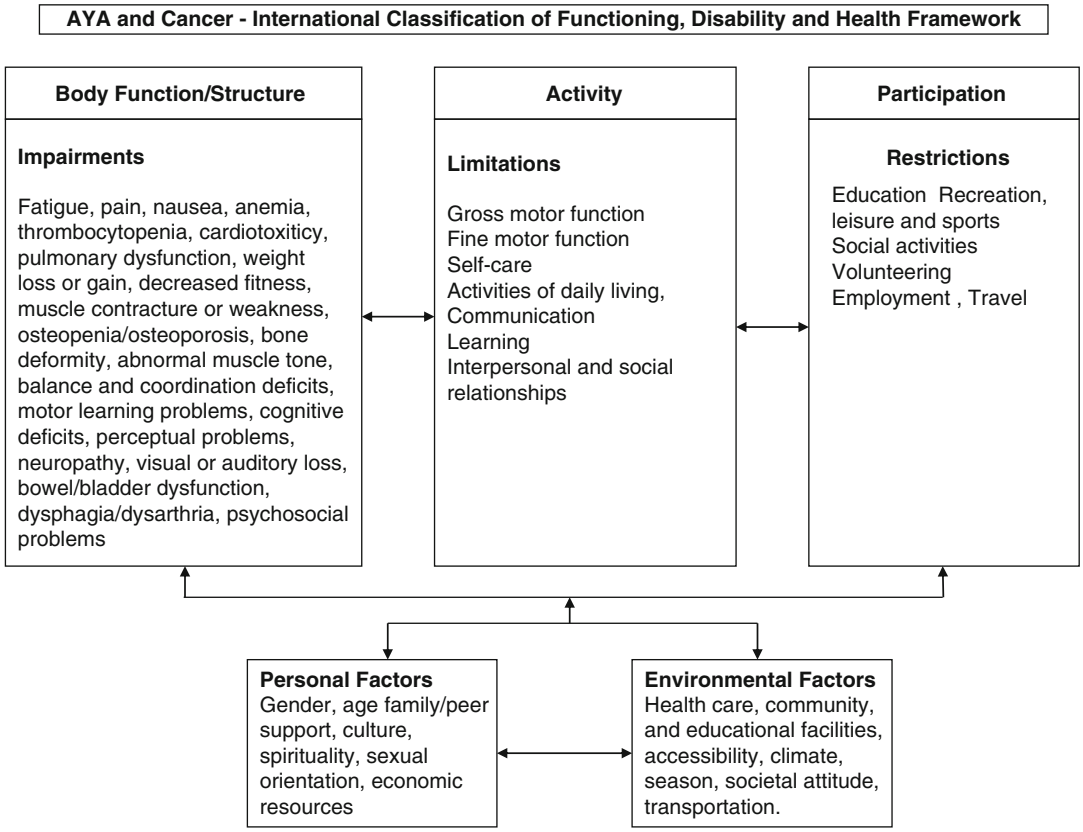

Fig. 26.1 Potential problems encountered by AYA during and following treatment for cancer according to the International Classification of Functioning, Disability and Health

Sleep quality and quantity are often impaired in AYA receiving treatment for cancer [67, 102]. A systematic review [101], summarizing 41 studies among 10–19-year-olds with a cancer diagnosis, reported problems with sleep initiation and sleep continuity, disordered breathing, parasomnias (bed-wetting, teeth grinding, sleepwalking, sleep eating), excessive napping, and excessive daytime sleepiness. Sleep disturbances are associated with fatigue and pain [112] and are exacerbated during chemotherapy administration [76].

Procedural, treatment-associated, and cancer-related pain are common and concerning problems during cancer treatment [48, 101]. Pain can limit activity to the extent that bed rest is necessary and can affect the quality and quantity of sleep. Specific examples include disease-related pain such as tumor pain or metastases to bones or the central nervous system, treatment-related pain including neuropathy, mucositis, constipation, myopathy and bone or joint pain, or pain during procedural postoperative periods [101].

Reduced cardiovascular and pulmonary function [32, 88], poor exercise tolerance, fitness, and endurance can occur [62]. These changes may be subtle during adolescence and young adulthood [109, 114], but are very likely to progress over time [95] and have a significant impact on health in long-term cancer survivors [82]. Anthracycline-induced cardiomyopathy [89], radiation-induced damage to vascular structures [93, 94], and/or treated-related impairments in pulmonary function [72, 80, 103, 116] contribute to reduced exercise capacity [35] which may interfere with motivation to exercise [103] or ability to participate optimally in rehabilitation programs [106]. Muscle wasting or excess fat deposition may also

occur during treatment for cancer, resulting in an undesirable body image, poor self-esteem, and the risk of subsequent higher morbidity and mortality rates [1, 3]. Mechanisms may include disease mechanisms, cranial irradiation, chemotherapy, inactivity, and poor diet [3, 62].

Skeletal impairments are also prevalent. Osteopenia is a common complication of cancer therapy. Contributing factors include high-dose corticosteroids and possibly reduced activity during times of illness [62]. Glucocorticoids, particularly when given concomitantly with asparaginase [118], can result in osteonecrosis/avascular necrosis (AVN) of the hips, knees, ankles, or shoulders [91, 96]. AVN is the result of reduced intramedullary blood flow, marrow ischemia, and ultimately bone necrosis. Patients with AVN may exhibit a painful range of motion, antalgic gait, or difficulty in climbing steps, although AVN may be present even when clinical symptoms are not apparent [84]. Diagnosis is typically made by magnetic resonance imaging [44].

Muscle weakness and loss of joint motion are not uncommon during and after cancer therapy. Treatment with corticosteroids is associated with myopathy of the proximal musculature [62] and is compounded by lack of activity due to bed rest, malaise, fatigue, or nausea. Loss of joint range of motion and skeletal deformity may be the result of general or specific chemotherapy-induced weakness like peripheral neuropathy or related to surgical procedures that either damage the joint or require prolonged immobilization. AYA whose treatments included neurotoxic chemotherapy agents, whose tumor location necessitates radiation to surrounding bone or muscle, and those who have solid tumors located in the extremities are particularly vulnerable. Vincristine-induced peripheral neuropathy is characterized by reduced deep tendon reflexes, paresthesia, pain or muscle cramps, and weakness that can result in contractures and gait abnormalities [98]. Those who have remaining growth and who receive either asymmetrical radiation or radiation near a growth plate are often left with a skeletal deformity like scoliosis or a shortened limb [73, 78, 104, 105]. Surgical reconstruction or amputation is required for many extremity sarcomas and can result in a permanent loss of function [10, 54, 100].

Central nervous system (CNS) damage from CNS tumors or treatments can result in cognitive and perceptual deficits and loss of motor control. These problems, compounded by other impairments such as weakness, decreased range of motion, and obesity, can contribute to multisystem impairments such as difficulties with balance, coordination, and motor learning [107]. Learning and cognitive skills may be affected due to neurosurgery, radiation therapy, or other central nervous system treatments which can impact success in educational or vocational activities [70]. Oral motor dysfunction of neurogenic or mechanical origin can disrupt communication, eating, and associated quality of life among AYA who are exposed to head and neck surgery or radiation, or chemotherapy agents that impact the cranial nerves [74, 115].

26.3 Activity and Participation

Physical and psychosocial impairments have the potential to impact all areas of activity. The associated limitations and participation restrictions can have a reciprocal impact on impairments, as disuse and inactivity perpetuate muscle weakness, poor fitness, and general feelings of well-being. Limitations in gross motor function are obvious in AYA treated for bone and CNS tumors; however, gross motor proficiency can also be compromised during treatment and following treatment in AYA receiving treatment for other cancers including leukemia and lymphoma [29, 97, 108]. Problems with fine motor skills including poor handwriting, manual dexterity, and drawing performance have also been identified [29]. Self-care skills such bathing, toileting, dressing, personal care, and grooming can also be affected [90]. This can be very devastating for AYA who are striving to be independent and maintain their privacy. Other activities of daily living such as establishing or maintaining a household or employment may be limited and affect the transition to and maintenance of productive and

healthy adult life [81, 85, 86, 99]. These may not be immediate priorities for adolescents, but they are important skills to learn to enable independent living as an adult.

Many papers have reported decreased participation in physical exercise amounts and intensities [14, 39, 64], whereas others have demonstrated levels similar to peer or sibling comparison groups but with both groups not meeting recommended levels [53, 68] and therefore not achieving optional health gains. Many AYA also make friends and maintain their social network through sports and identify with a strong and fit body [1]. Given that cancer and its treatment may result in impairments that make sports participation difficult, the impact of physical loss among AYA has social and emotional as well as physical implications. Studies of adolescents who had received treatment for cancer showed many reported decreased participation in leisure-time physical activity while receiving treatment and for some into survivorship [38, 39]. Those who remained active throughout their cancer experience reported better self-concept, perception of physical abilities, interactions with parents, and same and opposite sex relationships; many of the psychosocial areas are compromised in AYA with cancer [38]. A long-term follow-up study found that adolescents treated for acute lymphoblastic leukemia reported feeling less competent in physical activities were less likely to participate in physical versus sedentary activities, enjoyed physical education less, and were more prone to sports injury. These findings were associated with decreases in health-related quality of health measures [117]. These AYA are less likely to reap the potential physical and psychological benefits of physical activity.

Participation in normal activities may also be affected by isolation restrictions, hospitalization, or preconceived ideas of people they encounter in their school, workplace, or community [37, 71, 77, 83, 92]. Teachers, coaches, employers, peers, or family members may overprotect or over-restrict the AYA with cancer [79] and should be informed to allow/encourage the AYA with cancer to engage in as many as usual physical activities as he/she is capable during and after cancer therapy.

26.4 Principles of Rehabilitation in Oncology

Rehabilitation can involve restorative, compensatory, adaptive, or supportive approaches. It is provided by healthcare professionals who work collaboratively in acute care, outpatient, hospice, school, community, and recreational settings. Interdisciplinary rehabilitation teams may include physiotherapists, occupational therapists, speech and language pathologists, child life specialists, psychologists, nurses, physicians, recreation therapists, dieticians, social workers, prosthetists, and orthotists. Roles often overlap allowing professionals to support each other in helping AYA achieve their goals.

Rehabilitation should be incorporated into all stages of the cancer care continuum, from diagnosis, throughout treatment, following treatment, and in some cases at the end of life [58, 69]. Goals should be realistic, prevent or ameliorate impairments, promote participation in meaningful life activities, be matched with psychometrically rigorous outcome measures, and be coupled with reasonable interventions. They should be determined collaboratively with the AYA and customized to unique needs, strengths, and preferences within the context of family and peers, support systems, and environments. Respect for variation, values, culture, and autonomy reflect the tenets of client-centered care. During active cancer treatment, AYA may experience constant transitions in and out of their typical social, recreational, educational, and vocational roles depending on protocol phases, chemotherapy routines, hospitalizations, varying states of wellness, and vulnerability to infection or injury [14, 63]. Short-term goals and interventions may need to be realigned, sometimes on a daily basis, to be sensitive to a constantly changing array of impairments and associated physical and psychosocial issues. Long-term goals during and following treatment should emphasize function and a healthy lifestyle across the lifespan.

26.5 Knowledge

AYA and their families need and want knowledge across all phases of cancer care [5, 11, 57]. This includes education about vulnerability to and implications of current and future cancer-related impairments and limitations, awareness of the safety and multiple benefits of exercise, and an understanding that follow-up visits, surveillance testing, and preservation of health are lifelong responsibilities. This knowledge can have an impact on modifiable personal factors such as attitude and motivation, contribute to adherence, and build capacity for the autonomy, informed decision-making, and self-management skills AYA need to develop in order to accept responsibility for their outcomes [11, 57]. Completion of treatment, characterized by a transition from a focus on cancer interventions to an emphasis on wellness while dealing with late effects, is a pivotal time for education [27, 46]. AYA may become complacent with less frequent appointments and develop an attitude that cancer is part of a past life [27, 46]. Information regarding the transition from pediatric to adult services will be important for those experiencing this event [27, 46]. Education is also important for others who can provide informed, encouraging, and supportive environments for participation in rehabilitation and exercise programs. This knowledge can address attitudinal barriers, low expectations, overprotection, and unnecessary restrictions, which can limit opportunities for optimal participation in exercise and other activities [8, 63, 69].

Knowledge of oneself can be facilitated through the use of mobile applications. AYA can use these to track various symptoms, pain management, or eating patterns [61].

26.6 Exercise

The most researched, efficacious, and efficient intervention to address many of the adverse effects of cancer and its treatment is physical activity. However, many of the impairments associated with cancer and its treatment can make participation in physical activity challenging. This paradoxical effect can result in perpetuation of weakness, fatigue, and decreased fitness and endurance.

An increasing body of research has shown that exercise is safe, feasible, and beneficial during and after cancer treatment [7, 14, 16]. However, intervention studies tend to lack sufficient sample sizes/enrollment, adequate randomization, and adherence [8, 14, 31]. Despite challenging methodology and varying results, the evidence shows overall clinically and statistically positive effects on physiological and psychological cancer-related impairments, functioning, quality of life, and the prevention of future cancers [7, 9, 13, 14, 25, 31, 56, 64]. Randomized control trials including AYA have shown exercise to benefit muscle flexibility, body composition as measured by physical fitness, and cardiorespiratory fitness [9]. Other studies have documented beneficial associations between and effects of physical activity on pain, nausea, fatigue, sleep efficiency and duration, hematological indexes, muscle strength, aerobic capacity, exercise tolerance, body composition, anthropometrics, cardiopulmonary fitness, metabolic risk factors, physical functioning, and components of psychological and emotional well-being including anxiety, depression, mood, feelings of control, self-esteem, self-confidence, perceived physical competence, and satisfaction with life [1, 7, 14, 20, 31, 33, 36, 38, 42, 64]. There is some evidence that physical activity can have a beneficial effect on various immune system parameters. However additional research is necessary to understand the mechanisms underlying the impact of exercise on the immune system [41].

To promote exercise in the AYA cancer population, it is important to be aware of and anticipate the determinants of physical activity, particularly those that are modifiable. Motivators include the desire to feel good about oneself, have control over one's body, socialize, have fun, and achieve health benefits such as weight management, stress reduction, strength, flexibility, improved fitness, and increased energy [39, 40, 43, 68]. Barriers can include pain, anxiety, weakness, fatigue, nausea, neuropathies, overall poor health, safety concerns, and limitations in motor

skills such as running and jumping [4, 20, 63, 68, 69]. Low levels of pre-diagnostic activity, female gender, and challenges with cognitive, communication, and psychosocial abilities have been shown to be negative predictors of participation of physical activity during and following treatment [20, 38]. Survivors of CNS cancer are also more likely to be nonparticipants. Personal factors such as culture, preferences, intrinsic motivation, self-efficacy, availability of time, and age and environmental factors such as facilities, season, economics, readily available alternative sedentary activities, the support of family, friends, health professionals, educators, and even the media can be influential factors, many of which have the potential to be modified ([40, 53, 69]; Arroyave et al. 2014). Cancer-specific barriers including overprotection, isolation precautions, hospitalizations, and multiple medical appointments can also impact participation in physical activity ([4, 28, 68]).

Ongoing encouragement and reinforcement of the importance of regular activity by rehabilitation professionals should be a standard of care during and following cancer treatment. Extra effort should be focused on individuals with low incentive or other barriers, as they are most at risk for inactivity and its associated problems. Adolescence is a particularly critical lifespan period as patterns of physical activity and inactivity during these years have been shown to track into adulthood [59] impacting future fitness, obesity, bone density, and cardiovascular disease, factors associated with cancer late effects. Although there is a role for sedentary pastimes such as watching television, using the Internet, or playing video games, particularly when hospitalized or unable to be participate in other pursuits, AYA should be encouraged to choose more active pursuits when able. A tendency to partake in these activities may continue following completion of treatment.

Rehabilitation professionals are well positioned to combine general health promotion with individually targeted, tailored, or adapted interventions. Input should begin shortly after diagnosis, including pre-habilitation when appropriate (Jones 2013), and continue through all phases and transitions to prevent, mitigate, or treat treatment-related impairments ([18, 58]; Jones 2013). Service delivery models can include individual- or group-supervised exercise interventions, home-based programs, or combinations of these [7]. It is important to take personal preferences into account. For all age groups, menus of potential activities that involve fun, recreational, or daily activities and respect individual pre-diagnosis and current interests, preferences for timing, location, and service delivery options may optimize adherence, confidence, and self-management which can contribute to sustainable active lifestyle outcomes [11, 14, 53, 68].

Adolescents with or surviving cancer have indicated preferences for exercising with their friends or families reflecting the importance of relationships as critical sources of support for participation in physical activity (PA); few wanted to exercise with other teens with cancer [9, 39, 68]. They have shown an inclination for being active through recreational or daily activities as opposed to specific exercise programs, exercising in the afternoon or evening rather than the morning, and being active at home, school, or a club instead of hospitals or clinics and report enjoying activities that provide typical teen experiences such as swimming, biking, hockey, dance, basketball, and walking for transportation [68, 69]. Many of these activities can promote flexibility, strength, endurance, balance, and motor skills. Some AYA are able to maintain or resume competitive sports, although adaptations may be necessary at certain times.

In contrast, many young adults with cancer have reported a preference for home-based walking programs because of their low cost and skill level, minimal equipment or travel needs, and flexibility in intensity, duration, and socialization [11, 14]. Some young adults with cancer find comradeship and support in groups with other cancer patients [1], whereas others prefer a self-directed program with family and peers [11, 14]. Alternatives should be offered, particularly for those who have a busy school or work life. Web-based programs, social media, or phone monitoring of home programs can offer supervision and support for all ages.

Physical activity recommendations are grounded in guidelines developed for the general population and tailored individually based on specific impairments and limitations and precancer levels of activity and symptomatology as there is currently no evidence to determine the optimal intensities, durations, or types of activity for AYA during or following treatment for cancer [14, 60]. Recommendations for adolescents are typically at least 60 minutes per day of moderate-to-vigorous physical activity either continuous or spread throughout the day and limiting sedentary time. Moderate intensity is activity equivalent to a brisk walk, such as that when the participant might feel warm or slightly out of breathe. Vigorous intensity and muscle strengthening activities should be included at least 3 days per week (Tremblay et al. 2011). Activities that enhance muscle strength, flexibility, and bone health should be done twice weekly. It may be necessary to vary the intensities and frequencies of exercise depending on treatment schedules and variations in response to treatments.

This advice is similar to the recommendations developed by the Children's Oncology Group in an effort to encourage survivors of childhood cancer to maintain a healthy body weight and reduce the risk of recurrence, chronic disease, and health issues [14]. Exercise prescription for adults, including cancer populations, is to exercise, 3–5 days per week, 20–30 min per session to accumulate 150 min of moderate-to-vigorous activity throughout the week and to include strengthening and flexibility as well as aerobic activities [14, 113]. Daily exercise with lighter intensity, shorter bouts with rest intervals, and slower progressions may be preferable for patients of any age who have been inactive or are deconditioned [60].

Exercise prescription should include warm-up and cooldown activities and can be informed by principles such as FITTE to communicate and structure frequency, intensity, time, type, and enjoyment [16]. Exercise choices can vary from walking programs, aerobic exercise, and resistance training to high-intensity aerobic training [19, 36]. Recommendations regarding a physically activity lifestyle should be part of a comprehensive program to affect an overall healthy lifestyle. Rehabilitation professionals work with the healthcare team to promote/address holistic healthy practices including a healthy diet, nonsmoking, skin protection, cancer screening, and responsible sexual behavior and alcohol intake [4, 5, 6, 22, 45].

26.7 Precautions and Contraindications

Although there is growing evidence that exercise is safe for people with and following cancer [37, 64], it is important to be aware of the implications of cancer-related impairments such as hematological levels, cardiotoxicity, susceptibility to fractures, and effects of neuropathy when counseling AYA regarding exercise. Medical clearance should be obtained in these situations. In the absence of definitive evidence for risk thresholds, safety, including symptomatology and clinical judgment for individual cases, is often determined on institution-specific practices [65]. Precautions have been suggested in the literature but are not necessarily based on research [65]. These include uncontrolled and unstable cardiac disease, certain metastatic lesions, and recent intracranial hemorrhage or deep vein thrombosis with pulmonary embolus, extreme anemia, thrombocytopenia, active infection, significant neuropathies, surgical contraindications, and compromised bone integrity [65]. More specific precautions include the avoidance of the following: high-intensity activities if hemoglobin levels are less than 80 g/l, activities that present a risk of bacterial infection if absolute neutrophil counts are less than 0.5×10^9/l, and contact sports or high-impact activities that pose a risk of bleeding if platelet count is less than 50×10^9/l. However these are pragmatic rather than evidence-based suggestions [16, 60]. Weight-bearing restrictions and avoidance of high-impact activities which may be warranted for bone instability due to bone metastases, avascular necrosis, osteopenia, or surgery need to be developed in consultation with team members [16, 60]. AYA with peripheral neuropathies should exercise

caution when at risk for tripping or damage due to sensory or motor loss. Strength-training guidelines have been developed for childhood cancer survivors who have been exposed to cardiotoxic therapies [49].

26.8 Other Rehabilitation Interventions

AYA with cancer are a heterogeneous population and may require a wide array of tailored and targeted rehabilitation strategies to address body function and structure impairments, activity limitations, participation restrictions, and environmental barriers in addition to promotion of engagement in physical activity [30].

Rehabilitation professionals play important roles in the assessment and management of pain. Assessment can be complex as factors such as emotions or poor sleep can heighten pain, whereas some AYA may underreport pain if they fear social activities may be restricted as a result [2]. A variety of strategies to augment pharmacological pain management include massage, heat, cold, aromatherapy, music therapy, acupuncture, positioning, transcutaneous electrical stimulation, meditation, yoga, hypnosis, guided imagery, distraction, and relaxation or behavioral techniques. Research evidence is lacking or weak for many of these approaches; however they may improve well-being [51]. Pain management strategies may be optimized when combined with physical activity or graded activity for return to function. Mobility devices, adaptive equipment, and orthotics can address mechanical pain by unloading, stabilizing, and protecting body structures [17]. Therapeutic surfaces can provide comfortable positioning while offering skin protection. Neuropathic pain may respond to techniques such as desensitization. Rehabilitation professionals also play a role in the assessment of neuropathy to provide input regarding dosing of neurotoxic drugs.

AYA may be at risk for loss of range of motion due to surgery, neuropathy, inactivity, or graft-versus-host disease [16, 58]. Interventions using principles of contracture prevention and management should be implemented. These can include passive and active exercise and prolonged stretch through positioning, serial casting, splints, or orthoses. Orthoses may also provide stability for protection from injury or enhancement of function when muscle strength or skeletal stability is compromised. For example, ankle-foot orthoses may be used for foot drop resulting from chemotherapy-induced peripheral neuropathy. Some AYA may not accept adaptive devices due to appearance, cost, or inconvenience. When neurological impairments impact function or quality of life, a variety of therapeutic interventions such as spasticity management techniques and motor-learning principles may be incorporated into treatment.

Fine motor skills such as handwriting or gross motor skills such as walking, running, or stair climbing may require specific and individualized rehabilitation strategies. Maximal independence in activities of daily living such as bathing or dressing may be achieved through activity modification, energy conservation, or environmental adaptation of educational, workplace, home, or community settings.

Strategies to address the neurocognitive impairments and associated activity limitations of memory, attention, and organizational executive function deficits may need to be incorporated into rehabilitation programs [55]. Many are based on adaptations and applications of neurocognitive rehabilitation strategies or behavioral approaches from other clinical populations and include direct cognitive remediation, compensatory training, and environmental change [34]. Top-down activity interventions combined with metacognitive strategies such as guided problem solving (to identify, analyze, and address problems with everyday activities) are showing promise for improving performance and underlying neurocognitive function, but further research is necessary [55].

Rehabilitation professionals may also be involved in the facilitation of safe and efficient feeding for patients with swallowing dysfunction. Input for patients with dysarthria resulting from oral motor dysfunction of neurogenic or mechanical origin may involve the provision of

communication interventions including assistive devices.

Interventions may be coupled with approaches that are considered complementary or alternative, some of which may be within the scope of practice of rehabilitation professionals. Examples include acupuncture, massage, mindfulness meditation, supplements, touch therapies, aromatherapy, yoga, or relaxation training to mitigate physical and psychological impairments such as stress or fatigue or to boost immunity, promote general health, and relieve pain during and after treatment [12, 24, 47].

26.9 Facilitating Participation

Various strategies may be used to promote participation in an active life with respect to socialization, sports, leisure, recreation, education, volunteering, employment, and community. School reentry after a diagnosis of cancer can be very challenging if there are issues regarding independence in learning, mobility, or self-care, but is generally encouraged as it maintains some normalcy in life and allows for continued social and academic participation and provides hope for the future. Rehabilitation professionals may be involved in liaising with and educating school staff and peers about the diagnosis and its implications for school-based programs and to prescribe equipment for accessibility and computer-based systems. Recommendations regarding positioning, lifting, and transferring, learning needs, and physical education for AYA with significant impairments may facilitate the return to the educational setting. Vocational counseling may be helpful for some AYA as ongoing physical and/or psychosocial issues such as cognitive limitations, fatigue, depression, and anxiety, and difficulties with lifting can impact employment [23].

Participation in community activities can be enhanced by modifying or accessing existing environments that are conducive to challenges encountered by AYA with mobility or cognitive challenges. Families should be encouraged to access community recreational facilities, as these may be motivating, well equipped, and socially inviting. Alternatively, specialized groups or camps and adapted recreational programs may provide opportunities for those who desire involvement with peers who are experiencing similar health issues.

26.10 Intervention for the Acutely Ill, Isolated, or Hospitalized Patient

Rehabilitation and exercise are very important for hospitalized patients. Goals for an acutely ill patient will be focused on comfort, prevention of unnecessary secondary complications, and facilitating participation in activities as tolerated. Bed rest and immobility combined with cancer treatments can result in rapid loss of muscle strength and extensibility, pulmonary complications, skin damage, and osteoporosis. Interventions to prevent these problems may include positioning, frequent change of position, the use of pressure-relief mattresses, passive or active bed exercises, and breathing exercises. Patients should engage in weight-bearing activities such as walking to the washroom, climbing stairs, and other activities of daily living as soon as possible. Patients in isolation, such as recipients of bone marrow transplants, may need encouragement and adaptations to remain mobile and maintain functional skills. Activities can include the use of stationary bicycles, treadmills, ergometers, or gaming technology.

The temporary use of mobility or walking aids may facilitate earlier mobility. Leaving the hospital, even for short periods of time, can be very beneficial physically and psychologically.

26.11 End-of-Life Care

Providing end-of-life care for a young person is very difficult for all involved. Supportive care teams must work together closely to provide coordinated and comprehensive care [50, 52]. Rehabilitation professionals can make a significant difference to the lives of patients with terminal cancer and their families by managing symptoms,

optimizing comfort, and giving them the ability to participate in meaningful activities to achieve the best possible quality of life. This is accomplished through applying rehabilitation principles and practices in respect to pain, symptom management, and facilitation of independence in mobility and activities of daily living as tolerated and desired to achieve individualized goals. The ability to be at home may be facilitated with appropriate environmental or mobility aids, assistive devices, and the provision of in-home services.

Conclusion

Cancer rehabilitation is gaining more recognition due a growing appreciation of the positive impact on cancer care during and following treatment [58]. Despite the increased recognition and appreciation of the value of rehabilitation and exercise, there is a need for further research and resource allocation to serve the specific needs of the AYA population [15].

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27 Making Ends Meet: Financial Issues from the Perspectives of Patients and Their Health-Care Team

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Abstract

By several measures, adolescents and young adults (AYAs, age 15–39 years) represent the population segment at greatest risk for economic calamity. In particular, AYAs with cancer face numerous financial challenges that pose barriers to their receipt of appropriate and timely medical care. The health-related financial issues examined in this chapter include employment, health insurance, out-of-pocket expenses, and selected health-related quality-of-life issues that may influence them (e.g., education and marital status). For purposes of this discussion, the AYA population is divided into two groups, the younger adolescent (less than 18 years old) and the older adolescent and young adult (18–39 years old). Younger adolescents are nearly always financially dependent on their parents or guardians, making their financial issues essentially equivalent to those of younger children. These are mostly associated with active therapy and result in increased family financial burden, especially out-of-pocket expenses, which are estimated to represent one third of after-tax income. In contrast, older AYAs tend to be or aspire to become financially independent. Their issues relate to preserving income, paying for care, and providing for dependents. For

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some, the priority is completing higher education or career preparation, while for others it is launching, maintaining, or returning to work. For cancer survivors, these challenges do not necessarily abate, as clinically significant late effects require medical management, pose excess financial burdens, and diminish functional status. Although the landmark Affordable Care Act of 2010 has partially improved the situation in the USA, many AYAs remain vulnerable through remaining discontinuities, incompleteness, and sheer complexity of coverage. Further, many financial challenges are universally overrepresented among AYAs, regardless of payer system. A proactive, socio-ecological, multidisciplinary approach involving physicians, nurses, oncology social workers, and other professionals is likely to be most effective for assisting individual patients and developing systemic solutions.

27.1 Introduction

For most health-care professionals, the financial aspects of clinical practice are considerably less familiar than the medical care they render. At the same time, in today's world, few clinicians can fail to appreciate how tightly intertwined the financing and delivery of health care are. On an international level, the global economic crisis that began in 2008 has had far-reaching health consequences including pervasive job and insurance loss, increased mental health disorders and risk-taking behaviors, and lower national spending on health [1–5]. Meanwhile, in the United States (USA), implementation of landmark legislation known as the Affordable Care Act (ACA) in 2010 has resulted in newly won health insurance coverage for millions of at-risk Americans, particularly young adults [6]. Thus, an awareness of key economic issues has become essential for clinicians providing cancer care.

Which economic issues are most salient depends upon the perspective taken. This chapter will review key financial issues in the management of adolescent and young adult (AYA) patients with cancer. The perspective taken is that of patients and their health-care team consisting of the physician, nurse, social worker, and others. This perspective excludes certain vital economic issues, such as the cost utility of successfully treating young adults who subsequently contribute many years of productivity in a nation's workforce. However, this perspective enables this chapter to address the practical financial concerns facing patients and their families who struggle physically and emotionally during cancer treatment and look to their health-care providers for knowledgeable assistance.

The patient perspective entails costs that are both direct and indirect [7]. Direct medical costs arising from cancer care include those related to prescription drugs, procedures, diagnostic assessments, hospitalizations, and professional services. Unfortunately, out-of-pocket expenses are daunting, and lack or inadequacy of health insurance continues to plague many vulnerable Americans [8]. Substantial indirect costs are also associated with cancer care, which include lost wages due to unemployment or reduced hours, reduced work productivity due to fatigue and other symptoms, and costs of transportation for treatment and of securing child care. These costs do not necessarily end with completion of disease-directed treatment, as excess burdens associated with cancer survivorship care continue for patients needing monitoring and management of treatment-related complications [9, 10]. This observation has been confirmed among survivors of AYA cancer [11, 12].

As discussed in this chapter, many of these costs of cancer care are especially relevant to

the AYA population. Historically, about 30 % of individuals aged 21–29 years have lacked health insurance, making it the most underinsured segment of the US population [13]. Despite the ACA offering insurance mechanisms that benefit some of these patients, universal coverage does not exist and many continue to be challenged. For AYAs this remains a major barrier to accessing care [14], and with insurance status having been linked to survival disparities in several AYA cancers, the problem is of urgent importance [15, 16]. Further, the impact of out-of-pocket expenses is magnified in young adults facing cancer due to the interruption of successful work force entry, college education, and vocational training necessary for financial independence. Because AYAs with cancer tend to be treated in community settings more than younger children are, they encounter greater costs to overcome geographical barriers and access optimal care [17–20]. It is sobering that in a study where approximately 200,000 adults with cancer were found to be 2.65 times more likely to go bankrupt than those without cancer, young adults age 20–34 years had the highest rate of bankruptcy [21].

The health issues examined in this chapter include employment, health and life insurance, out-of-pocket expenses, and selected health-related quality-of-life issues that may influence them (e.g., education and marital status). For purposes of this discussion, the AYA population is divided into two groups, the younger adolescent (less than 18 years old) and the older adolescent and young adult (18–39 years old). Younger adolescents are nearly always financially dependent on their parents or guardians, and their financial issues are essentially equivalent to those of younger children. These are mostly associated with active therapy and result in increased family financial burden, especially out-of-pocket expenses. In contrast, older adolescents and young adults tend to be or aspire to become financially independent. Their issues relate to preserving income, paying for direct and indirect costs of care, providing for dependents, and planning for the future.

27.2 Overview of Financial Issues in Adolescents/Young Adults

AYAs are in a time of life replete with developmental transitions. These include shifts in family and personal relationships as well as changes in school and/or work settings. These transitions move AYAs toward new levels of autonomy personally, professionally, legally, and financially. Simultaneously, they face undue financial challenge because of increasing legal and professional independence. For AYAs who are diagnosed with cancer during this timeframe, they are simultaneously navigating normal adjustment and demands associated with diagnosis. To understand the full financial burden of cancer care in this age group, it is important to examine the costs of care, insurance-related challenges, and implications for care access, as well as economic burden due to employment changes in this population.

The financial burden of cancer has been demonstrated consistently for cancer patients and survivors of all ages, including expenses related to medical treatment, out-of-pocket costs, and lost wages [9, 22–24]. Additionally, historically, young adults (regardless of health or disease status) have been an age group most likely to lack health insurance in the USA, with rates of noninsurance ranging from 28 to 31 % [25, 26]. Though coverage from the ACA has improved overall insurance access particularly for those under 26 years of age [27], substantial differences have been shown for young adults age 18–34 in Medicaid expansion vs. nonexpansion states [28]. As new insurance options are made available via the ACA over the coming years, it will be important to determine its full effect on the coverage for AYAs, particularly those older than age 26 years and in nonexpansion states.

Regardless of the shifting policy landscape, more financial problems are reported by more young adults with cancer than middle-aged or older adults [29]. Research suggests that AYAs have greater costs than pediatric patients when treated for the same cancer [30]. Further, nation-

ally representative data in the USA suggest that those diagnosed with cancer as AYAs experience substantial economic burden, albeit from different sources, relative to cancer survivors diagnosed at older ages. Though the total economic burden is similar to that of survivors diagnosed at older ages, there are different sources of that burden. Guy and colleagues [11] showed that while survivors of cancer diagnosed at older ages have greater per capita medical expenses, survivors of AYA cancer have an annual loss in productivity that is $2250 more per person, per year, than those diagnosed as older adults. (Loss in productivity was defined as a combination of employment disability, missed work days, and additional days spent in bed multiplied by median annual wage.) These data highlight the importance of examining expenses and economic burden from multiple perspectives.

AYAs with cancer also have challenges obtaining or maintaining health insurance [14, 31] with research suggesting that rates of uninsurance among all AYAs peak in the early twenties [32]. These insurance changes have real impact on outcomes. For example, uninsured young adult cancer patients are more likely to present with metastatic disease and have higher all-cause mortality than insured patients [33]. Additionally, population-based data from over 1300 AYA survivors diagnosed in the USA showed that uninsured AYAs are less likely to enroll onto clinical trials than those with insurance [17]. These data are consistent with the few other studies that have examined this issue and show the disproportionately low enrollment of uninsured AYAs onto clinical cancer trials [34, 35]. This is not entirely surprising, given that not all states require insurance companies to cover patient care costs in cancer clinical trials [36]. Data from the population-based AYA HOPE cohort study show that while most AYAs were insured during initial treatment, insurance rates decreased over time such that over 25 % of AYAs experienced some period without insurance [31]. Although AYAs currently receiving cancer care were more likely to have insurance than those not receiving care, health insurance was lost in 11 % of the whole cohort and 25 % of AYAs who did not receive medical care in the past 12 months [14, 31]. Uninsured patients were more likely to be older (25–39 vs. 15–19 years) and have only a high school education or less.

There are still other tangible effects of uninsurance or under insurance during cancer care for AYAs. Data from The Samfund (a nonprofit organization that provides financial assistance and education to young adults with cancer) indicate that the types of financial support needed by young adult cancer survivors are diverse and include housing payment assistance, residual or current medical debt, health insurance supplementation, car payments or insurance, and student loan repayment [37]. National surveillance research suggests that costs associated with cancer care may have implications for care receipt. Data from the Behavioral Risk Factor Surveillance System suggest that AYAs with cancer are more likely than those without cancer to report not receiving care due to cost [12]. Results from AYA HOPE indicate that for more than 20 % of AYAs, there were tests or treatments not covered by insurance [31]. However, 81 % of those received the treatment or test anyway, presumably paying for care out of pocket, though this was not directly assessed. Lacking insurance in this cohort was associated with unmet service needs and worse physical and mental health-related quality of life, emotional functioning, and fatigue [38, 39]. Financial advice was also the most common unmet service need reported by AYAs [39]. In addition to insurance-related effects, additional financial burden experienced by AYAs occurs via employment. In the AYA HOPE cohort, 30–40 % (depending on age) reported negative impacts of cancer on plans for education and/or employment [40]. Additionally, 28 % of full-time workers/students did not return to work or school, while an even greater proportion (66 %) of those who were previously part-time workers/students did not return [41]. Adjusted models showed that those less likely to return to work were uninsured or had quit working shortly after they were diagnosed. Further, more than half of all full-time workers or students reported problems with work or studies after diagnosis.

Taken together, research indicates that the economic burden and impact of cancer in the AYA population are profound. However, many of

the data described above were collected before the full implementation of the ACA. Longitudinal information will be needed on a state-specific basis in order to define residual gaps and to develop appropriate solutions.

27.3 Younger Adolescents: The Financially Dependent Patient

27.3.1 Case Vignette

A 17-year-old young man was diagnosed with acute lymphoblastic leukemia (ALL) in December 2011. His parents had separated and he was living with his father while attending high school and pursuing his passion for playing guitar. He achieved complete remission at the end of induction, but early in consolidation, he developed methicillin-resistant *Staphylococcus aureus* septicemia causing shock and disseminated intravascular coagulation and requiring intensive care for inotrope support and intubation with eventual tracheostomy. His course was complicated by deep venous thrombosis in a leg, pulmonary embolism, acute renal failure requiring hemodialysis, and a brief episode of cardiac arrest. Further deterioration attributed to septic embolism and thrombosis was accompanied by the formation of a mycotic aneurysm in a posterior cerebral artery that was treated by coil embolization. However, ischemic changes related to arterial occlusion progressed in his limbs. His parents agonized over withdrawal of life support, but his sedation was reduced sufficiently for him to make the decision to undergo quadruple forelimb amputation. Thereafter, he recovered well and recommenced modified chemotherapy after a hiatus of more than 2 months. He achieved remarkable physical rehabilitation, obtained his high school diploma, and completed treatment for ALL.

Now 21 years old, this young man has been living with his mother. He is not pursuing further education and is unemployed. While on therapy, he and his family were receiving funding support from governmental and philanthropic sources, but these ceased on his 19th birthday. He then qualified for another government program at $800 per month, while the cost of his four limb prostheses was covered by The War Amps program (www.waramps.ca). A community-based fund-raising campaign was highly successful, including a contribution of $50,000 from the lead singer of the rock band, Coldplay! While his physical functioning is quite exceptional, the future for this young man remains uncertain with respect to long-term independence and the pursuit of age-appropriate goals.

27.3.2 Major Financial Issues

27.3.2.1 Costs of Care: Nomenclature and Historical Limitations in Analysis

To the best of our knowledge, there are no published studies that report exclusively on the financial challenges faced by adolescents with cancer and their families. However, for patients and survivors in this age group (15–19 years) who live in the parental home, the costs are believed to be similar to those incurred by the families of children with cancer because studies having that focus commonly include the adolescent population.

Until the publication of a systematic review in 2011 [42], there were only 13 published reports on this topic. The review identified considerable methodological variability in those reports, and some notable gaps, including that costs were not (1) identified, measured, or valued consistently with validated instruments, (2) analyzed according to a uniformly determined set of categories, or (3) disaggregated according to components of these categories [43].

Costs can be categorized as direct, indirect, and psychosocial [44]. Direct costs include actual "out-of-pocket" expenditures related to an illness; indirect costs are the value, in monetary terms, of lost productivity at paid and unpaid work (opportunity costs) due to morbidity and mortality. Psychosocial costs are brought about by disease and reduce quality of life, but these are not estimated usually in monetary terms and so are excluded customarily from cost analyses.

Table 27.1 Cancer care-related costs incurred by families and their support networks

	Family		Family support networks	
	Direct	Indirect	Direct	Indirect
Median	$3503	$23,130	$575	$3215
Range	$754–$51,906	$1259–$48,236	$6–$10,315	$58–$29,061
Reference	46		47	

In Canadian dollars

27.3.2.2 Cost of Care Estimates

Costs incurred by families of young people with cancer are usually "front-end loaded," i.e., disproportionately great at diagnosis and during early, often intensive treatment. Using a mixed-method approach that included the Ambulatory and Home Care Record (AHCR) [45], Tsimicalis and colleagues undertook a prospective study of families of children during the first 3 months after being newly diagnosed with cancer in Ontario, Canada [46]. This identified median direct costs, in Canadian dollars, of $3503, with a range of $754–$51,906. Corresponding indirect costs were a median of $23,130 with a range of $1259–$49,236. Again using multiple data collection methods consisting of diaries, calendars, and interviews, a similar study was undertaken that focused on out-of-pocket expenses that, for a variety of reasons, are often underestimated [43]. Nearly 75 % of the total costs were attributed to travel and food, though some single costs were high (such as for a car and equipment).

The Canadian investigators who form the Childhood Cancer Cost Study have devoted attention to another component of cost, namely, that associated with families' support networks (FSNs) [47]. Attention was focused on the initial 3-month period and was based on the AHCR. As depicted in Table 27.1, during this interval FSNs incurred substantial costs compared with costs experienced by the families themselves. It must be emphasized that not all families have FSNs.

It has been suggested that the costs incurred by families of children with cancer may be comparable in publicly funded health-care systems, such as in Canada and in employer-based insurance systems exemplified by the USA; on average, these costs were estimated to amount to a third of after-tax income [48]. For reference, costs amounting to 15 % or more of gross income have been designated "catastrophic" [49, 50], a situation experienced by the majority of families in the Childhood Cancer Cost Study [46] in Canada and in an early study in the USA [49].

As discussed in the previous section, there is an excess burden of cost associated with cancer that occurs in the AYA versus older population, which continues throughout active therapy and beyond [11]. There has been optimism that the ACA would impact favorably on this burden, especially the requirement that parental insurance plans offer coverage to children until they reach the age of 26 years. However, a recent report from the Childhood Cancer Survivor Study (CCSS) [51] indicates that the majority of survivors, especially those who were uninsured, were not familiar with the ACA, and only a minority believed that the ACA would improve their prospects of obtaining quality coverage. There remains an obvious need to help such survivors navigate the ACA and equivalent opportunities in other countries.

27.4 Older Adolescents and Young Adult: The Financially Independent Patient or Survivor

27.4.1 The Young Adult on Therapy

27.4.1.1 Case Vignette

A 23-year-old young man was diagnosed with ALL. With vague symptoms, he avoided going to the doctor because he remained uninsured due to the cost and did not want to be penalized for violating the new ACA insurance mandate. He lived 3 hours from the nearest academic cancer center

and 1 hour from the community hospital with adult oncology where he was diagnosed and received initial treatment. Fortunately, he met an oncology social worker who helped him secure health insurance coverage on his mother's employer-sponsored plan and negotiate receipt of care at the closer facility. However, the patient did not access the several nonprofit oncology resources that she recommended to mitigate out-of pocket costs related to gas, meals, and unreimbursed treatment-related expenses.

He missed multiple appointments because he did not have his own car, and public bus transportation proved unfeasible as it would have taken three times longer and caused nausea, and he was worried about exposure to sick people. His mother worked long hours as a school bus driver during the day and a hotel operator at night. Although she drove him whenever she could, she was worried about losing her job that provided health insurance. Out-of-pocket expenses mounted with minimal prescription coverage.

He was not able to work at his minimum-wage job because it required frequent, heavy lifting incompatible with his performance status. With the help of his oncology social worker, he successfully navigated the complex application procedure for the government Supplemental Security Income (SSI) program. However, even with SSI, he and his mother had difficulty meeting weekly expenses. He missed multiple appointments and had numerous treatment delays, and maintenance therapy was discontinued after only 6 months because his local oncologist felt he was too neutropenic to tolerate it. The patient relapsed 3 months later and was referred to the academic cancer center 3 h away where he underwent re-induction therapy and an allogeneic bone marrow transplant.

Being far from home, he struggled through the transplant period feeling isolated and not engaging in AYA-directed inpatient activities. Transportation challenges and out-of-pocket expenses remained significant in the posttransplant period, leading to missed appointments, missed prescription refills, and battles with graft versus host disease. He wanted his independence back, but was forced to live with his mother and abide by her rules so as to remain on her health-care insurance plan. Although he attempted to use his SSI to move into his own apartment, he was unable to keep up with the lifestyle of his friends and moved back with his mother. To earn back some of his independence, he enrolled in online junior college courses and used money he saved from SSI and part-time jobs to buy his own car.

27.4.1.2 Major Financial Issues

In most countries, government-funded health insurance and work protection programs offer substantial benefits for cancer patients. In the USA, such programs form a relatively complex landscape that is challenging for the AYA patient to understand and navigate (see Table 27.2).

Health Insurance and Access in the USA

In contrast to economically developed countries that provide citizens with government-funded health insurance, in the USA a long-standing issue for young adults has been a notable gap in coverage caused by "aging out" of government-sponsored programs designed for young children and teens. Many uncovered young adults were employed at jobs offering no group benefit or by small companies exempt from federal regulations to provide an insurance plan. Programs historically aimed at protecting health insurance when changing employers are summarized in Table 27.2. While each of these introduced incremental improvements in coverage for AYA cancer patients, numerous gaps remained.

To address these, the ACA was signed into law in March 2010 [54] and has been implemented in stepwise fashion. Two of the first provisions that benefit AYAs with cancer were allowing young adult dependents to remain on a parent's private plan until 26 years of age, regardless of student status, and disallowing exclusions based on preexisting medical conditions. More recent was establishment of a health insurance marketplace exchange, a mechanism whereby public plans are offered without employer sponsorship for a pool of patients with income up to 400 % of the federal poverty limit. The intention is to offer affordable premiums and eliminate the practice of medical underwriting where high

Table 27.2 Selected US legislation addressing financial issues of young adults and adolescents with cancer

	Family and Medical Leave Act (FMLA)	Americans with Disabilities Act of 1990 (ADA)	Health Insurance Portability and Accountability Act (HIPAA)	Consolidated Omnibus Budget Reconciliation Act of 1986 (COBRA)	Affordable Care Act (ACA)
Primary function	• Continuation of employment	• Procurement and retention of employment and benefits (including health insurance)	• Retention of health insurance	• Retention of health insurance	• Expanded access to health insurance via increased coverage, affordability, and options
Persons covered	• Employee-cancer patients • Employees with spouse, child, or other dependents with cancer	• Cancer patients and survivors • Employees or prospective employees with dependent cancer patient or survivor	• Employees who become cancer patients	• Employee-cancer patients • Dependent children and spouse (regardless of marital status)	• Patients of all ages, notably young adults
Entities regulated	• Employers with ≥ 50 employees	• Employers with ≥15 employees • State and local governments • Legislative branch of federal government • Employment agencies • Labor unions	• All employers	• Public and private employers with ≥20 employees	• Payer individuals (mandate for health insurance)
Qualifying conditions	• Serious health conditions rendering employee unable to perform job • Childbirth, adoption, family medical emergencies	• Any disability in qualified individual able to perform essential functions of job • Usually includes cancer whether cured, controlled on treatment, or in remission	• Any prior diagnosis, including cancer	• Any prior diagnosis, including cancer	

Major benefits	• 12-week unpaid leave during any 12-month period • Employer must continue benefits (including health insurance) during leave • Restoration of employee at the same or equivalent position • Employee must be allowed reduced or intermittent work schedule when necessary	• Prohibits discrimination in hiring, firing, and providing benefits on the basis of disability • Employers may not ask applicants whether they have had cancer—only whether he/she can perform essential job functions • Employees needing extra time or assistance are entitled to "reasonable accommodation" (e.g., adjustment of work hours or duties to accommodate medical appointments or treatment of side effects)	• Allows employees insured for ≥12 months to change jobs without losing coverage, even if previously diagnosed with cancer • Reduces "job lock" (inability to change jobs for fear of losing health insurance) • Group plans may not impose exclusion clauses of > 12 months for preexisting conditions if medical care received for it within previous 6 months • Requires health plans to renew coverage for groups and individuals • Increases tax deduction for health insurance expenses of self-employed persons	• Requires continuation of group medical coverage to employees who would have lost it due to individual circumstances, including a reduction in work hours or termination for any reason except gross misconduct • Coverage must be continued for 18 months and must be equivalent to group plan offered to other employees • Premiums must be paid by employee but cannot exceed group premium by more than 2% • Secures valuable time to shop for replacement coverage after changing jobs • Extends coverage for employee's childhood cancer survivor who becomes independent and must find new coverage	• Extends eligibility to remain on parental plan until 26 years of age • Prohibits denial for preexisting conditions • Eliminates underwriting policies (limits cost of premiums for higher-risk conditions) • Expands coverage for preventive services
References	[52, 53]	[52, 53]	[52]	[52]	[54, 55]

rates penalize patients with chronic medical conditions. Regulation also eliminates the practice of annual or lifetime payout caps on insurance policies, which often affect cancer patients. The somewhat controversial ACA "mandate" requires individuals to secure some form of health insurance plan or face a financial penalty.

Hospitals that see a disproportionate share of indigent or uninsured patients temporarily received federal aid to cover cost of care for these patients (the so-called ACA "bump"), but federal priorities are now focused on funding the ACA provisions themselves. Despite these improvements, understanding the ACA and other insurance mechanisms remains a significant challenge for patients and providers alike. Thus, the assistance of experienced oncology social workers or financial counselors is invaluable and can be accessed at larger hospital-based programs if unavailable locally.

With variability across states, the majority of adolescent cancer patients in the US are eligible to receive supplemental health care coverage for catastrophic conditions through public health insurance programs including Medicaid, the State Children's Health Insurance Program (S-CHIP) and state programs funded by federal Title-V block grants. Unfortunately, this coverage usually terminates when patients "age out" at 17 to 21 years of age. Although the ACA provides for AYAs to remain on their parents' health insurance plans until 26 years of age, this is of no value for patients whose parents do not have a private policy. Some federal income assistance (SSI) is available for young adults with severe disability, but this fails to benefit the majority of AYA survivors who, in fact, are able and desire to work. Expanded Medicaid-based coverage represents an option for lower-income young adults, but presents challenges as federally contracted plans usually determine treatment facility, sometimes forcing patients to change physicians, clinics, or hospitals in the midst of active treatment. Recent data suggest that treatment at an NCI-designated comprehensive cancer center is associated with superior survival in AYAs with central nervous system tumors and adult-type breast, lung, colorectal, gastric, pancreatic, hepatobiliary, and oral cancers [18, 56] and possibly other malignancies [57]. However, these and other studies have also found that barriers to accessing NCI-designated comprehensive cancer centers include insurance, socioeconomic status, and distance to the facility [17, 58].

Despite the continuing complexity of health insurance coverage in the USA, there is evidence that the ACA is beginning to achieve its aims. Before ACA implementation, some states enacted legislation allowing eligible young adults to remain as dependents on their parents' insurance plans. Although young adult dependent coverage increased, this was offset by declines in employer-sponsored insurance [59]. However, after federal implementation of young adult dependent coverage via the ACA, there were not only a substantial increase in young adults with dependent coverage but also a reduction in the proportion of uninsured [60]. Following the first ACA open enrollment period, the uninsured proportion for 19–34-year-old persons declined from 28 to 18 %. Furthermore, 60 % of newly covered used their coverage to visit a doctor or hospital or to fill a prescription; 62 % of these individuals said that they would not have been able to afford this care previously [61]. In the same period of time, 13.7 million young adults remained on their parents' plans, nearly 6.6 million of whom would not have been able to do so before passage of the ACA [62].

Reduced Work and Loss of Income

Loss of household income is a crucial issue for young adults on therapy and results primarily from decreased work hours of their own or their spouse. Some patients may be so medically compromised that they may not be able to work at all temporarily. While support infrastructures for this situation differ internationally, options exist in the USA to offset income loss. However, these are inconsistent, vary by state or region, and must be pieced together in patchwork fashion, often requiring a multitude of applications to various agencies or groups. There are US federal and local options, such as SSI for patients medically unable to work. Patients with employee qualified benefits may be able to apply for short- or long-term disability insurance.

Assistance for miscellaneous living expenses including housing and gas is available from non-profit organizations but may be restricted by diagnosis or age. Social networks such as

churches also often make charity funds available to offset lost income by paying for food, housing, or transportation. Support networks (families, community organizations) occasionally hold fundraisers to help with expenses, although this practice appears more common with the families of childhood cancer patients. Finally, several major airlines offer tickets for medically necessary travel issued on frequent flier miles donated by other travelers. Again, the assistance of an experienced and creative oncology social worker can be invaluable for addressing loss of income.

27.4.2 The Young Adult Survivor of Childhood/Adolescent Cancer

27.4.2.1 Case Vignette

A 22-year-old woman underwent her first evaluation in the transitional care clinic for young adult survivors of childhood/adolescent cancer 10 years following completion of therapy for stage 4 nodular sclerosing Hodgkin lymphoma diagnosed at 11 years of age. Her treatment consisted of an intensive, multimodal regimen that included cumulative chemotherapy doses of cyclophosphamide 9.6 gm/m^2, procarbazine 5.6 gm/m^2, doxorubicin 280 mg/m^2, etoposide 4.8 gm/m^2, and bleomycin 80 units/m^2, as well as external beam irradiation 21 Gy to a mantle field. She was in good health except for having primary hypothyroidism treated with thyroid hormone replacement. Menarche occurred at 14 years old; menses were currently of normal frequency and duration. Her family medical history was noncontributory; she was in a stable, long-term relationship with her boyfriend with plans to have children. She was a college graduate, was employed at a charitable foundation, and had private health insurance. Her physical examination was remarkable only for the presence of obesity. On the basis of her treatment history, she was determined to be a substantial risk for premature menopause. In addition to undergoing other risk-based surveillance for potential late effects that included late-onset cardiomyopathy, pulmonary fibrosis, and secondary malignant neoplasms (principally breast cancer), the patient was referred to the female fertility preservation program for possible oocyte preservation. In that assessment, she was found to have an estradiol, gonadotropin, and anti-Müllerian hormone profile suggestive of diminished ovarian follicle reserve. Given the patient's strong desire to have children one day, the recommendation was made either to become pregnant by natural means within the next 1–2 years or consider ovarian follicle or embryo harvesting and preservation. In consultation with her boyfriend and with his financial support, she underwent ovarian oocyte stimulation and harvesting wherein 16 oocytes were retrieved, 14 of which were deemed suitable for freezing and successfully processed. At her annual cancer survivorship evaluation 1 year later, the patient eloquently expressed heartfelt gratitude for being able to preserve her fertility options and described how decision-making with her boyfriend and his essential financial support made it affordable, even though it was not fully covered by her private health insurance. They are now paying out of pocket for the annual cryostorage fee and plan to have children through in vitro fertilization in a few years, after she has completed graduate education and they are more financially secure.

27.4.2.2 Major Financial Issues

The major financial challenges facing AYA cancer survivors vary by age and largely resemble those of their healthy peers, but are exacerbated by increased costs resulting from continued medical surveillance or care [11]. In general, younger AYAs face the developmental tasks of completing education, launching careers, obtaining health insurance, and forming committed relationships with partners. Health insurance options, which have recently expanded for AYAs in the USA following passage of the ACA, are summarized in the preceding Sect. (32.4.1.2.1). This section will focus on the issues of unreimbursed medical expenses, underemployment, and other factors contributing to financial insecurity.

Major Unreimbursed Medical Expenses

Like many young adult survivors of childhood/adolescent cancer, the patient in this vignette faces a lifetime of continued medical surveillance for late-onset complications of treatment. For example, international risk-based consensus

guidelines recommend regular, long-term cardiac imaging studies to screen for asymptomatic left ventricular dysfunction in childhood cancer survivors who received >250 mg/m^2 of anthracycline and mediastinal irradiation [63]. The exact cost to the patient for a single echocardiogram in the USA varies by region and insurance coverage, but is substantial. According to a current consumer information website, for patients covered by health insurance, the out-of-pocket cost is about 10–50 % of the charge. Without health insurance, the cost is estimated to be $1000–$3000 [64].

This vignette also raises the issue of fertility preservation in female cancer survivors, where effective medical options are currently relatively expensive. Young women previously treated with for cancer using high cumulative doses of alkylators are known to be at risk for developing premature menopause [65]. For patients like the young woman in the vignette who are evaluated at a time when they still have ovarian reserve, oocyte retrieval and cryopreservation have been endorsed as an effective, non-research clinical procedure by the American Society of Clinical Oncology [66]. Although the cost for this procedure in the USA varies considerably by region, it is currently estimated to be about $10,000 plus annual cryostorage fees of about $500 [67, 68]. The process of oocyte thawing, in vitro fertilization, and embryo transfer back to the patient represents an additional subsequent cost of about $5000 [67]. Loss of fertility is a significant quality-of-life concern among female cancer survivors [69]. At present, oocyte retrieval/preservation and related procedures are not covered benefits for most health insurance plans. This means that in order for female AYA survivors to preserve their fertility, most must identify other ways of paying for this procedure even with discounted prices offered by some fertility centers. Fortunately for the patient in this vignette, she and her partner were employed and able to pool their financial resources to afford the procedure and storage. However, the current affordability bias in favor of the wealthy is a practical limitation to routine utilization of this form of fertility preservation [69].

Employment

Additional financial concerns affecting many AYA survivors are the risks of unemployment, underemployment, or job insecurity. As summarized by the Institute of Medicine in the USA, prior to protective legislation, about 10–25 % of childhood cancer survivors historically experienced discrimination or difficulties in employment as adults [52]. In accounting for this, concerns voiced by employers relating to childhood cancer survivors included increased costs due to insurance and lost productivity, as well as negative psychological impact on other employees [52]. Other issues may have included out-of-date personnel policies and uninformed managers, difficulty interpreting existing legislative requirements, and misconceptions about a survivor's ability to work.

Currently, the employment picture for this group remains mixed, perhaps improving, but difficult to assess due to the effects of changes in government protection and workplace attitudes that may be difficult to ascertain. In the USA, studies have found statistically higher levels of unemployment among childhood cancer survivors compared with controls. A study of young adult survivors by the CCSS found that 5.6 % of survivors had never been employed, compared with 1.2 % of siblings [70]. In that study, factors associated with unemployment included not finishing high school, age less than 4 years at diagnosis, cranial irradiation, and female sex; further, a diagnosis of a brain tumor was associated with the lowest likelihood of employment in the prior 12 months. In a related study from the CCSS that assessed reasons for unemployment, 10.4 % of adult survivors of childhood cancer reported health-related unemployment compared with 1.8 % of siblings, a significant difference that was associated with female sex, non-White race/ethnicity, higher doses of cranial irradiation, and brain tumor surgery, amputations, and limb-sparing procedures [71]. The highest levels of unemployment were reported among survivors of brain tumors (25 %) or bone tumors (13 %). Of note, survivors with health-related unemployment reported significantly lower physical and mental health functioning than those who were

seeking work or working. In general, studies from other countries have found similar results. A Swedish study of adult survivors of childhood cancers found higher unemployment and lower net income from work among those treated for brain tumors but not other cancers [72]. Similar differences predominantly affecting brain tumor survivors and others with neuropsychological sequelae have been published from Japan [73], Germany [74], and Norway [75]. All remain in agreement with the large meta-analysis of 24 controlled studies of employment outcomes in adult survivors of childhood cancer reported in 2006 by de Boer and colleagues [76], which found that the risk of unemployment was fivefold higher among those with brain tumors than in healthy controls; the risk was higher but not statistically significant among survivors of blood or bone cancer. Interestingly, the risk was threefold higher in the USA but not elevated in European settings. Similar predictors for unemployment including younger age, lower education, female sex, irradiation, and motor impairment or epilepsy were identified. Collectively, these studies indicate that AYA survivors of childhood cancer are at increased risk for financial problems due to unemployment, especially if they have lower levels of physical functioning as commonly seen among those previously treated for brain and possibly bone tumors.

The correlate for effectively supporting care of AYA survivors is to provide targeted interventions that optimize physical and mental health functioning. Relevant to this is acquiring knowledge about the challenges that adult cancer survivors face in the workplace. A recent cross-sectional survey study of 1520 cancer survivors diagnosed 18 years of age or older was undertaken to investigate the relationships among sociodemographic characteristics, symptom burden, functional impairment, and work environment on work ability and sustainability [77]. The mean age was 49 years (range 20–74 years). Although the sample was somewhat biased toward Caucasians with higher income and education level, a model was developed where both functional limitations (physical, cognitive, and/or social) and work problems (poor treatment, discrimination, being passed over, and lack of accommodations) were significantly related to the outcome of work ability. In contrast, only work problems were significantly related to the outcome of work sustainability.

The above study suggests the importance of several factors in assisting the AYA survivor. One of these is providing legal rights information and advice. As summarized in Table 27.2, several US federal and state laws protect employment rights of survivors. The most significant is the Americans with Disability Act (ADA) of 1990, which prohibits covered employers from discriminating on the basis of disability (including cancer) in hiring, firing, and providing benefits [52, 53]. Most US states have similar laws, with a few, including California and Vermont, expressly prohibiting discrimination against cancer survivors [53]. The prevalence of legal difficulties in the workplace is not entirely certain, but according to one recent survey of 112 AYA survivors, legal difficulties were relatively common (40.7 %), which usually involved discrimination rather than insurance denial, and were associated with history of a brain tumor [78].

However, the subject of returning to work or beginning a career for the AYA survivor clearly extends beyond and is more complex than simply addressing issues of job discrimination. As summarized recently by Mehnert and colleagues [79], in both North America and Europe, employment for cancer survivors involves a multifaceted model that brings into play diverse factors such as national and corporate policies and procedures, individual characteristics, physical health, and support for those seeking to return to work (See Fig. 27.1). Of note, work outcomes should be conceptually richer than one-dimensional measures such as employment and include income, work satisfaction, opportunities for promotion, and sustainability.

For AYA survivors, concepts relevant to this are career readiness and occupational "fit." In a recent study from the St. Jude Lifetime Cohort Study, 385 adult survivors of childhood cancer were surveyed using measures of career readiness and vocational identity [80]. Low career readiness was identified in 17.4 % of the cohort

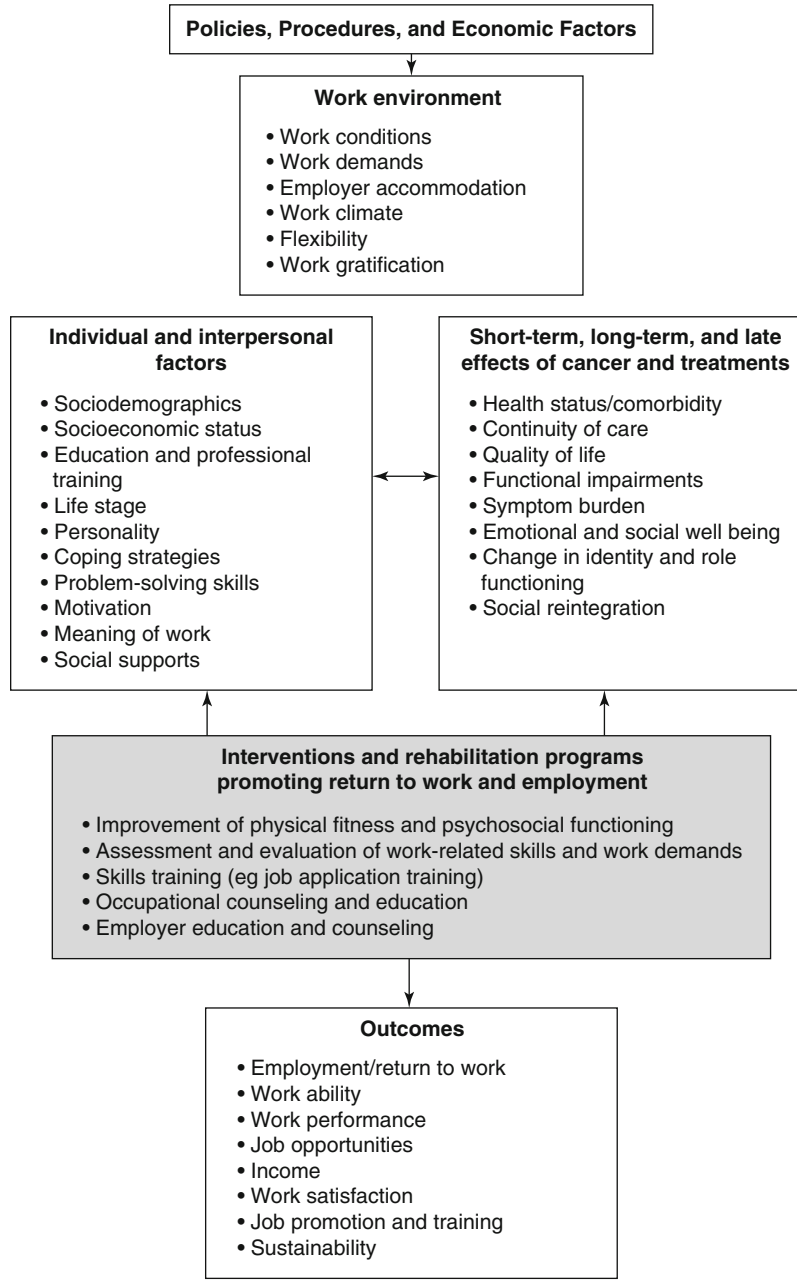

Fig. 27.1 The cancer survivorship and work model. This model for adult cancer survivors illustrates how successful work outcomes are influenced by factors including the work environment, individual and social characteristics, physical health following treatment, and the availability of interventions that promote return to work (Used with permission; Mehnert [79])

and was associated with being unemployed and less educated and having lower income. Not unexpectedly, prior treatment intensity, age at diagnosis, and physical health status exerted indirect effects on career readiness. In a study of occupational outcomes from the CCSS, employed young adult survivors were found less often in higher-skilled managerial/professional occupations than their siblings, and this was associated with being Black, diagnosed at a younger age and

treated with higher-dose cranial irradiation [81]. Because AYA survivors of childhood cancer were diagnosed with cancer before their careers were established, specially tailored programs are required for assisting them with employment. These should be oriented toward completion of education, tailored career selection, and vocational training rather than the rehabilitation, reentry, and retraining more typical of older adults who are returning to an established occupation. In some instances, programs are available to assist in vocational training and placement, requiring a medical assessment of physical capabilities. Disabilities generally represent consequences of treatments that were necessary to save the patient's life. As such, the oncology team should endeavor to manage key disabilities in order to maximize function. Because these are often complicated and require the involvement of other surgical or rehabilitation specialists, the issue should be anticipated and undertaken early enough to benefit the survivor seeking to enter the workforce. In addressing employment issues, oncology teams should utilize the expertise of the medical social worker, whose knowledge will be most current in the complex and changing world of survivor employment opportunities and rights. In the years of follow-up leading to young adulthood, adolescent survivors should be counseled to think ahead, stay in school, obtain their diplomas, and seek stable living arrangements. In responding to employment problems, Hoffman has pointed out that lawsuits are not the only or optimal approach [53, 82]. Rather, preemptive strategies for survivors should include (1) keeping their cancer history private unless it directly affects their job qualifications, (2) asking about benefit packages only after receiving a written job offer, and (3) stressing their current ability to do the job in question. If necessary, other informal and formal responses to perceived discrimination can be pursued before resorting to expensive and time-consuming litigation [82].

Other Threats to Financial Stability: Education and Marital Status

In the general adult population, both employment and job opportunities are related to educational level [83, 84]. Thus, higher education for AYA cancer survivors could enhance employment prospects and provide a potential buffering effect against job loss during economic downturns. However, most studies of AYA survivors of childhood cancer have documented lower levels of educational attainment compared with controls. In a report from the CCSS, only 28.8 % of survivors were college graduates compared with 37.2 % of their siblings [85]. In multiple CCSS reports, lower educational level is associated with unemployment in survivors [70, 86, 87]. Compared with the general population, the British Childhood Cancer Survivor Study found that AYA survivors had a significantly lower likelihood of attaining university degree, teaching certificate, or secondary education; the lowest levels of attainment were among those who had received irradiation for brain tumor or ALL [88]. Similar findings have been documented across educational systems in Germany [89] and Norway [90].

Finally, marital status could be viewed as an indirect indicator of financial risk because unmarried survivors might not enjoy the security of spousal income or medical and life insurance benefits. Here again, most studies suggest that childhood cancer survivors are at increased risk. In a study from the CCSS, survivors were more likely to be never married than siblings (relative risk [RR] 1.21, 95 % confidence interval 1.15, 1.26) and the US population (RR 1.25, 95% confidence interval [95%CI] 1.21, 1.29), after adjusting for age, sex, and race/ethnicity [91]. Survivors with a history of brain tumor, cranial irradiation, and short stature were more likely not to marry. Divorce patterns among survivors were similar to peers. Similar findings were found in a more recent Swiss Paediatric Oncology Group comparison of life partnerships in AYA cancer survivors, their siblings, and the general population; additionally, bone marrow transplant was associated with not marrying [92]. A study from the Italian Association of Pediatric Hematology and Oncology found lower likelihood of marriage among survivors [93], while a study from the Danish Cancer Registry confirmed that brain tumor survivors were less likely to marry [94]. However, both the Danish study and another

study from the UK found no higher likelihood of divorce among those AYA survivors who had married [95].

Interventional strategies to improve financial stability for the AYA survivor should also encompass these complementary domains of education and marriage/long-term partnerships. As many long-term outcome studies involve cross-sectional designs, it cannot be deduced whether lower educational level is causal for or simply associated with lower levels of unemployment. Nevertheless, as an interventional strategy, it makes sense to encourage AYA survivors to stay in school and obtain the highest possible level of education consistent with their functional capabilities. Similarly, supporting psychological adjustment as part of quality cancer survivorship care may help AYA survivors achieve stable, long-term interpersonal relationships that offer both personal fulfillment as well as an added degree of financial stability.

Conclusion

It is clear that a diagnosis of cancer creates significant financial pressures for the AYA population, whether as patients on treatment or survivors in long-term follow-up. Some of these are due to financial vulnerabilities associated with their developmental stage, characterized by emerging personal independence, separation from family, completion of education, launching of career, and formation of life partnerships. Others are caused by excess direct costs of cancer treatment and indirect costs of lost income and productivity to both AYA and their family support networks. In the USA, the historical challenge of poor health insurance coverage for the AYA population appears to have eased somewhat since the enactment of the ACA in 2010. Despite this, certain AYA subsets remain at risk, and many AYA patients are still unaware of how to access the benefits of this and other resources and legislative protections. Several other challenges in the form of unemployment, job insecurity, and lower educational attainment seem to affect AYA patients disproportionately around the world, regardless of health-care funding system. In developing strategies to address these challenges, a model needs to be applied that involves a holistic view of work, including the work environment, individual factors, and physical health, in pursuit of a vocational outcome that includes satisfaction and sustainability, as opposed to merely having a job. Through heightened awareness of physicians, nurses, and similar providers and particularly involvement of oncology social workers, an individualized, proactive approach is likely to be most effective in addressing these diverse and significant challenges.

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28 Adolescent and Young Adult Cancer Survivors: Late Effects of Treatment

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Abstract

The incidence of cancer in YAs has steadily increased over the past 25 years, and cancer remains a leading cause of non-accidental death in this age group. Unlike older cancer patients, AYAs tolerate the acute side effects of therapy relatively well. However, the cancer therapies can produce complications that may not become apparent until years later, hence the term "late effect" for late-occurring or chronic outcomes – either physical or psychological – that either persist or develop beyond 5 years from the diagnosis of cancer. Approximately two out of every three survivors will experience at least one late effect, and about one out of four will experience a late effect that is severe or life threatening. These complications may involve all organ systems. The resulting complications include cardiopulmonary compromise, endocrine dysfunction, renal impairment, gastrointestinal dysfunction, musculoskeletal sequelae, and subsequent malignancies. These complications are related not only to the specific therapy employed but may also be determined by individual host characteristics. This chapter will review the known late effects in survivors of cancer occurring during adolescence and young adulthood and discuss the relationship between these effects and individual therapeutic modalities (surgery, radiation, or chemotherapy) or combined-modality regimens, including those used for blood and marrow transplantation. Screening recommendations, options for providing survivorship care, and the future research opportunities that need to be explored are also discussed.

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28.1 Introduction

The incidence of cancer in Young Adult (YAs) has steadily increased over the past 25 years, and cancer remains a leading cause of non-accidental death in this age group [10]. Specifically, among adolescents 15–19 years of age in the United States during the 1990s, there were 203 new cases per year per million persons, a rate that is 100 % higher than the incidence of cancer in children less than 15 years of age. Recent figures published by Cancer Research UK [19] indicate that for the years 2008–2010, the incidence of cancer among 15–24-year-olds in the UK was 269 cases per year per million. With the use of risk-based therapies, the overall 5-year survival rate exceeds 75 % [117]. For individuals diagnosed between 2001 and 2005, the percentages surviving at least 5 years were 84 % among females and 81 % among males.

Unlike older cancer patients, AYAs tolerate the acute side effects of therapy relatively well. However, the cancer therapies can produce complications that may not become apparent until years later, hence the term "late effect" for late-occurring or chronic outcomes – either physical or psychological – that either persist or develop beyond 5 years from the diagnosis of cancer. Approximately two out of every three survivors will experience at least one late effect [42, 105, 137, 153], and about one out of four will experience a late effect that is severe or life threatening. These complications may involve all organ systems.

Topics that will be reviewed in detail in this chapter include issues related to the potential late effects faced by the survivors (Table 28.1), the options for providing survivorship care, and the future research opportunities that need to be explored (Table 28.4). We will review the known late effects in survivors of cancer occurring during adolescence and young adulthood and discuss the relationship between these effects and individual therapeutic modalities (surgery, radiation,

Table 28.1 Late effects associated with common therapeutic exposures

Therapeutic exposure	Potential late effect
Vincristine, vinblastine	Peripheral neuropathy, Raynaud's phenomenon
Corticosteroids	Cataracts, osteopenia, osteoporosis, avascular necrosis
Mercaptopurine	Hepatic dysfunction, veno-occlusive disease
Methotrexate	(Systemic) osteopenia, osteoporosis, renal dysfunction, hepatic dysfunction
	(Intrathecal) neurocognitive deficits, clinical leukoencephalopathy
Cytarabine (high-dose)	Neurocognitive deficits, clinical leukoencephalopathy
Anthracyclines	Cardiomyopathy, arrhythmias, secondary AML
Alkylating agents	Hypogonadism, infertility, secondary AML/MDS
Busulfan, carmustine, lomustine	Pulmonary dysfunction, infertility
Cyclophosphamide, ifosfamide	Hemorrhagic cystitis, dysfunctional voiding, bladder malignancy, renal dysfunction (ifosfamide only)
Heavy metals (platinum)	Ototoxicity, peripheral sensory neuropathy, renal dysfunction, dyslipidemia
Etoposide, teniposide	Secondary AML
Bleomycin	Pulmonary dysfunction
Mantle radiation	Hypothyroidism, premature cardiovascular disease, cardiac valvular disease, cardiomyopathy, arrhythmias, carotid artery disease, scoliosis/kyphosis, second malignant neoplasm in radiation field (e.g., thyroid, breast), pulmonary dysfunction
Inverted Y radiation	Hypogonadism, infertility, adverse pregnancy outcome, second malignant neoplasm in radiation field (e.g., gastrointestinal)
Cranial or craniospinal radiation	Neurocognitive deficits, clinical leukoencephalopathy, cataracts, hypothyroidism, second malignant neoplasm in radiation field (e.g., skin, thyroid, brain), short stature, scoliosis/kyphosis, obesity
Splenectomy	Acute life-threatening infections
Blood products	Chronic viral hepatitis, HIV

AML acute myeloid leukemia, *MDS* myelodysplastic syndrome, *HIV* human immunodeficiency virus

or chemotherapy) or combined-modality regimens, including those used for blood and marrow transplantation. The resulting complications include cardiopulmonary compromise, endocrine dysfunction, renal impairment, gastrointestinal dysfunction, musculoskeletal sequelae, and subsequent malignancies. These complications are related not only to the specific therapy employed but may also be determined by individual host characteristics. The research leading to our current state of knowledge began almost 30 years ago in single institutions and multi-institution consortia. With the recognition that large cohorts of survivors would be needed to evaluate the effects of multiple therapies on individuals treated for a variety of neoplasms at different ages, and with funding from the National Cancer Institute, the Childhood Cancer Survivor Study (CCSS) was established [119]. The publications of the CCSS include analyses of some of the late effects reported below; the website may be accessed for more details and a list of published research (https://ccss.stjude.org). However, while there exists extensive literature regarding long-term outcomes in children and adult survivors of childhood cancer, and a growing literature in survivors of cancer in middle to older age adults, specific data regarding late effects in survivors diagnosed as adolescents and/or young adults is lacking.

28.2 Medical Issues

28.2.1 Late Mortality

Overall mortality among AYA cancer survivors has been described to be tenfold that of the general population [90, 93]. The CCSS assessed overall and cause-specific mortality in a retrospective cohort of 20,227 5-year survivors of childhood cancer and demonstrated a 10.8-fold excess in overall mortality [90]. Risk of death was statistically significantly higher in females, individuals diagnosed with cancer before the age of 5 years, and those with an initial diagnosis of leukemia or brain tumor. The excess mortality was due to death from primary cancer, second cancer, cardiotoxicity, and noncancer death and existed for up to 25 years after the initial cancer diagnosis. Specific data regarding late mortality in individuals first diagnosed with cancer as young adults is more limited, but a population-based study from the Finland Cancer Registry identified 16, 769 5-year survivors of early-onset cancer (age 0–34 at diagnosis, 5,352 age 0–19, and 11,417 age 20–34) and examined the differences in late mortality between these two age groups [71]. The overall standardized mortality ratio (SMR) for the entire cohort was 4.6 (95% confidence interval (CI) 4.4–4.8). The highest SMRs were for cancer-related deaths including primary and secondary malignancies (SMR = 12.8), followed by infectious diseases (SMR = 4.8), all cardiovascular causes (SMR = 1.9) and cardiac ischemia (SMR 1.9), and respiratory diseases (SMR = 1.7). The majority of the SMRs were higher in the childhood cancer survivors than in the survivors of adult cancer, with overall SMRs of 7.6 and 4.2, respectively. The highest cumulative nonmalignant mortality was due to cardiovascular disease with an ongoing rise throughout the period of follow-up. A second population-based study from the British Columbia Cancer Registry included 1,248 5-year survivors who had been diagnosed with cancer between the ages of 20 and 24 and were assessed for the risk of late mortality and second malignant neoplasms [158]. Compared to the general population, the overall mortality rate was almost six times higher (SMR = 5.9, 95% CI 4.9–6.9). The most common cause of mortality was due to the primary cancer diagnosis, but the SMR for death from a second malignancy was 5.2 (95% CI 3.3–7.8) and for noncancer-related deaths was 1.7 (95% CI 1.1–2.4). These data all highlight the importance of long-term follow-up of AYA survivors with particular attention focused on modifiable risk factors, particularly those related to cardiovascular disease and surveillance for SMNs.

28.2.2 Subsequent Malignant Neoplasms

Subsequent malignant neoplasms (SMN) are a significant cause of morbidity and premature mortality in survivors. Etiological factors for the

development of subsequent malignant neoplasms include elements of treatment for the first primary neoplasm – particularly radiotherapy and specific chemotherapies as well as genetic predisposition, hormonal factors, immunosuppression, and the potential interactions between these risk factors. Among survivors of cancer diagnosed in adolescence and young adulthood, there is relatively little opportunity during the initial years of follow-up for environmental factors (e.g., smoking, alcohol, and diet) to be important etiologically, when compared with survivors of primary neoplasms diagnosed in middle age or older adulthood. Both solid cancers and leukemias can present as an SMN in this population.

28.2.2.1 Solid Subsequent Malignant Neoplasms

Among a cohort of over 14,000 survivors of childhood, adolescent, and young adult cancer treated prior to age 21 years, 7.9 % developed an SMN by 30 years after their primary cancer [41]. When compared to the age-matched general population, the risk (measured by standardized incidence ratio [SIR]) was particularly elevated for subsequent cancers of bone, head and neck, thyroid, central nervous system, and soft tissue. The most common subsequent malignancies were breast and thyroid cancers. Exposure to radiation therapy resulted in an almost threefold increase in risk for subsequent cancers.

Even when accounting for radiation, survivors of Hodgkin lymphoma are at particularly elevated risk for development of a solid SMN. Among female survivors of Hodgkin lymphoma treated prior to age 21 years with therapy that includes radiation to the breast, approximately one-third will develop a subsequent breast cancer by age 50 years, a rate comparable to that observed in women with BRCA1 mutations [95]. The risk of breast cancer is also in excess of that expected following Hodgkin lymphoma diagnosed in young adulthood (ages 20–29 years), but the SIRs are lower than for those treated in childhood and adolescence. Unfortunately, lower SIRs are not necessarily accompanied by lower absolute excess risk, as several investigators have reported absolute excess risks of comparable magnitude for patients treated between the ages of 20 and 29 years and below 20 years of age [62]. Breast cancer risk in women who have received chest radiation has been shown to decrease with increasing numbers of alkylating agent cycles or increased radiation dose to the ovaries, suggesting that that hormonal stimulation is important for the development of radiation-induced breast cancer [149, 151]. This mechanism might explain why breast cancer risk declines with age at irradiation for Hodgkin lymphoma; women irradiated at age 30 years or older experience much lower excess risk than those irradiated before this age [62]. Progressive reductions in the extent of the radiation field targeted for Hodgkin lymphoma therapy, and the adoption of new radiotherapy techniques, might reduce the long-term risk for subsequent breast cancers, although further follow-up of survivors treated on contemporary regimens will be needed to accurately quantify reductions in risk [31].

Radiation therapy has also been associated with cancers of the lung, thyroid, stomach, bone, soft tissue, skin, and possibly colon and pancreas in survivors of Hodgkin lymphoma [65]. Doses of radiation to the lungs are substantial as a result of several radiotherapy field configurations used to treat Hodgkin lymphoma. An international collaborative case-control study of the role of radiotherapy, chemotherapy, and smoking in the development of lung cancer after Hodgkin lymphoma reported on 227 patients who developed second primary lung cancer and 455 matched controls who did not [43, 148]. There was a significant increase in the excess risk of lung cancer associated with a greater number of cycles of alkylating agents and increasing radiation dose. Statistically significant elevated risks of lung cancer were apparent within 1–4 years of treatment with alkylating agents, whereas the excess risks after radiotherapy began 5 years after treatment and persisted for more than 20 years. Tobacco use increased lung cancer risk more than 20-fold; risks from smoking appeared to multiply risks from treatment [148].

Recent research has investigated whether there is a genetic predisposition to subsequent malignancies in survivors of Hodgkin lymphoma.

One study identified variants in the PRDM1 gene located on chromosome 6q21 as being associated with an increased risk for SMN development after radiation [9]. PRDM1 is a radiation-responsive tumor suppressor gene. Another research is investigating whether polymorphisms in genes associated with drug metabolism or DNA repair and injury response interact with cancer therapies to increase the risk for SMN.

As noted above, the risk for SMN is elevated in survivors of all cancers treated during adolescence and young adulthood but particularly those that have been treated with radiation therapy. Young women treated for a primary breast cancer are one group vulnerable to the development of SMN. Before the implementation of breast-conserving surgery and localized radiotherapy to treat node-negative breast cancer, the principal method of local control was radical mastectomy and extensive radiotherapy to the chest wall and lymph nodes [65]. Consequently, such women have experienced an excess risk of cancers of the contralateral breast and lung and possibly of the esophagus, bone, connective tissue, and thyroid gland [11, 28, 53, 66, 102]. The radiation dose to the contralateral breast can amount to several Gy, and a review [65] has inferred that women irradiated in young adulthood are probably at increased risk of contralateral breast cancer, based mainly on one study [11]. However, another review suggests no convincing evidence of such an effect [30]. Women given radiotherapy who survived at least 10 years appear to have about double the risk of lung cancer experienced by nonirradiated women [66, 102, 147]. This risk is likely to be less following modern radiotherapy techniques. Smoking and radiation have been implicated as risk factors for secondary lung cancer in breast cancer survivors [33, 40].

28.2.2.2 Development of Subsequent Leukemia

Subsequent leukemias (usually acute myeloid leukemia [AML] and myelodysplastic syndrome [MDS]) after cancer therapy have been associated with specific chemotherapy exposures, particularly alkylating agents and topoisomerase II inhibitors (epipodophyllotoxins and anthracyclines). The mean interval between primary cancer and development of secondary AML after alkylating agent exposure is 5–7 years, and AML is often preceded by MDS. Monosomy or partial deletions of chromosomes 5 and 7 are the most common genetic aberrations [59]. In contrast, topoisomerase II inhibitors tend to lead to secondary AML in the first 2–3 years after the primary cancer. These leukemias are usually acute in onset with no preceding MDS and are most frequently associated with rearrangements of the *MLL* gene on chromosome 11q23 [59]. For example, an analysis of 754 adults treated on Stanford Hodgkin lymphoma protocols over a 30-year period revealed 24 patients (3.2%) who developed a treatment-related secondary leukemia (particularly AML) or MDS [73], at a median of 4.6 years from their primary cancer. Alkylating agent exposure was demonstrated to be the most important risk factor for secondary leukemia. Males treated for testicular tumors have been shown to be at increased risk for secondary leukemias as a consequence of etoposide exposure [130]. Whereas the risk for solid SMN after a primary cancer does not appear to plateau, the risk for secondary leukemias tends to diminish after the risk period in the first decade after cancer therapy.

The Children's Oncology Group (COG) has published surveillance guidelines for the detection of SMN in survivors of cancer treated during childhood, adolescence, and young adulthood (available at survivorshipguidelines.org). These include specific recommendations for the types, frequency, and age at initiation for surveillance for breast cancer, colorectal cancer, and skin cancer in survivors deemed to be at high risk (Table 28.2). At the present time, there is no recommendation for routine blood tests to screen for secondary leukemias. Guidelines are reviewed every 5 years, facilitating the addition of new guidelines (such as for lung cancer surveillance) if sufficient evidence exists.

28.2.3 Cardiovascular Complications

The impact of treatment exposures on cardiovascular (CV) function or disease is twofold, the first being related to exposure to anthracyclines which

Table 28.2 Surveillance in survivors at high risk for SMN (COG)

Type of SMN	Exposure risk	Screening recommendation
Breast	≥20 Gy radiation therapy to the chest	Annual mammography starting 8 years after radiation or age 25 years, whichever is last
Colorectal	≥30 Gy radiation therapy to the abdomen, pelvis, or spine	Colonoscopy every 5 years starting at age 35 year
Skin	Any radiation therapy	Annual dermatologic examination of irradiated areas

www.survivorshipguidelines.org

can classically lead to cardiomyopathy. However, both chemotherapy and radiation can lead to alteration in metabolic functions which contribute to the development of insulin resistance with subsequent development of "metabolic syndrome" and the associated clinical features of hypertension, hyperlipidemia, and hyperinsulinemia. In the general population, these conditions are all known risk factors for the development of cardiovascular disease.

The anthracyclines doxorubicin and daunomycin are well-known causes of cardiomyopathy [48, 129]. Anthracyclines have a wide range of clinical activity, and about 40–50 % of adolescent and young adult cancer survivors were treated with anthracyclines, making them one of the more common treatment exposures. The incidence of cardiomyopathy is dose dependent and may exceed 30 % among patients who received cumulative doses of anthracyclines in excess of 600 mg/m^2. With a total dose of 500–600 mg/m^2, the incidence is 11 %, falling to less than 1 % for cumulative doses less than 500 mg/m^2 [13]. This has formed the basis for considering 500 mg/m^2 as the threshold cumulative dose for cardiotoxicity. However, a lower cumulative dose of anthracyclines may place individuals at increased risk for cardiac compromise [75]. The same investigators evaluated the cumulative incidence of anthracycline-induced clinical heart failure in a cohort of 607 patients who had been treated with a mean cumulative anthracycline dose of 301 mg/m^2 and were followed for a median of 6.3 years. A cumulative dose of anthracyclines greater than 300 mg/m^2 was associated with an increased risk of clinical heart failure (relative risk 11.8) compared with a cumulative dose lower than 300 mg/m^2. The estimated risk of clinical heart failure increased with time and approached 5 % after 15 years.

Several investigators have described subclinical anthracycline-induced myocardial damage. Steinherz et al. [136] found 23 % of 201 patients to have echocardiographic abnormalities, a median of 7 years after therapy. The median cumulative dose of doxorubicin received by these patients was 450 mg/m^2 (range 200–1,275 mg/m^2). Lipshultz and colleagues evaluated cancer survivors who had received a median doxorubicin dose of 334 mg/m^2 (range 12–550 mg/m^2). They concluded that doxorubicin causes progressive elevation of afterload or depression of left ventricular contractility in about 75 % of the patients. However, the clinical relevance of subclinical myocardial injury is not clearly established, in part due to widely varying methods used to define and assess such injury. These studies and others emphasize that cardiomyopathy can occur many years after completion of therapy (15–20 years) and that the onset may be spontaneous or coincide with exertion or pregnancy. During the third trimester, the cardiac volume increases, increasing the cardiac workload, leading to overt symptoms in women with left ventricular dysfunction [60, 108]. Risk factors known to be associated with anthracycline-related cardiac toxicity include mediastinal radiation (especially doses ≥30 Gy); uncontrolled hypertension; exposure to other chemotherapeutic agents, especially cyclophosphamide; younger age; and female gender [79]. In general higher cumulative doses (≥550 mg/m^2 in patients 18 years or older at time of treatment or ≥300 mg/m^2 in patients younger than 18 years of age at the time of treatment) are associated with a higher risk of developing clinically significant cardiomyopathy.

Treatment of breast cancer with trastuzumab can also lead to cardiac compromise in up to one-third of patients. In the vast majority of patients, this results in a reversible decrease in LVEF, although some patients may have ongoing heart

failure. Patients who have an elevation of troponin levels following trastuzumab may be at higher risk for lack of LVEF recovery [20]. Exposure to higher cumulative doses of anthracyclines (>240 mg/m^2 doxorubicin or >500 mg/m^2 epirubicin) was found to increase the risk of trastuzumab-induced cardiotoxicity by over threefold [37]. There are no specific recommendations related to the need for any ongoing monitoring in patients in whom LVEF has not been affected or in those who had a reversible decline in LVEF that subsequently normalized. End of therapy assessment of LVEF status is advisable with consideration for additional follow-up if there has been a decline in LVEF from baseline.

Radiation-induced cardiac toxicity can present in a variety of different clinical conditions including congestive heart failure, cardiomyopathy, pericarditis, valvular disease, myocardial infarction, arrhythmia, or atherosclerotic heart disease. Cardiac toxicity associated with radiation alone most commonly involves pericardial effusions or constrictive pericarditis, sometimes in association with pancarditis [1]. Although 40 Gy of total-heart radiation dose appears to be the usual threshold, the risks are also higher in patients who have received anthracyclines with radiation doses ≥30 Gy. However, the risks of pericarditis, congestive heart failure, myocardial infarction, and valvular abnormalities have been reported to be increased by two- to sixfold after as little as 15 Gy compared to nonirradiated survivors [97]. Symptomatic pericarditis, which usually develops 10–30 months after radiation, is found in 2–10% of patients [92]. Subclinical pericardial and myocardial damage as well as valvular thickening may also be common in this population [110], and there can be a significant latency in the development of symptomatic pericarditis which may first appear as late as 45 years after therapy [51, 127].

Coronary artery disease has been reported following radiation to the mediastinum, although the mortality rate was not significantly higher in patients with Hodgkin lymphoma who had received mediastinal radiation than in the general population [12]. A Dutch study of Hodgkin lymphoma survivors reported a cumulative risk for ischemic heart disease of 21% at 20 years after radiation [116]. In another study that followed 415 Hodgkin lymphoma survivors, 10% developed coronary heart disease [64].

Prevention of cardiotoxicity is a primary focus of investigation. Certain analogs of doxorubicin and daunomycin, and liposomal anthracyclines, which appear to have decreased cardiotoxicity, with equivalent antitumor activity, are being explored. The anthracyclines chelate iron, and the anthracycline-iron complex catalyzes the formation of hydroxyl radicals. Agents that are able to remove iron from the anthracyclines, such as dexrazoxane, have been investigated as cardioprotectants. Clinical trials of dexrazoxane have been conducted with encouraging evidence of short-term cardioprotection [16, 155], although the long-term avoidance of cardiotoxicity with the use of this agent needs to be determined. In a prospective, randomized study of pediatric ALL patients, Lipshultz et al. have demonstrated that patients treated with doxorubicin at 300 mg/m^2 alone were more likely than those treated with dexrazoxane and doxorubicin to have cardiac injury as reflected by elevated troponin T levels (50% vs. 21%, $p<0.001$) and extremely elevated troponin T levels (32% vs. 10%, $p<0.001$), without compromising the antileukemic efficacy of doxorubicin [81]. However, longer follow-up is necessary to determine the influence of dexrazoxane on echocardiographic findings, hence, the clinical significance of these findings. Lower doses of anthracyclines and reduced port sizes of radiation therapy may also help in decreasing the incidence of myocarditis. Management of survivors with asymptomatic deterioration of left ventricular function is controversial. Angiotensin-converting enzyme (ACE) inhibitors have been known to improve morbidity and mortality in patients with cardiomyopathy. There appear to be theoretical risks with such therapy in adolescence, since the ACE inhibitors, while lowering the afterload in the short term, may also limit the cardiac growth potential by inhibiting cardiac growth factors. Thus, the role of ACE inhibitors and beta-blockers in asymptomatic survivors with cardiac dysfunction remains in question [80, 132].

Patients who received anthracycline chemotherapy need ongoing monitoring for late-onset cardiomyopathy, with frequency of evaluation based on total cumulative dose and age at the

time of initial therapy. In addition to monitoring for cardiomyopathy, survivors who received radiation potentially impacting the heart (i.e., chest, spine, upper abdomen, or total body irradiation, TBI) also need monitoring for early-onset atherosclerotic heart disease, valvular disease, and pericardial complications. Specific recommendations for monitoring, based on age and therapeutic exposure, are delineated in the COG Long-term Follow-Up Guidelines (described below).

The risk of CV disease can also be related to effects from cancer therapy that impact noncardiac organs/tissues and result in the development of CV risk factors including obesity, dyslipidemia, hypertension, and insulin resistance, all of which are known to be potent risk factors for premature CV disease in adults. While there have not been studies specifically performed in the AYA population, a large study of childhood cancer survivors ≥5 years after diagnosis who were a mean age of 14.5 years when they were carefully evaluated for CV risk and insulin resistance found that compared to siblings, they had greater adiposity (abdominal waist circumference 73.1 vs. 71.1 cm $p=0.02$), percent fat (28.1 % vs. 25.9 %, $p=0.007$), and lower lean body mass (38.4 vs. 39.9 kg, $p=0.01$) [135]. Even after adjusting for adiposity, survivors also were found to have higher total cholesterol (154.7 vs. 148.3 mg/kg, $p=0.004$, LDL cholesterol (89.4 vs. 83.7 mg/kg, $p=0.002$), triglycerides (91.8 vs. 84 mg/kg, $p=0.03$) and were more insulin resistant as measured by euglycemic insulin clamp study (M_{lbm} 12.1 vs. 13.4 mg/kg/min, $p=0.002$) than controls. These findings are significant as CV risk factors track from childhood into adulthood and when already present at such a young age are very likely to contribute to their risk of early CV disease and potentially mortality. A second analysis from the same cohort identified treatment exposures including platinum agents, cranial radiotherapy, and steroids as being associated with insulin resistance and CV risk factors [7]. AYA survivors should have baseline fasting lipid profile and blood glucose obtained at their entry into survivorship. Blood pressure should be monitored on a yearly basis. Counseling regarding the importance of exercise, a nutritionally balanced diet, and maintaining a healthy body weight should be encouraged at each follow-up visit.

28.2.4 Pulmonary Function

Pulmonary fibrosis and pneumonitis can result from pulmonary radiation. Thus, these problems are seen most often in patients with thoracic malignancies, notably Hodgkin lymphoma. Radiation-related pulmonary injuries in AYAs are likely to be mediated by cytokine production, which stimulates septal fibroblasts, increasing collagen production, and resulting in pulmonary fibrosis [72, 122]. Asymptomatic radiographic findings or restrictive changes on pulmonary function testing have been reported in more than 30 % of patients treated with thoracic radiation [61, 89, 103]. Of 25 Hodgkin lymphoma survivors treated with standard mantle radiation before age 35 years, 60 % had an abnormal chest radiograph at a mean follow-up of 9 years [94]. Of the 19 who had pulmonary function testing, 89 % had an abnormality, with 72 % having a reduced diffusion capacity. None of the patients were symptomatic. These changes have been detected months to years after radiation therapy, most often in patients who suffered radiation pneumonitis during or shortly after therapy [154]. Clinically apparent pneumonitis with cough, fever, or dyspnea occurs in only 5–15 % of patients and is generally limited to those who received more than 30 Gy in standard fractions to more than 50 % of the lung [154]. Craniospinal radiation for patients with malignant brain tumors and scatter from abdominal ports contribute to the development of late restrictive lung disease [67]. Obstructive changes have also been reported after conventional radiation therapy. Following hematopoietic stem cell transplantation, both restrictive and obstructive lung diseases including bronchiolitis obliterans are well described [49, 134]. Impaired carbon monoxide diffusing capacity (DLCO) after radiation is predictive of persistent pulmonary morbidity [22]. Refinements in radiation techniques and reductions in doses have decreased the risks for radiation-induced late pulmonary toxicity [54, 152, 157].

In addition to radiation therapy, chemotherapeutic agents are responsible for pulmonary disease in long-term survivors. Bleomycin toxicity is the prototype for chemotherapy-related lung injury, presenting as interstitial pneumonitis and pulmonary fibrosis [107, 133]. The chronic lung toxicity usually follows persistence or progression of abnormalities developing within 3 months of therapy. Like the acute toxicity, it is dose dependent above a threshold cumulative dose of 400 units/m^2 and is exacerbated by concurrent or previous radiation therapy [124]. Above 400 units/m^2 in the absence of other risk factors, 10 % of patients develop fibrosis [124]. At lower doses, fibrosis occurs sporadically in less than 5 % of patients, with a 1–2 % mortality rate. In some reports, bleomycin toxicity was anticipated on the basis of DLCO abnormalities.

Alkylating agents can also cause chronic lung injury. As with bleomycin, carmustine and lomustine pulmonary toxicity is dose related. Cumulative carmustine doses greater than 600 mg/m^2 result in a 50 % incidence of symptoms [6]. A marked increase in pulmonary fibrosis appears at doses exceeding 1,500 mg/m^2 . Pulmonary fibrosis has also been observed in 16–40 % of transplant recipients treated with cytotoxic conditioning agents including carmustine at doses of 500–600 mg/m^2; the incidence of fibrosis declines considerably when doses are limited to less than 300–450 mg/m^2 [123, 156]. Case reports and small series suggest that cyclophosphamide can cause delayed-onset pulmonary fibrosis with severe restrictive lung disease in association with a marked reduction in the anteroposterior diameter of the chest [8, 24]. Melphalan and busulfan are also known to cause pulmonary fibrosis in a dose-related manner. Busulfan toxicity is most predictable in transplantation doses exceeding 500 mg and may be associated with a progressive, potentially fatal restrictive lung disease. Lung injury associated with busulfan is characterized by diffuse interstitial fibrosis and bronchopulmonary dysplasia.

Additional factors contributing to chronic pulmonary toxicity include superimposed infection, underlying pneumonopathy (e.g., asthma), cigarette or respirator toxicity, chronic graft versus host disease, and the effects of chronic pulmonary involvement by tumor or reaction to tumor. Increased oxygen concentrations associated with general anesthesia may exacerbate pulmonary fibrosis, and efforts should be made to minimize exposure to high concentrations of oxygen [46]. There is controversy as to whether the high oxygen pressure associated with scuba diving can exacerbate pulmonary damage [78, 126].

Monitoring for pulmonary dysfunction in cancer survivors includes asking about symptoms such as chronic cough or dyspnea on yearly follow-up. All patients must understand the risks of smoking. The best approach to chronic pulmonary toxicity of anticancer therapy is preventive and includes respecting cumulative dosage restrictions of bleomycin and alkylators, limiting radiation dosage and port sizes, and avoiding primary or secondhand smoke. Pulmonary function tests (including DLCO and spirometry) have been recommended as a baseline upon entry into long-term follow-up for patients at risk, in patients with symptoms, or in those who require general anesthesia for any reason.

28.2.5 Endocrine Function

The endocrine system is particularly susceptible to the long-term effects of cancer therapy. In a survey of the patients attending one late effects clinic, 41 % had an endocrinopathy directly attributable to their disease or treatment. This is almost certainly an underestimate as it did not take into account the risk of growth hormone (GH) deficiency which has since been recognized to have important implications in adult life. Within the same group, a further 14 % were reported to have problems related to fertility [137]. The endocrine system is particularly affected by radiotherapy which impacts the normal function of the hypothalamic-pituitary axis, the thyroid, and the gonads. Chemotherapy can have a significant effect upon gonadal function affecting steroid hormone secretion and reproductive potential. The recent introduction of biological agents that modulate the immune system inducing an autoimmune reaction in the tumor

has seen an advance in the way cancer may be treated; however, these agents are associated with significant endocrine side effects.

28.2.6 Pituitary Function

Hypopituitarism, deficiency of one of more anterior pituitary hormones [gonadotrophins (GH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH), adrenocorticotrophic hormone (ACTH), and thyroid-stimulating hormone (TSH)], may be present at diagnosis caused by pathology in the sellar or suprasellar region, which destroys normal pituitary tissue or disrupts the pituitary stalk, or by the treatments used, either surgery or irradiation. Deficiencies of the posterior pituitary hormones, antidiuretic hormone (ADH) and oxytocin, may occur in the presence of large suprasellar lesions such as a craniopharyngioma or germinoma, but are not caused by irradiation [26].

Patients at risk of radiation-induced hypopituitarism may have been treated for an intracranial tumor, malignancy of the nasopharynx, and ALL or with radiation as preparation for blood or marrow transplantation [45]. Pituitary dysfunction may develop several years after treatment and can be progressive; GH secretion is the most vulnerable to irradiation, followed by the gonadotrophins, ACTH, and finally TSH [76, 82]. The risk of hypopituitarism increases with time from radiation and as the radiation dose increases [145, 146]. Patients treated for ALL, the most common childhood malignancy, have been found to have abnormalities of GH secretion up to 25 years after they received prophylactic cranial irradiation at doses of 18–24 Gy [15]. Patients exposed to higher doses, such as those used to treat nasopharyngeal tumors or malignant brain tumors, are at greater risk; 50 % will have abnormal GH secretion within 5 years of treatment, and many will go on to develop other abnormalities of anterior pituitary function [76].

Cytotoxic chemotherapy has not been shown to have a clinically significant effect on pituitary function in cohort studies. However, immunotherapies used in adults have caused autoimmune hypophysitis and hypopituitarism. These antibodies, so-called immune checkpoint inhibitors, disrupt the immune system generating an immune reaction against the tumor [112]. One such agent, ipilimumab, is directed against the cytotoxic T-lymphocyte antigen-4 receptor (CTLA4) enhancing immunological antitumor activity by decreasing tumor immune tolerance [25]. Up to 17 % of patients treated with ipilimumab develop hypophysitis. The effect is dose dependent. Management includes suspending treatment and replacing affected endocrine axes. High-dose glucocorticoid treatment has been used in an attempt to reduce the impact of the hypophysitis, but the benefit is questionable.

The majority of patients diagnosed with malignant disease between the ages of 15 and 39 years will have completed growth and development. However, GH is now known to play an important role throughout the adult lifespan but particularly up to the age of 25 years. Studies have shown that GH-deficient adults complain of fatigue, have abnormal body composition (fat mass is increased and lean mass decreased), are osteopenic [27], and exhibit an adverse cardiovascular risk profile, which may contribute to the twofold increased cardiovascular mortality observed in patients with hypopituitarism [144]. GH replacement therapy, administered to adults as a single nightly injection, improves quality of life, increases lean mass, decreases fat mass, increases bone mineral density, and improves the cardiovascular risk profile. Although the improvements in the cardiovascular risk profile would support an improvement in cardiovascular risk, it is not yet known whether GH replacement therapy reduces mortality in adults [145].

GH is important for skeletal health, particularly in the years immediately after achieving final height, when it is vital to optimize peak bone mass, which is achieved in the middle of the third decade. A study in adolescents treated for GH deficiency during childhood has shown that continuing GH replacement beyond achievement of final height doubles the rate of bone mass accrual [128]. Thus, young adults that develop GH deficiency may not reach peak bone mass, which will increase their risk of osteoporosis in

the future. In a patient cohort that may have been exposed to other agents that have a negative impact upon bone mass, such as high-dose glucocorticoids, it is important to ensure that peak bone mass is achieved in order to minimize the risk of fracture in later life.

28.2.7 Gonadal Function

The ovaries and testes are both sensitive to the effects of chemotherapy and radiotherapy. The risk of premature ovarian failure increases as the age at treatment increases or when treatment contains radiation below the diaphragm with alkylating agent chemotherapy. Treatment before the age of 13 is less likely to be associated with an increased risk, but treatment between the ages of 13 and 19 was associated with a twofold increase in risk of developing premature ovarian failure [17, 18]. This risk increases further as the age of the women at diagnosis increases. The majority of adolescent women undergoing treatment with combination chemotherapy will retain ovarian function. However, women undergoing bone marrow transplant are at particular risk of ovarian failure. Some series suggest that the frequency of ovarian failure in women pretreated with high-dose alkylating agents may be as high as 100% [125].

The ovaries are particularly sensitive to radiation. Abdominal irradiation for Hodgkin lymphoma or Wilms' tumor is associated with a high risk of ovarian failure. TBI used in preparation for blood and marrow transplantation is associated with ovarian failure in 100% of women at the time of treatment, of whom a small number will experience subsequent recovery of function [45].

In the male there are two aspects of testicular function to consider in those undergoing treatment for malignant disease: the germinal epithelium responsible for production of spermatozoa and testosterone production by the Leydig cells. Chemotherapy, particularly alkylating agents such as cyclophosphamide and procarbazine, can cause failure of the germinal epithelium resulting in oligospermia or azoospermia. The Leydig cells produce testosterone under the control of LH. Although Leydig cell function may be impaired, with testosterone levels in the low normal range associated with an elevated LH level, testosterone deficiency is rarely seen following chemotherapy. Radiation to the testes can cause germinal epithelium failure at doses as low as 2 Gy. Doses in excess of 20 Gy may cause Leydig cell failure and testosterone deficiency [63]. Men undergoing treatment which is known to cause azoospermia should be counseled and offered semen storage, to be used later in life when they are considering fertility.

Estrogen deficiency in women causes menopausal symptoms and abnormalities of cholesterol, which may impact cardiovascular risk. There is also increased loss of bone mass, and in younger women peak bone mass may be affected, increasing the risk of osteoporotic fractures. Testosterone deficiency in men causes reduced libido, erectile dysfunction, reduction in muscle mass, increased bone loss, and lipid abnormalities. Replacement therapy should be undertaken to promote well-being and to protect against osteoporosis and the risk of fracture in later life. Men should receive testosterone replacement either as an intramuscular injection or via the transdermal route using a gel. Women should receive estrogen therapy, which can be given orally or via the transdermal route. Women who have an intact uterus should receive progesterone during the latter part of the month to promote a menstrual bleed, reducing the risk of endometrial hyperplasia and subsequent development of endometrial carcinoma. It is not yet known what the optimal dose of estrogen replacement is in young women; the oral contraceptive may provide too much estrogen, with a week's break, while traditional HRT used in menopausal women may not provide sufficient estrogen. Further work is required to clarify this.

28.2.8 Other Endocrinopathies

Radiation may affect the thyroid gland. Patients that received radiation to the neck for Hodgkin disease or non-Hodgkin lymphoma or craniospinal irradiation for brain tumors are at risk of

thyroid dysfunction. This may take the form of hypothyroidism [14], thyrotoxicosis, or thyroid nodules which may be malignant. Patients at risk should have regular thyroid function tests performed, and their thyroid should be examined by palpation on an annual basis. Thyroid dysfunction should be managed as for any patient with hypo- or hyperthyroidism. The presence of nodules should be treated seriously and referral for thyroidectomy made where appropriate [68].

The parathyroid glands may also be affected by irradiation. Retrospective studies suggest that patients who received neck irradiation may be at increased risk of hyperparathyroidism compared with the background population which may develop up to 50 years after irradiation. Therefore, patients treated with neck irradiation should have their serum calcium monitored regularly [115].

Biological agents that manipulate the immune system to induce an autoimmune effect against tumor tissue have also been associated with primary hypothyroidism and autoimmune adrenalitis. Patients undergoing treatment with these agents should be monitored for these important endocrine sequelae.

Increasing numbers of patients are surviving malignant disease in early adult life. Endocrine dysfunction is one of the most common long-term effects of cancer therapy; in some cases the endocrinopathy evolves with time. Such patients should remain under long-term follow-up in a multidisciplinary service which includes an endocrinologist with experience of the conditions that these patients are likely to face.

28.2.9 Genitourinary Function

28.2.9.1 Renal

Long-term renal damage in individuals treated for cancer is most often associated with drugs such as cisplatin or ifosfamide and radiation therapy. Cisplatin can damage the glomerulus and distal renal tubules, potentially causing diminished glomerular filtration rate (GFR) and electrolyte wasting, most commonly involving magnesium, calcium, potassium, and sodium [114]. Ifosfamide damages the proximal renal tubule, potentially resulting in Fanconi's renal syndrome (hypokalemia, hypophosphatemia, glucosuria, proteinuria, renal tubular acidosis, and rickets) [113]. Individuals at particular risk include those who received treatment with more than one nephrotoxic agent and those with concomitant renal damage related to surgery or radiation. Although the GFR may improve over time, the electrolyte wasting associated with ifosfamide therapy and hypomagnesemia associated with cisplatin therapy appear to persist in some patients [50, 99]. Yearly surveillance should include monitoring of serum creatinine, blood urea nitrogen and serum chemistries, urinalysis, and measurement of blood pressure. Ongoing management includes electrolyte replacement, treatment of hypertension, and avoidance of further nephrotoxic agents. Patients with a history of nephrectomy should be counseled regarding the importance of protecting the remaining single kidney. These patients should be cautioned to avoid potentially nephrotoxic agents (e.g., ibuprofen, aminoglycosides), maintain normal weight, obtain early intervention for urinary tract infections, and consult with their healthcare provider prior to participating in contact sports.

28.2.9.2 Bladder

Cyclophosphamide and ifosfamide are both capable of inducing hemorrhagic cystitis as a result of accumulation of acrolein in the bladder [114]. Urgency, frequency, and dysuria are symptoms commonly associated with hemorrhagic cystitis, which can be a long-term complication of cancer therapy in some patients [47]. Radiation to the bladder at doses ≥30 Gy or in combination with cyclophosphamide and/or ifosfamide may also increase the risk of hemorrhagic cystitis [86, 138]. Radiation to the pelvis or bladder can result in fibrosis and scarring, with resultant decreased bladder capacity and predisposition to urinary tract infections [85]. Bladder cancer has developed in some patients who received bladder-toxic agents during treatment for cancer. Yearly urinalysis should be done in these patients to evaluate for the presence of microscopic hematuria.

28.2.10 Gastrointestinal Function

Fibrosis and enteritis are the most common pathologic abnormalities of the gastrointestinal tract in long-term survivors of cancer. These can arise as late complications of radiation to any site from the esophagus to the rectum [97–102] and have been associated with adhesions or stricture formation, sometimes with obstruction, ulcers, fistulae, and chronic enterocolitis or incontinence [35, 36, 58, 84, 109]. Their frequency depends on the radiation dosage delivered by external beam or by brachytherapy. The stomach and small intestine appear to be more radiation sensitive than the colon or rectum. Overall, the incidence of fibrosis after 40–50 Gy is 5 % and as high as 36 % after 60 Gy or more. Most complications of intestinal fibrosis arise within 5 years, but strictures have developed as late as 20 years after treatment [109, 121]. Once they occur, radiation-induced gastrointestinal strictures may be progressive or recurrent. The incidence of clinically significant problems is enhanced by radiomimetic chemotherapy or abdominal surgery [35, 121]. Abdominal surgery itself can result in late-onset obstruction [106, 118]. Radiation to the abdomen can also induce liver disease and is associated with dose (≥30 Gy), hepatic volume irradiated, younger age at treatment, prior partial hepatectomy, and prior or concomitant use of hepatotoxic chemotherapy [39, 91].

Chemotherapy agents including mercaptopurine, thioguanine, and methotrexate may be a cause of chronic hepatopathy [21]. In several early prospective studies of patients given methotrexate for ALL or psoriasis, the incidence of biopsy-proven hepatic fibrosis was as high as 80 % after 3–5 years of low-dose daily oral methotrexate [29, 131]. However, with intermediate or even high doses of intravenous methotrexate, the incidence of fibrosis has been below 5 % [88]. In general, and apparently in contrast to what occurs after radiation therapy, methotrexate-related hepatic fibrosis stabilizes or resolves after discontinuation of the drug. Radiation- or chemotherapy-induced sinusoidal obstructive syndrome (SOS)/veno-occlusive disease (VOD) (acute onset and dose related) has been reported in some patients after exposure to dactinomycin [69]. This has most often been reversible but can be fatal. The more common setting for SOS/VOD is in the post-hematopoietic stem cell transplant (HCT) setting occurring after conditioning regimens containing busulfan and cyclophosphamide or total body irradiation [32]. SOS/VOD after transplant typically occurs in the first 3 weeks and again may be self-limiting and reversible but is associated with a higher mortality rate. There are no known long-term hepatic consequences after SOS/VOD in HCT survivors.

Viral hepatitis, most often related to transfusion of blood products prior to 1992, is another cause of chronic liver disease in long-term survivors [23, 83, 141]. In one retrospective series of 658 cancer survivors who had been treated before routine screening of blood products, 117 (17.8 %) were seropositive for hepatitis C [83]; 35 % of these also were positive for hepatitis B with or without delta virus. Eighty percent of the seropositive patients had been transfused, so that in 20 % other risk factors appeared to have been responsible. In one series of 10-year survivors of bone marrow transplantation for hematologic malignancy, hepatitis C was the major risk factor for late development of cirrhosis: of 16 patients with cirrhosis, 15 had disease attributable to hepatitis C [139]. Hepatitis B has largely been eliminated in populations treated after 1972 [34].

Patients at risk for gastrointestinal complications should be monitored by history or physical examination for hepatomegaly, icterus, and malabsorption. Especially for those patients with acute hepatotoxicity during therapy and for patients treated with hepatectomy, methotrexate, or hepatic radiation, the potential consequences of excessive alcohol and other high-risk behaviors should be emphasized. In such patients, we consider a posttreatment baseline screen including transaminase and bilirubin levels to be cost-effective. Prothrombin time and serum albumin for evaluation of liver synthetic function may be indicated. If persistent, abnormalities should be evaluated further in collaboration with a gastroenterologist. The Center for Disease Control recommendations for hepatitis C screening include patients transfused or transplanted before 1992,

even when transaminases are normal [120]. Hepatitis A and B testing should be considered in unimmunized patients with abnormal liver function tests.

Newer approaches to the treatment of gastrointestinal malignancy, including both administration of radiolabeled monoclonal antibodies for the therapy of hepatomas and intrahepatic arterial chemotherapy, have not yet been examined with respect to possible delayed effects.

28.2.11 Musculoskeletal and Related Tissues

Functional and cosmetic disabilities involving bone, teeth, muscle, and other soft tissues are common and are reported in up to one-third of survivors of various cancers affecting AYA, notably solid tumors. Most clinically significant problems involve avascular necrosis (AVN) and osteoporosis (bone density ≥2.5 standard deviations (SD) below mean)/osteopenia (bone density 1–2.5 SD below mean).

Young adult cancer survivors may develop reduced bone density, as measured by dual energy x-ray absorptiometry (DXA) scans [2, 4, 70]. Although several studies have demonstrated decreased bone density at diagnosis in patients with ALL [150], osteopenia and osteoporosis are well recognized to progress following exposure to corticosteroids or from radiation therapy in doses used in patients with soft tissue sarcomas or Ewing sarcoma [143]. Osteopenia in ALL survivors, as documented by quantitative computed tomographic scans, has also been related to cranial irradiation [44]. Exposure to radiation at a dose less than 25 Gy may result in osteopenia significant enough to cause spontaneous fractures, but which may go undetected by plain radiographs. Antimetabolites have been linked to decreased bone density in a manner that appears to be dose dependent. Following methotrexate, this problem appears primarily during therapy and resolves once the drug has been discontinued [100]. Both genders are at risk for reduced bone mineral density, although Caucasians may be at greater risk than blacks [70]. Contributing factors include treatment-related gonadal and growth hormone failure, hyperthyroidism, poor calcium intake, and lower body weight [2, 56]. Some data suggest that bone density may increase 1 year off treatment of ALL but that the risk of fracture remains high, suggesting that changes in bone architecture not assessable by DEXA scans may be relevant [150].

Avascular necrosis is a radiographic diagnosis, which may be asymptomatic until the involved bone is subject to fracture or infection. Although AVN usually develops during therapy, the latency period has been as long at 13 years after treatment. Major risk factors are radiation therapy and systemic corticosteroids. Clinically significant AVN presenting as pain is well described in Hodgkin lymphoma and non-Hodgkin lymphoma and in patients with ALL in whom the overall incidence has been about 5 %, but in a higher percentage of adolescents [38, 52, 87]. Dexamethasone appears to have more bone toxicity than equivalent doses of prednisone, and increased cumulative exposure conveys increased risk [52]. In one retrospective review, almost 15 % of adolescents treated with dexamethasone experienced symptomatic AVN [57]. AVN most commonly involves the femoral heads, where it may be accompanied by slipped capital femoral epiphysis, but it has been described in virtually all locations and commonly is multifocal.

While not entirely secondary to musculoskeletal-related late effects, long-term survivors may experience functional limitations that impact their ability to engage in routine activities of daily living such as shopping or housework or to attend work or school. In comparison to siblings, survivors were found to be more likely to report performance limitations (relative risk (RR) 1.8, 95 % confidence interval (CI) 1.7–2.0), restrictions in ability to carry out person care tasks (RR 4.7, 95 % CI 3.0–7.2), limitations in their routine activities (RR4.7, 95 % CI 3.6–6.2), and an impaired ability to attend school or work (RR 5.9, 95 % CI 4.5–7.6) [101]. The greatest impact was seen in survivors of CNS and bone cancers.

Detection and diagnosis of musculoskeletal and connective tissue toxicities depend largely upon anticipating these issues in vulnerable hosts,

of taking a careful history, and performing a thorough physical examination. The need for diagnostic radiographs and appropriate referral in the case of clinically apparent disease is obvious. The relative benefit of surveillance radiographs of bones encompassed by radiation ports and of bone densitometry is less clear. However, because of progress with various interventions (including the use of calcium supplementation, calcitonin, bisphosphonates, and sex hormone replacement in postmenopausal patients), a baseline DXA scan should be considered in high-risk survivors at their entry into long-term follow-up, with repeat studies as clinically indicated. Survivors should also be counseled regarding additional health behaviors that can impact bone health including inadequate intake of vitamin D and calcium, lack of weight-bearing exercise, smoking, and alcohol use.

28.3 Delivering Survivorship Care

Chapter 29 "Promoting Health and Care Transitions in the Long-term AYA Survivor" describes appropriate healthcare for survivors of cancer who are transitioning from pediatric to adult healthcare. As described in these chapters, this topic is emerging as one of the major challenges in medicine. Young cancer survivors, an especially high-risk population, currently approach 400,000 in the United States [111] and seek and receive care from a wide variety of healthcare professionals, including oncologists, medical and pediatric specialists, surgeons, primary care physicians, gynecologists, nurses, psychologists, and social workers [104]. The challenge arises from the heterogeneity of this patient population treated with numerous therapeutic modalities in an era of rapidly advancing understanding of late effects. The Institute of Medicine has recognized the need for a systematic plan for lifelong surveillance that incorporates risks based on therapeutic exposures, genetic predisposition, lifestyle behaviors, and comorbid health conditions. As described by Oeffinger, several key components are required for optimal survivorship care. These include (1) longitudinal care utilizing a comprehensive multidisciplinary team approach; (2) continuity, with a single healthcare provider coordinating needed services; and (3) an emphasis on the whole person, with sensitivity to the cancer experience and its impact on the entire family.

Providing comprehensive risk-based care that is readily accessible to survivors presents a significant challenge. Although the number of young cancer survivors is ever increasing, healthcare professionals outside academic centers are unlikely to see more than a handful of survivors in their practice, and unless those patients share a similar diagnosis and receive similar treatment, there will likely be little similarity in their required follow-up care. Recently reported surveys of the preferences and knowledge about the care of adult survivors of childhood cancer among general internists and family physicians found that neither specialty was particularly comfortable in caring for these survivors without ongoing participation of a cancer center-based physician or long-term follow-up clinic and that their knowledge regarding surveillance recommendations was limited [140, 142]. Access to surveillance guidelines and a letter from a specialist that outlined surveillance recommendations along with treatment summaries were identified as the most useful tools needed to assist them in providing long-term follow-up care to these survivors. Academic settings may allow for the establishment of a specialized multidisciplinary follow-up team to care for large numbers of survivors; however, the paucity of such centers and their limited geographic access often make them an option only for survivors who live nearby or who can afford time and expenses in order to travel to a distant center. Therefore, finding ways to educate primary healthcare providers regarding needed follow-up is a priority. Efforts focusing on educating survivors regarding the indicated follow-up may be efficacious, with survivors in turn providing the necessary link in order to direct healthcare providers to specialized information regarding appropriate long-term follow-up care.

Regardless of the setting for follow-up, the first step in any evaluation is to have at hand an outline of the patient's medical history and comprehensive treatment summary (Table 28.3), as well as a list of potential late effects of therapy, and the

Table 28.3 Elements of a comprehensive therapeutic summary

Topic	Data elements
Demographics	Name
	Date of birth
	Sex
	Race/ethnicity
	Record number/patient identification number
Diagnosis	Date/age at diagnosis
	Treating physician/institution
	Diagnostic details (sites involved, stage, laterality), pertinent past medical history, hereditary/congenital conditions
	Family history
	Relapse(s) dates/age at relapse(s), site(s) (if applicable)
Treatment	Treatment dates (initiated/completed)
	Protocols used
	Chemotherapy agents received, including:
	Route of administration
	Cumulative doses for alkylators, anthracyclines, bleomycin
	Cytarabine and methotrexate
	Biologics and/or immunotherapy
	Radiation fields, doses, dose fractions
	Surgical history
	Transfusion history
	Stem cell transplant(s), including donor source, preparative regimen, GVHD prophylaxis/treatment
Complications/late effects	Significant therapy-related complications (e.g., tumor lysis, septic shock, typhlitis, acute GVHD)
	Significant complications following completion of therapy (e.g., acute life-threatening infection following splenectomy, cardiomyopathy, second malignancies)
Graft-versus-host disease	Acute (maximum grade, site(s) involved)
	Chronic (limited vs. extensive, sites involved)

recommended screening and surveillance strategies. The American College of Surgeons Commission on Cancer has mandated that all accredited cancer centers provide such a Survivorship Care Plan (SCP) to all survivors [140]. Following completion of therapy, this SCP should be reviewed with the patient and family. Correspondence between the treating oncologist and subsequent healthcare providers should address these potential long-term issues.

28.4 Recommendations for Screening

In 2003, the COG released risk-based, exposure-related guidelines (Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers) [77] that were designed specifically to direct follow-up care for patients who were diagnosed and treated for pediatric malignancies. These guidelines represent a set of comprehensive screening recommendations that are clinically relevant and can be used to standardize and direct the follow-up care for this group of cancer survivors with specialized healthcare needs. These guidelines provide recommendations for ongoing monitoring that facilitates early identification of and intervention for treatment-related complications in order to increase quality of life for these patients. Specially tailored patient education materials, known as "Health Links," accompany the guidelines, offering detailed information on guideline-specific topics in order to enhance health maintenance and promotion among this population of cancer

survivors. The entire set of guidelines, with associated Health Links, can be downloaded from www.survivorshipguidelines.org.

Several other national groups, including the Scottish Intercollegiate Guidelines Network (SIGN), the United Kingdom Children's Cancer Group, and the Dutch Children's Oncology Group, have also published guidelines for the long-term follow-up of survivors. Recently, an international collaboration of survivorship experts from around the world created the International Late Effects of Childhood Cancer Guideline Harmonization Group with the goal of creating consensus guidelines for long-term follow-up for specific late effects [74]. This group has published recommendations for surveillance for secondary breast cancer [96] and cardiomyopathy [5]. Several recommendations are currently being developed (e.g., for surveillance for male and female gonadotoxicity and secondary thyroid cancers). The published recommendations can be accessed at www.ighg.org.

28.5 Cancer Survivorship: Future Research Opportunities

Because of its heterogeneity and the significant individual and public health burden, the growing population of young cancer survivors deserve an increase in research relating to the etiology and pathogenesis of cancer and early detection and prevention of adverse outcomes. This also presents important opportunities for researchers. Therapeutic exposures occurring at known time points, with close follow-up after the exposure, enable researchers to study testable hypotheses and to determine the effects of host and therapy-related factors in the development of adverse outcomes ranging from carcinogenesis and organ dysfunction to psychosocial consequences. Opportunities also exist to explore gene-environment interactions that may modify individual responses to treatment, as well as the susceptibility to develop adverse outcomes, thus providing insights into the identification of high-risk populations.

Notwithstanding the unique opportunities, several challenges exist to the conduct of survivorship research (Table 28.4). Cancer survivorship research is an evolving field. With more than 20% of young cancer patients in need of better treatment options, new agents and combinations of agents are being developed [3]. Targeted therapies, including small molecules and monoclonal antibodies, will likely contribute to increased survivorship, and evaluation of the potential late effects of these new agents will need to keep in step with their increased usage. Recent refinements in radiation therapy such as proton beam therapy and popularization of surgical techniques such as laparoscopy have been intended largely to minimize late effects. Evidence-based medicine will need to determine whether they will live up to this expectation. Furthermore, the influence of genetic profiles on susceptibility to late effects, as well as their interaction with lifestyle exposures such as tobacco, alcohol, and diet, is of growing interest and has not been fully explored. However, the multifactorial etiology of the adverse effects, coupled with the heterogeneous nature of the patient population, necessitates large sample sizes within the context of well-characterized cohorts with complete long-term follow-up, and this remains the

Table 28.4 Challenges in survivorship research

Treatment for cancer in AYAs undergoes constant change, including introduction of new:
Therapeutic agents/combinations of agents
Radiation techniques
Surgical procedures
Supportive care agents/techniques
Most current data relates to outcomes within the first decade following treatment; only minimal data addresses longer-term outcomes
Research is needed to:
Determine the potential long-term impact of cancer therapy in the young
More clearly define survivors at greatest risk for specific outcomes
Identify genetic predisposition to certain key outcomes, including the role of gene-environment interactions
Identify the role of lifestyle choices (e.g., alcohol, tobacco, diet, exercise) and their impact on risk of late outcomes
Develop intervention strategies to prevent or minimize the impact of adverse late effects

biggest challenge in conducting sound survivorship research.

In 1996, the National Cancer Institute established the Office of Cancer Survivorship (www.cancercontrol.cancer.gov/ocs), which promotes research into the effects of cancer and its treatment. To investigate adverse health outcomes among survivors, large-scale epidemiological investigations are required, particularly because of the complex and multifactorial etiology and rarity of many adverse outcomes. Two large ongoing cohort studies are addressing a wide spectrum of adverse health outcomes that may be increased following cancer and its treatment in the young. The CCSS was established in 1994 and comprised 25 clinical centers in the United States and Canada. Eligible cancer patients were aged less than 21 years at diagnosis between 1970 and 1986 and survived at least 5 years [119]. This cohort has now been expanded to include survivors diagnosed between 1987 and 1999, and 31 centers now participate. Of 35,937 eligible participants, 24,466 have participated, and the study has stored DNA from 8,646 participants. Details about the study, including study questionnaires and manuscripts, are available at ccss.stjude.org.

In 1998, the population-based British Childhood Cancer Survivor Study (BCCSS) was established [55]. Using the National Registry of Childhood Tumors, 17,981 individuals diagnosed with cancer before the age of 15 years between 1940 and 1991 in England, Wales, or Scotland and who survived at least 5 years were identified as eligible. The overall cohort has been used to study long-term survival and causes of late deaths and the incidence and etiology of second primary cancers. A postal questionnaire was sent via primary care physicians to 14,836 survivors aged 16 years or older. In response 10,500 questionnaires (71 %) were returned completed (for further information, visit http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/CCCSS/bccss/index.aspx). The BCCSS has recently been extended to include 16,509 individuals who survived at least 5 years after diagnosis between 1992 and 2006 and therefore now includes 34,490 individuals. Both of these research initiatives provide examples of the practicality and usefulness of large-scale follow-up of survivors employing minimally intrusive methodologies using mostly postal questionnaire and telephone contact. The considerable uncertainties relating to the long-term health of survivors of cancer diagnosed in adolescence and young adulthood provide a strong justification for comparable surveillance. In relation to survivors of cancer in adolescence and young adulthood, the evidence base is currently very limited; nevertheless, it is important that guidelines for standardized clinical follow-up be used and regularly updated as the evidence base grows. Recently in the UK a population-based cohort has been established of 200,945 individuals who were diagnosed with cancer when aged between 15 and 39 years inclusive, in England and Wales, between 1971 and 2006 inclusive and who survived at least 5 years from diagnosis. The work relating to this cohort is termed the Teenage and Young Adult Cancer Survivor Study (TYACSS; for further information, visit http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/CCCSS/bccss/index.aspx). Identifying information relating to each of the individuals included has been used to undertake deterministic electronic record linkage to:

1. The national death registries to ascertain underlying causes of death for those deaths occurring more than 5 years from diagnosis
2. The national population-based cancer registries to ascertain all occurrences of subsequent primary neoplasm
3. The national hospital episode statistics (HES) database for England of outpatient, inpatient, and emergency care

Linkage is planned with the national Patient Episode Database for Wales (PEDW) and the national registers of cardiac disease and procedures maintained by the "National Institute for Cardiovascular Outcomes Research" (NICOR) (www.ucl.ac.uk/nicor). The composition of this cohort in relation to key factors is provided in the Table 28.5. Manuscripts are in preparation which will investigate risks of specific causes of death,

Table 28.5 Cohort characteristics of the Teenage and Young Adult Cancer Survivor Study (TYACSS)

	N	%
Total	200,945	100
Sex		
Male	76,666	38.2
Female	124,279	61.9
First primary neoplasm type		
Breast	36,236	18.0
Testicular	24,309	12.1
Cervix	23,281	11.6
Melanoma	22,446	11.2
Hodgkin lymphoma	16,971	8.5
CNS	17,280	8.6
Non-Hodgkin lymphoma	9,467	4.7
Thyroid	7,809	3.9
Gastrointestinal	7,224	3.6
Soft tissue sarcoma	6,130	3.1
Ovary	4,885	2.4
Bladder	4,685	2.3
Other genitourinary organs	4,672	2.3
Head and neck	3,961	2.0
Leukemia	5,073	2.6
Bone tumor	2,241	1.1
Lung	1,219	0.6
Others	3,056	1.5
Age at diagnosis		
15–19 years	12,249	6.1
20–24 years	21,257	10.6
25–29 years	35,894	17.9
30–34 years	54,541	27.1
35–39 years	77,004	38.3
Years since diagnosis[a]		
5–9 years	38,162	19.0
10–19 years	77,995	38.8
20–29 years	53,001	26.4
30–39 years	28,335	14.1
40+ years	3,452	1.7
Attained age at exit[a]		
20–29 years	4,393	2.2
30–39 years	24,273	12.1
40–49 years	71,604	35.6
50–59 years	58,428	29.1
60–69 years	32,855	16.4
70–79 years	9,104	4.5
80+ years	288	0.1
Vital status[a]		
Alive	166,757	83.0
Dead	34,188	17.0

[a]As of 28 February 2014

subsequent primary neoplasms, cardiac diseases, cerebrovascular diseases, renal diseases, and adverse outcomes in pregnancy and birth. It is also important that the field expand efforts beyond epidemiologic-based studies to increase research that will examine therapeutic interventions for the treatment and/or prevention of potential late effects.

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29 Promoting Health and Care Transitions in the Long-Term AYA Survivor

Melissa Maria Hudson, Karen Kinahan, Lisa K. Sharp, and David R. Freyer

Abstract

A large proportion of survivors of cancer diagnosed when they were AYAs experience some adverse effects on their health, some that do not become apparent for years or even decades after the exposure to the anticancer therapies. The developing and maturing organ systems of AYAs have different sensitivities to radiation therapy, chemotherapy, and surgery than do those of younger or older cancer patients. Virtually all organ systems can be affected, depending upon the therapeutic exposure, leading to a wide array of late effects, including second cancers, cardiovascular and pulmonary disease, cognitive dysfunction, and musculoskeletal problems. Some initially subclinical effects may exacerbate common diseases associated with aging, such as cardiovascular, skeletal, and endocrine disorders, and contribute to poor quality of life and premature death. Sociodemographic factors, details of treatment, and health behaviors also influence the magnitude of impairment in specific health status domains. Through risk-based care and education about the health risks conferred by the cancer experience, clinicians caring for long-term survivors play a critical role in the prevention, diagnosis, and rehabilitation of cancer-related complications and adjustment to chronic health conditions predisposed or exacerbated by cancer. Consequently, health professionals caring for AYA cancer survivors

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may influence their future health positively by correcting knowledge deficits, addressing factors that enhance an individual survivor's vulnerability to health problems, and providing personalized health counseling that promotes the practice of health-promoting behaviors. This chapter describes the healthcare of survivors of cancer diagnosed during the AYA years, including risk-based screening and surveillance for late effects, transition of AYA healthcare, and models of AYA survivorship care. The promotion of healthy lifestyle habits is discussed, emphasizing the impact of such habits on the expression of late effects.

29.1 Introduction

Survivors of cancer diagnosed during adolescence and early adulthood face lifetime risks associated with their previous cancer and cancer therapy. It is well understood that the developing and maturing organ systems of an AYA are sensitive to radiation therapy, chemotherapy, and surgery that are delivered to cure the cancer [1, 2]. When alterations in the development or aging of normal tissues reach a critical threshold, organ system dysfunction can result. Virtually all organ systems can be affected, depending upon the cancer therapy exposure, leading to a wide array of late effects, including second cancers, cardiovascular and pulmonary disease, cognitive dysfunction, and musculoskeletal problems [3–9]. Commonly, late effects may not become apparent for years or even decades after the exposure to the cancer therapies. Of concern is the potential that persistent, often initially subclinical, effects may exacerbate common diseases associated with aging, such as cardiovascular, skeletal, and endocrine disorders, and contribute to poor quality of life and premature mortality [3, 4, 6–11]. Among aging survivors in the Childhood Cancer Survivor Study (CCSS), an increasing burden of chronic health conditions was linked to a higher prevalence of poor general health (prevalence ratio [PR], 2.37; 95 % CI, 2.09–2.68), adverse mental health (PR, 1.66; 95 % CI, 1.52–1.80), functional impairment (PR, 4.53; 95 % CI, 3.91–5.24), and activity limitations (PR, 2.38; 95 % CI, 2.12–2.67) compared to age-matched sibling controls [12]. Sociodemographic factors, cancer treatment, and health behaviors also influenced the magnitude of risk of impairment in specific health status domains. These data underscore the importance considering both physical and emotional consequences of cancer as well as the multiple factors known to contribute to development of cancer treatment-related morbidity when counseling AYA survivors about cancer-related health risks (Fig. 29.1) [13]. This chapter describes the role of two important components in the lifelong care or future health of survivors of cancer diagnosed during AYA years. First, the healthcare of survivors, including risk-based screening and surveillance for late effects, transition of AYA healthcare, and models of AYA survivorship care, is described. After this, the promotion of healthy lifestyle habits is discussed, focusing on the interaction of lifestyle habits and the expression of late effects. It should be noted that the literature presented in this chapter includes outcomes of individuals diagnosed with cancer during adolescence and young adulthood as well as those of AYA survivors of cancer diagnosed during childhood.

29.2 Healthcare of Cancer Survivors

From the perspective of health and chronic disease models, cancer survivors represent an interesting population with health needs and healthcare utilization patterns that vacillate between a wellness and an illness model (Fig. 29.2). Prior to the symptomatic onset of the cancer, most individuals are "healthy" and operate in a wellness model, with preventive healthcare needs that are usually addressed by a primary care physician (PCP). With the onset of symptoms

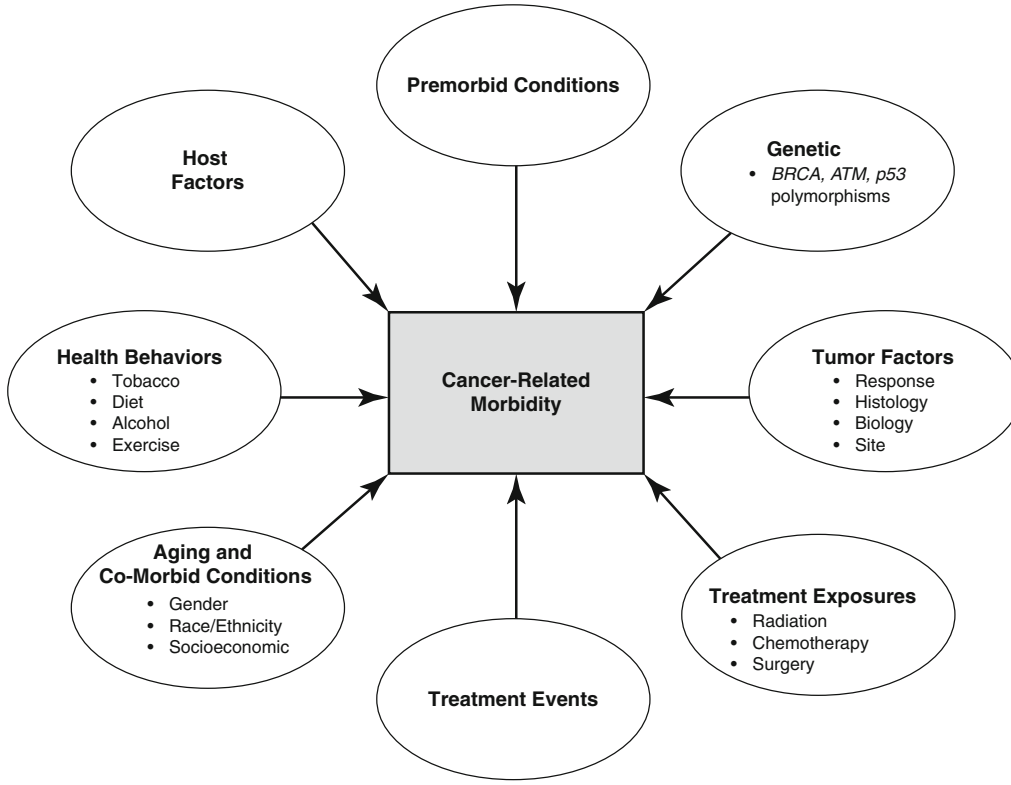

Fig. 29.1 Multiple factors contribute to cancer-related morbidity The risks of late effects may be modified, either positively or negatively, by host (gender, age, race, genetics), cancer (location, histology, biology), or treatment (type, intensity) factors as well as behavioral practices. Practicing healthy lifestyles is the primary method survivors of adolescent and young adult cancers can use to reduce the risk of future health complications (Adapted with permission from Hudson [13])

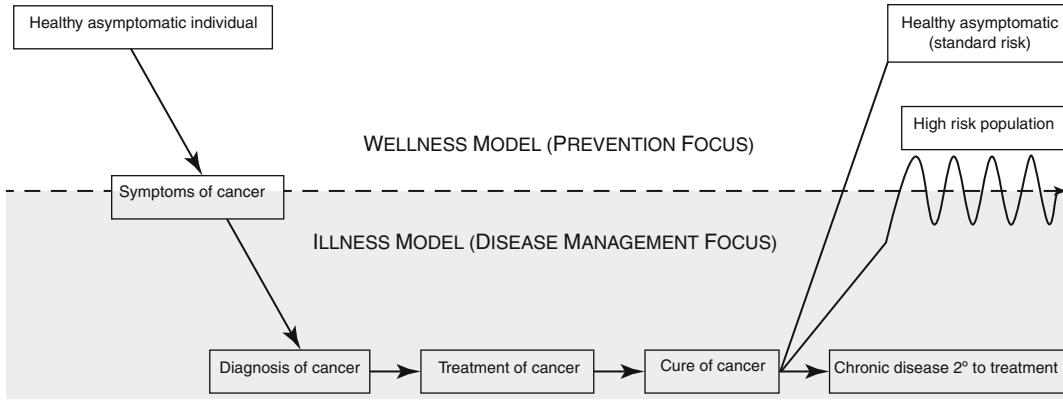

Fig. 29.2 Health needs and healthcare utilization of survivors of adolescent and young adult cancer vacillate between a wellness and an illness model. Prior to the symptomatic onset of the cancer, most individuals are "healthy" and operate in a wellness model, with preventive healthcare needs that are usually addressed by a primary care physician With the onset of symptoms and the diagnosis of cancer, the individual then assumes the role of "cancer patient" and is treated for the disease, generally in a chronic-care model with care focusing on the disease and provision of care provided largely by the oncology team. Upon completion of therapy and some interval thereafter, depending on the cancer, the patient is declared "cured." Some survivors who develop a chronic health problem as an early consequence of the cancer or cancer therapy remain in a chronic-care model

and the diagnosis of cancer, the individual then assumes the role of "cancer patient" and is treated for the disease, generally in a chronic-care model with care focusing on the disease and provision of care provided largely by the oncology team. Upon completion of therapy and some interval thereafter, depending on the cancer, the patient is declared "cured." Some survivors develop a chronic health problem as an early consequence of the cancer or cancer therapy. For instance, a seizure disorder may result from the location of a brain tumor or the curative surgery or radiotherapy. Such a survivor may continue in a chronic disease model and be monitored by a neurologist. As another example, an adolescent with an osteosarcoma may require limb-sparing surgery involving a lower extremity. The musculoskeletal system is permanently altered by the tumor and its treatment and long-term monitoring by an orthopedic surgeon would be anticipated. In both of these examples, the survivor would be cared for in a chronic disease model but would also have preventive care needs to be addressed.

Most AYA survivors, however, do not have a chronic health problem upon completion of their cancer therapy and thus, in a sense, enter back into the wellness model. Importantly, though, they have new long-term health risks, many of which have not been well characterized. Most survivors are not cognizant of their long-term health risks associated with the cancer therapy. Mentally and emotionally, many if not most survivors of AYA cancers figuratively close the door on the cancer chapter of their life. Similarly, most clinicians that provide care for a survivor outside of a cancer center setting are not familiar with the health risks of this relatively small and heterogeneous population. Operating in this mode, most clinicians will note the previous history of the cancer in the medical record, but will usually not consider the survivor as a high-risk individual and will rarely order screening or surveillance studies different than would be warranted in the general population.

Due to enhanced understanding of cancer treatment-related effects and risk adaptation of contemporary protocols, a sizeable proportion of survivors will have relatively minimal risk for clinically significant late effects [14]. For them, receiving healthcare that does not address their previous cancer likely will make little difference in their lives. Most, though, can be stratified into either middle- or high-risk groups. In the traditional wellness model, in which preventive care is delivered to the general population, a similar stratification of risk is incorporated. Most screening recommendations are based on genetic predispositions, comorbid health conditions, or lifestyle behaviors.

29.2.1 Risk-Based Healthcare of Survivors

Faced with these risks and challenges, how can the healthcare delivered to survivors be optimized? It is important to recognize that there is a window of opportunity to modify the severity of health outcomes by prevention or early intervention. Early diagnosis and intervention or preventive care targeted at reducing risk for late effects can benefit the health and quality of life of survivors [15, 16]. The outcomes of the following late effects can be influenced by early diagnosis and early intervention: second malignant neoplasms following radiation therapy (breast, thyroid, and skin), altered bone metabolism and osteopenia, obesity-related health problems (dyslipidemia, hypertension, diabetes mellitus, cardiovascular disease), liver failure secondary to chronic hepatitis C following blood transfusion, and endocrine dysfunction following chest/mantle or cranial radiotherapy. Primary, secondary, and tertiary prevention, including tobacco avoidance/cessation, physical activity, low-fat diet, and adequate calcium and vitamin D intake, can modify risk. Longitudinal care addressing other late effects, such as infertility, musculoskeletal problems, cognitive dysfunction, and psychosocial issues, may also improve survivors' health outcomes and quality of life.

Based on these precepts, the concept of risk-based healthcare of survivors has evolved over the years. The term "risk-based healthcare," coined by Meadows, Oeffinger, and Hudson, refers to a conceptualization of lifelong healthcare

that integrates the cancer and survivorship experience into the overall lifetime healthcare needs of the individual [15, 16]. We endorse the following basic tenets of risk-based care: (1) longitudinal care that is considered a continuum from cancer diagnosis to eventual death, regardless of age; (2) continuity of care consisting of a partnership between the survivor and a single healthcare provider who can coordinate necessary services; (3) comprehensive, anticipatory, proactive care that includes a systematic plan of prevention and surveillance—a multidisciplinary team approach with communication between the PCP, specialists of pediatric and adult medicine, and allied/ancillary service providers; (4) healthcare of the whole person, not a specific disease or organ system, that includes the individual's family and his cultural and spiritual values; and (5) a sensitivity to the issues of the cancer experience, including expressed and unexpressed fears of the survivor and his or her family/spouse. A systematic plan for lifelong screening, surveillance, and prevention that incorporates risks based on the previous cancer, cancer therapy, genetic predispositions, lifestyle behaviors, and comorbid health conditions should be developed for all survivors. To achieve continuity of risk-based management over the lifespan for AYA survivors of childhood cancer, the need for effective transition of survivorship care from pediatric-centered to adult-focused settings is implied [17].

Delivery of risk-based care is a core component featured in long-term follow-up (LTFU) programs that have been organized in academic cancer centers and community oncology programs in the United States, Canada, Europe, Asia, and Australia [18, 19]. However, geographic and financial barriers as well as age limits may preclude many AYA cancer survivors' access to these programs that provide screening for late effects, including subsequent neoplasms, education regarding risks, and promotion of healthy lifestyles. These operations are resource intense and generally a low clinical revenue generator because of the limited or lack of reimbursement for significant components of the care [20]. Even in cancer centers with a LTFU program, most survivors gradually disconnect from oncology care as they age or move away and become "lost to follow-up." Apart from cancer centers, few healthcare professionals see more than a handful of survivors, each with different cancers, treatment exposures, and health risks. This has led to increasing numbers of survivors who are not being followed by a clinician familiar with their risks and a general lack of risk-based care. To assist the clinician, regardless of setting, who cares for survivors, the following two sections describe briefly the general care of symptomatic and asymptomatic survivors.

29.2.2 Asymptomatic Survivors

As noted above, depending upon risks, survivors may benefit from early intervention or prevention. To assist the clinician in caring for the asymptomatic survivor, several groups have developed health screening recommendations to facilitate risk-based care of AYA survivors and are currently working collaboratively in an international forum to harmonize recommendations [21]. These guidelines are a hybrid, based on evidence and consensus. There is abundant evidence linking cancer treatment exposures to late effects [2]; however, because of the relatively small size of the heterogeneous survivor population, there are no studies (nor will there be in the near future) that show a reduction in morbidity or mortality with screening. As with other high-risk populations that are relatively small, limiting the types of studies evaluating the risks and benefits of screening and surveillance, there are two options in assessing the evidence. The first option is to state that, based on these limitations, there are no high-quality studies, thus limiting the strength of recommendation. However, to do so belies the wealth of high-quality studies from standard-risk populations that are applicable. Evidence gathered from studies in standard-risk populations can be extrapolated and used in the scientific basis of guideline development for high-risk populations. As principles from standard-risk populations are applied to high-risk groups, the two primary differences are timing of initiation and frequency of screening. By virtue of a lack of

studies capable of answering these two questions, decisions must be founded on the biology in question within the grounded framework of risk and benefits.

29.2.3 Symptomatic Survivors

Although many survivors will remain asymptomatic, some will experience symptoms that may or may not be related to their risks and their previous cancer therapies. Clinicians who are not familiar with the population and are faced with uncertainty will often diverge to the extremes in evaluating a new problem. When young adult survivors present with symptoms not typical of their age group, their symptoms may be dismissed as anxiety or similar conditions, or conversely they may be over tested. Following are three recurrent themes that we have heard through our experience. A survivor who was treated with mantle or chest radiation faces an increased risk of premature coronary artery disease [10, 22]. When a survivor of Hodgkin lymphoma presents as a young adult with chest pain, clinicians who are not cognizant of this risk often attribute the pain to anxiety or gastroesophageal reflux disease. Likewise, clinicians may not be aware of the substantial risk of breast cancer during young adulthood experienced by women treated with chest radiation for an AYA cancer to advise early initiation of breast cancer surveillance [23, 24]. Another example is the obstetrician who is not familiar with the risks of late-onset cardiomyopathy following exposure to anthracyclines [3]. In young women with compromised subclinical ventricular systolic function, the increased intravascular volume associated with pregnancy and the increase cardiac workload during labor and delivery may trigger overt congestive heart failure secondary to an underlying, unrecognized cardiomyopathy [25].

Two methods can help to remedy this situation: educating survivors regarding the potential late effects of therapy and communicating with other healthcare professionals about the risks and needs of this population. First, it is critically important that the cancer center team educate the survivor and his or her family regarding potential late effects and their presenting symptoms as this information provides an important foundation to promote advocacy for survivorship care and resources. To be effective, education about late effects should be provided over time, beginning during or soon after completion of therapy. A summary of the cancer and cancer therapy should be provided to all cancer survivors. As needed, this summary should be updated and supplemented by exposure-specific educational materials. An excellent source of such survivor-targeted materials can be found in the Health Links that are provided with the *Children's Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers* (*COG Guidelines*) available at www.survivorshipguidelines.org [26].

Communicating with other healthcare professionals is a time-intensive, but critically important endeavor. Regardless of whether a survivor is followed in a LTFU program, he or she will inevitably interface with other healthcare professionals away from the cancer center. Cancer centers should provide contact information and easy accessibility for questions from survivors or their other healthcare providers. Online portals providing secure, interactive, remote access to a patient's electronic health records are associated with high levels of engagement in chronic disease [27] and in a recent Dutch study were shown to be of interest among cancer survivors and health professionals as a means for obtaining health information and managing care [28]. Assisting other healthcare professionals in the interpretation of a survivor's presenting symptoms or problems can be life altering.

29.3 Transition of Care

AYA cancer patients are a population with poorer survival outcomes that are hypothesized to be related to impaired access to appropriate care, advanced disease at diagnosis, differences in cancer and host biology, insurance barriers, and lack of clinical trial participation [1]. Characteristic age-related issues in the AYA population include

fertility and psychosocial concerns, long-term side effects from cancer treatment, risk of chronic disease and future neoplasms, and insurance/financial barriers [29, 30]. With almost 70,000 AYA cancer patients (15–39 years old) diagnosed each year, the numbers of long-term AYA cancer survivors in need of cancer-focused follow-up care in the primary and tertiary care settings will increase significantly in the coming years [31].

In addition to the abovementioned issues, there is also a general lack of overall care coordination, transition from pediatric to adult care, or on-therapy to off-therapy care for this at-risk population of cancer patients. These care disparities require improvements in AYA patient and survivor programming, transition services, and care coordination strategies. Care coordination and transition of care are challenging for all cancer patients, but even more so for AYA patients who face many years at risk for late effects of therapy [32, 33]. Outcome data on AYA cancer patients are still evolving, but what is known is that "risk-based" medical care is essential for all cancer survivors. This level of medical care—which includes both the patients' and physicians' (e.g., PCP, oncologist) understanding of the cancer, the types of treatment that took place, and potential or actual late effects—can be a particular challenge for some AYA survivors due to their own lack of knowledge regarding treatment exposures and late effects, as well as limitations of access to care including insurance coverage [1, 34–36]. The Institute of Medicine (IOM) has recommended risk-based care, which has become a benchmark for quality survivorship care [37]. However, at the same time, risk-based care is complex and may be challenging to implement especially in resource-restricted healthcare settings [15, 16].

AYA cancer patients and survivors have physical and emotional health issues of which medical practitioners need to be aware [38]. PCPs and advanced practice providers (advanced practice nurses and physician assistants) currently play an important role in cancer-survivor care. Their comfort and expertise with this growing population of patients will be even more important during the next decade due to aging population of survivors and the decreasing number of medical oncologists resulting from an aging workforce [39]. The AYA cancer-survivor population is a small proportion (approximately 4 %) of the overall number of cancer survivors in the United States [31]. Transitioning from oncology-focused care to long-term follow-up care delivered by healthcare professionals often outside a cancer center requires education of providers. Recognizing that provider education is essential, the American Society of Clinical Oncology (ASCO) and AYA partner organizations have developed "Focus Under Forty" educational programs for oncology professionals, fellows, nurses and nurse practitioners, physician assistants, and PCPs. These programs were designed to increase awareness and enhance the understanding of care issues and challenges associated with the AYA patient population. The programs are free of charge, offer continuing medical education credits, and are available online at http://university.asco.org/focus-under-forty [40]. Promotion and distribution of educational and clinical resources like "Focus Under Forty" and published guidelines pertinent to the AYA population are vital in efforts to bridge the follow-up and knowledge gaps in AYA cancer-survivor care [23, 38, 41–45].

Establishing transition practices is one challenge within AYA cancer, but patient attendance in follow-up care is also of great concern. This concern stems from several studies of long-term childhood cancer survivors that have examined this transition process and report low participation rates for AYA-aged survivors in survivor-focused care. Among 9,434 adult participants in the Childhood Cancer Survivor Study (CCSS), mean age at interview 26.8 years (range 18–48 years), only 19.2 % reported having a follow-up evaluation at a cancer center in the preceding 2 years [46]. This is especially concerning because most survivorship programs are housed within a cancer center. In a follow-up CCSS investigation specifically evaluating receipt of risk-based care by adult survivors of childhood cancer (mean age 31.4 years), only 31.5 % of survivors endorsed receiving care that focused on their prior cancer and even fewer (17.8 %)

reported survivor-focused care that included advice about risk reduction or discussion or ordering of screening tests [36]. The treating oncologists' desire to continue to see long-term survivors may also adversely impact their access long-term follow-up programs and successful transition of care [1]. This may result from the strong relationship forged during treatment as well as lack of confidence in the ability of the new provider to provide ongoing care.

29.4 Models of Survivor Healthcare Delivery

In general, there are three basic models of healthcare transition available to the AYA cancer patient that will be reviewed in this section: continued care at the original cancer center, care that is transitioned from the cancer treatment center to a PCP, and a hybrid model in which care is transitioned to a PCP in the community but with ongoing support from the cancer center [47]. AYAs are treated in a wide variety of academic medical centers and community-based clinics. They are a highly mobile population, which poses significant challenges for maintaining coordination and continuity of care. Establishing long-term follow-up care for AYA survivors is important regardless of where they received their initial cancer treatment. AYA survivors have potential for decades more life to live. However, over time a significant number of long-term AYA cancer survivors will suffer from chronic, debilitating medical conditions as a result of their cancer and treatment [3–7, 9, 12, 48, 49]. Our current understanding of these adverse outcomes come from reports published by cohort studies tracking the health of AYA cancer patients followed into the fourth and fifth decades of life [50–53]. At present, national standards provide important recommendations and suggest resources for both general and AYA-specific cancer survivorship care. In the United States, the American College of Surgeons Commission on Cancer now requires accredited programs to implement treatment summaries and survivorship care plans for a portion of the patients and eventually all cancer patients [54]. These standards aim to improve communication, quality, and coordination of care for survivors.

As cancer centers across the country attempt to meet these new standards, the ASCO has diligently developed online resources to help guide program development via the ASCO Cancer Survivorship Compendium (available at http://www.asco.org//practice-research/asco-8907ecancer-survivorship-compendium) [55]. These online resources include a list of eight long-term follow-up care models and acknowledge that many factors such as the patient population and available resources will dictate which model is most appropriate at any particular institution. Models differ most notably in terms of location and who is providing the survivorship care and are categorized as (1) oncology specialist care, (2) multidisciplinary survivorship clinic, (3) disease-/treatment-specific survivor clinic, (4) general survivorship clinic, (5) consultative survivorship clinic, (6) integrated survivorship clinic, (7) community generalist model, and (8) shared care of survivor [55]. The ASCO Cancer Survivorship Compendium lists characteristics and limitations of each model which is provided for optimizing the success of the model chosen [55].

The model best suited for an individual AYA survivor will depend on variables such as the availability of resources and risk stratification (e.g., actual and potential late effects from therapy; risk for cancer recurrence or second malignant neoplasms) [15, 56]. In general, a few proposed models of care include a cancer center follow-up by the primary treatment team in a specialized long-term follow-up clinic or a primary care follow-up by the patient's PCP, or most commonly it may be a combination of both types of providers [32].

In the first model, cancer center follow-up, an oncology team, or a specialized survivorship clinic within an oncology setting takes the lead in survivorship care [32, 47]. This broad model encompasses several models from the ASCO Cancer Survivorship Compendium's list [55]. Examples range from follow-up visits with the primary oncologist to specialty survivor clinics

that are specific to disease (e.g., breast cancer) or specific to AYA survivors. A growing number of academic medical institutions are developing multidisciplinary, LTFU survivorship programs. Each program is unique in their care delivery mode and some of the leaders for these programs include nurses and pediatric oncologists who have experience building survivorship programs [56]. If available, this type of model would be a good option for those survivors with the highest risk for adverse long-term outcomes including those treated with combined modality therapy for Hodgkin lymphoma or central nervous system tumors or those treated with hematopoietic cell transplantation [32, 57].

A second survivorship model is follow-up care that occurs within the scope of primary care and is provided by the patient's PCP, e.g., nurse practitioner or family practice physician. A study regarding cancer survivorship practices for adult survivors of childhood cancer reporting from 179 Children's Oncology Group institutions showed that 21 % of participating institutions utilize a "Community Referral Model" in which survivors are transitioned at adulthood to their PCP for routine cancer-related care. Care is managed and coordinated by the PCP, with the survivorship team/oncology team serving as consultants to multiple PCPs [18]. In general, this model may be a better choice for survivors assessed to be at lower risk for late treatment effects [15, 32]. The disadvantages of this model include some providers' low comfort level with independently providing survivorship care and assuring that the appropriate and up-to-date knowledge about late effects and survivorship is maintained over time [58].

A third model, sometimes referred to as a hybrid model or "shared-care" model, involves the patient's need for regular engagement with a team of providers, both oncologist and PCP. The shared-care model refers to care of a patient that is shared by two or more clinicians of different specialties. The basis of this model of care is periodic and ongoing communication between the specialist (e.g., oncologist) and PCP. The shared-care model has demonstrated improved patient outcomes in patients with chronic illness such as diabetes, hypertension, and chronic renal disease [59–61]. When patients are on therapy or recently off therapy, they will have close contact with their team of oncology providers. However, when patients have completed therapy and the frequency of follow-up visits lapses, patients can become "lost in transition" and lose contact with their providers [37]. Therefore, a cancer survivorship model that includes care from both an oncologist and a PCP along the cancer trajectory can reduce the potential for patients becoming lost in transition. One potential disadvantage of this model is the extensive resources necessary to establish and maintain this model. Barriers of this model include the PCP's lack of knowledge of various cancer drugs' action, adverse effects, and long-term complications and the oncologist's preference and internal medicine expertise in managing the patient's comorbid conditions [56]. Overcoming these and other barriers with the shared-care model needs further investigation and attention from both primary and subspecialty providers. However, the feasibility of this model has been tested successfully in a pilot study of adult survivors of childhood cancers within the setting of a strong national health service [62]. A similar model promoting the PCP's awareness of cancer survivorship-related issues through practice and education is a new role termed "the oncogeneralist" [63]. In this model of care, the PCPs have acquired deeper knowledge and familiarity with cancer survivorship through educational seminars, workshops, conferences, online programs, or shadowing in environments caring for cancer survivors [63, 64].

Another concept related to the shared-care model mentioned above is that of risk-stratified survivorship care [15]. The risk stratification assesses the questions of each survivor individually with focus on which type of provider should follow them, where the care should take place, the frequency, and screening modalities of follow-up. These stratifications will differentiate a survivor with mild or no toxicity from treatment, with low risk of recurrence, and with minimal risk of late effects from therapy. This is in contrast to a survivor who has established organ dysfunction, is at high risk for recurrence, or is at high risk for

serious late effects from their cancer treatment [15]. Strategizing and planning for this type of risk-stratified survivorship care may be optimal in terms of patient outcomes, surveillance, and cost of care for patients and survivor programs alike. Figure 29.3 illustrates the Risk-Stratified Shared Care Model for Cancer Survivors.

Future studies are needed to assess the efficacy of various models of care specifically for AYA survivors. Ultimately, the goal of care for AYA cancer patients and survivors must be consistent with the specific needs of this population of patients. Salient survivorship issues to address include education and guidance with fertility, sexuality, contraception, self-management, interpersonal relationships, and psychosocial/emotional risk factors in addition to late effects screening and health maintenance. In addition,

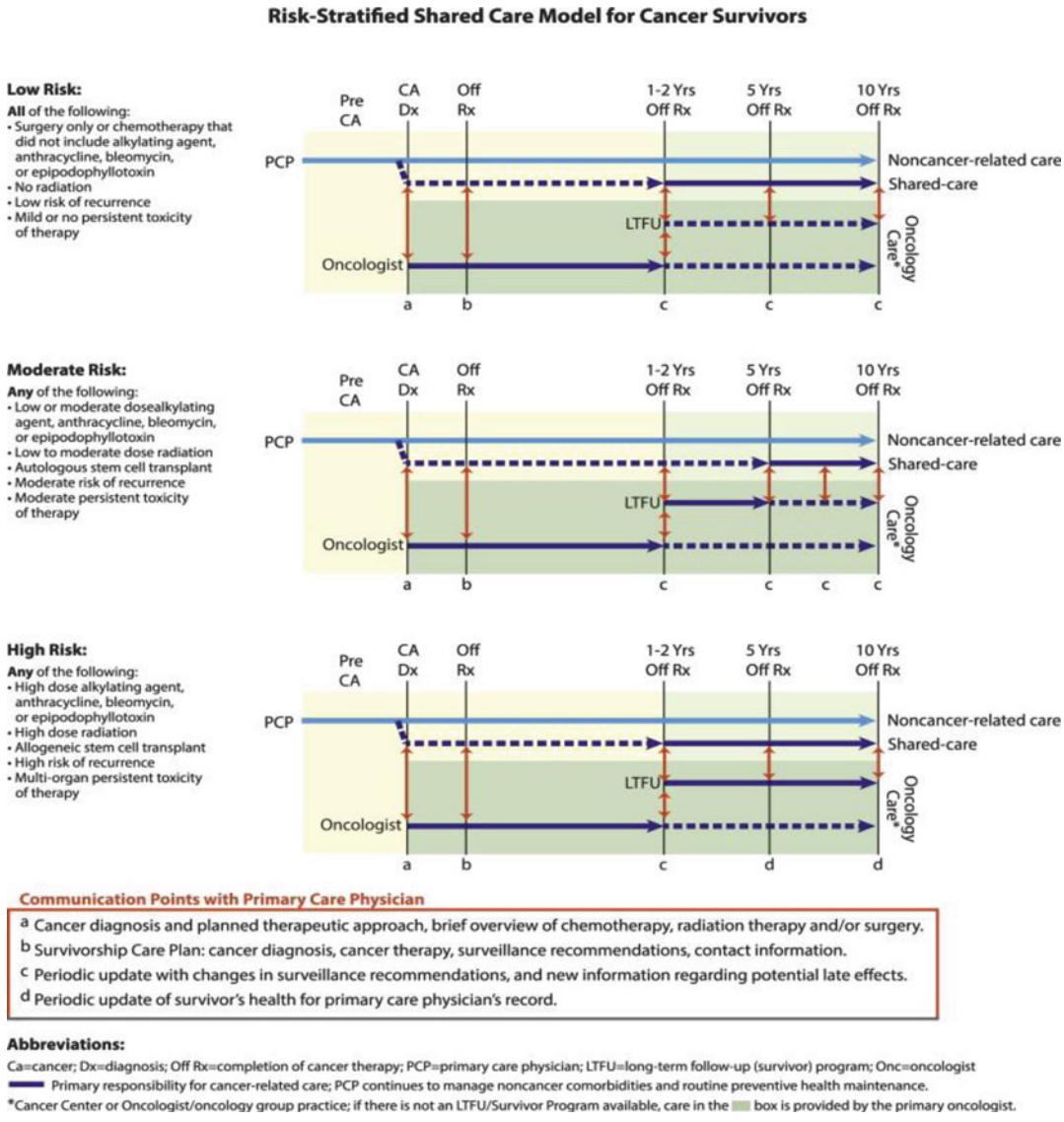

Fig. 29.3 A risk-stratified shared-care model for cancer survivors assigns follow-up services based on intensity of therapy and risk of long-term and late effects. In the shared-care model, the roles and responsibilities of the oncology and primary care provider are defined to enhance coordination and reduce duplication of care (Reprinted with permission from McCabe [15])

AYA care must provide guidance from providers on how to maintain effective access to insurance and healthcare services for the remainder of their lives [1, 17].

29.5 Promoting Healthy Lifestyles

29.5.1 Health Behavior Counseling of the AYA Cancer Survivor

Cancer and its treatment render AYA cancer survivors at greater risk for morbidity from health-risk behaviors than their peers without cancer [3, 11]. Chronic or subclinical changes persisting after treatment recovery may result in premature onset of common diseases associated with aging such as obesity, diabetes mellitus, cardiovascular disease, hypertension, and second cancers [10]. In young people who are already at risk for many of these conditions, the addition of health-risking behaviors, such as smoking, poor nutrition, and inactivity, may increase this risk further [65–67]. Consequently, health professionals caring for AYA cancer survivors have the responsibility and challenge of motivating the practice of healthy lifestyles in this vulnerable group. Education about cancer-related health risks and risk-modifying measures for the adolescent and young adult cancer survivor can be readily integrated into routine follow-up evaluations. Health education in the oncology setting has several advantages. AYA cancer survivors have a close, long-term relationship with their oncology staff and generally respect them as credible medical experts. This relationship provides a strong foundation on which to introduce discussions about cancer-related health risks and risk-modifying behaviors. Survivors' enhanced perceptions of vulnerability during the check-up may also create a "teachable moment" that facilitates reception of health promotion messages [68]. In particular, evaluations after completion of therapy in long-term survivors that focus on health surveillance, rather than disease eradication, provide an atmosphere favorable for health promotion discussions.

The optimal components of health promotion counseling of survivors described in detail by Tyc et al. are summarized in Table 29.1 [68]. To be truly informed about potential health risks, survivors need accurate information about their cancer diagnosis, treatment modalities, and cancer-related health risks. This is critical information that many survivors lack [35]. Health counseling should be personalized to consider the unique educational needs related to the individual survivor's cancer experience. The content of traditional health programs can be modified to include information that enhances the survivor's perception of increased vulnerability. Health behavior discussions should avoid characterizing the survivor as being different from healthy peers. An approach that starts first with a discussion of the adverse effects of health-risking behaviors followed by an explanation of the additional risks predisposed by cancer should reduce the survivor's anxiety and permit identification with peers. The knowledge that certain behaviors are riskier for them than for others may provide some teens with a welcome excuse to resist peer pressure.

Table 29.1 Components of health promotion interventions with adolescent and young adult cancer patients

Inform of potential health risks
Address increased vulnerability to health risks relative to healthy peers
Provide personalized risk information relative to treatment history
Establish priority health goals
Discuss benefits of health protective behaviors
Discuss barriers to/personal costs of engaging in self-protective behaviors
Provide follow-up counseling

Reprinted with permission from Tyc et al. [68]

Healthcare professionals should also be prepared to address the increased vulnerability of individual patients to specific cancer-related health risks that may be related to sociodemographic factors, cancer treatment modalities, familial or genetic predisposition, and maladaptive health behaviors. Following this discussion, survivors should also be reminded that cancer treatment may accelerate the presentation of common health conditions associated with aging, including organ dysfunction and malignancy. Incorporating personal risk information may

increase the significance of the discussion, heighten the survivor's perception of vulnerability, and enhance their reception to health counseling.

In health promotion counseling, clinicians should encourage survivors to establish priority health goals. Behavioral goal setting should include an extensive discussion of the personal benefits of practicing healthy behaviors. Fear of future illness does not provide strong motivation to change for many AYA; therefore, the clinician must think broadly when discussing the personal benefits with AYA—including financial, cosmetic, and social reasons to choose healthier behaviors. For example, AYA may chose not to smoke because of the cost, the effect on yellowing of teeth and nails, the smell, and the conflict it creates with parents and, hopefully, with friends. Deterring an adolescent girl from excessive drinking might include a discussion of avoidance of situations where she can't defend herself from unwanted sexual advances. Potential barriers to and personal costs associated with behavioral change should be explored in detail to identify potential solutions. In these discussions, role playing regarding alternative health actions and problem-solving may be beneficial. Importantly, providers should inquire about the progress of health goals and provide follow-up counseling at subsequent evaluations.

29.5.2 Lifestyle Recommendations for the AYA Cancer Survivor

Cardiovascular disease, obesity, and osteoporosis are among the common health problems seen in childhood cancer survivors [3, 6, 10, 69, 70]. Within the general population, these problems can be positively impacted or prevented by adopting certain health behaviors such as regular physical activity or a low dietary fat intake [71]. Evidence is emerging to suggest that the same may be true for certain cancer treatment-related health problems [12, 67, 72–75]. Six health behaviors are discussed in the context of childhood cancer survivorship—diet, physical activity, tobacco use, alcohol consumption, sun protection, and dental care. Counseling childhood cancer survivors on diet and physical activity may be complicated by the current lack of specific guidelines for this population. However, available data can provide important insights to support health behavior counseling which is a fundamental component of healthcare. The aforementioned Health Links (www.survivorshipguidelines.org) also provide additional information to guide counseling.

29.5.2.1 Diet and Physical Activity

Diet and physical activity have assumed a greater target of health counseling because of the excess prevalence of overweight and obesity observed in survivor cohorts [6, 69, 70, 76]. Studies describing the dietary and physical activity habits of childhood and AYA cancer survivors primarily describe outcomes among small single institutional cohorts in the United States, Canada, and Australia with data now emerging from larger prospectively followed cohorts like the CCSS and St. Jude Lifetime Cohort [67, 77–83]. Because there are no diet and physical activity recommendations outlined for AYA cancer survivors, studies use benchmarks set for the general population, most often the USDA recommendations (http://www.cnpp.usda.gov/sites/default/files/dietary_guidelines_for_americans/PolicyDoc.pdf).

Early investigations of dietary practices in childhood cancer evaluated the relationship of caloric intake with energy expenditure [84–86], nutrient intake with bone mineral density [87–89], or cholesterol intake with cardiovascular disease risk factors among small cohorts [90]. Results demonstrated concerning trends, with energy intake exceeding energy expenditure, suboptimal dietary calcium correlating with osteopenia, and dietary fat intake in levels that will not reduce cholesterol. More contemporary studies describing dietary patterns in childhood cancer survivors are limited in number; however, results are thus far strikingly consistent and suggest that unhealthy dietary intake trends persist with the majority of survivors consuming diets high in fat, red meat, and salt with fewer than five servings of fruits and vegetables daily [67, 77, 82]. Stolley compared the dietary patterns of a multiethnic group of 452

adult childhood cancer survivors to an ethnically matched sample of the general population finding no significant differences between the African American or white survivors and controls [91]. However, Hispanic survivors consumed higher fat diets than Hispanic controls. The majority of all survivors and controls reported diets that failed to meet the USDA recommendations. Similar results were noted in a study of 91 adult childhood cancer survivors compared to 30 siblings where both groups were noted to report low consumption of green leafy vegetables, whole fruits, and whole grains [79]. Several studies have observed that calcium and whole grain consumption are also both below recommendation among survivor cohorts [77, 82, 91].

Limited empirical data have explored physical activity in childhood cancer survivors despite the fact that low levels of physical activity among survivors have been associated with development of metabolic syndrome, decreased bone density, and obesity [67, 72, 74, 75]. Available data suggest that both aerobic training and resistance training are safe in childhood cancer survivors and cardiovascular outcomes improved in most studies [60, 78, 92]. Tailoring exercise prescriptions for some survivors may be required because of cancer-related effects such as amputation, avascular necrosis, pulmonary disease, or neurological problems [93]. Additional consideration on safety and screening for physical activity in childhood cancer survivors is provided by Kelly [93].

Most descriptive studies in childhood and AYA cancer survivors rely on the Centers for Disease Control and Prevention's recommendation of 150 min of moderate physical activity per week as a benchmark [94, 95]. Overall, results demonstrate that childhood cancer survivors are less likely to be physically active or to meet guidelines for physical activity [77, 96]. Two studies suggest that low physical activity is similar across survivors from different racial/ethnic groups [51, 91]. International studies are limited, but data show similarly low levels of physical activity in childhood cancer survivors recruited in Australia and Canada [78, 81]. Survivors with cancer-related pain, anxiety, fatigue, or limited stamina report lower levels of physical activity [97].

Several studies highlight the benefits of regular physical activity [65, 67]. In a subset of 1,187 Hodgkin lymphoma (HL) survivors participating in the CCSS, self-reported participation in vigorous exercise was associated with a dose-dependent decrease in risk of experiencing a cardiovascular event after controlling for cardiovascular risk and cancer treatment [65]. Among 1,598 survivors (median age of 32.7 years) participating in the St. Jude Lifetime Cohort Study, only 25 % of male and 28 % of female survivors adhered to ≥4 of 7 health protective lifestyle habits recommended by the World Cancer Research Fund/American Institute for Cancer Research (BMI, physical activity, servings of fruit/vegetable, complex carbohydrates, alcohol, red meat, sodium) [67]. However, after adjusting for race, age, smoking status, education, and cranial radiation, more adherent survivors experienced a significantly lower risk of metabolic syndrome than those adhering to fewer habits with relative risks of 2.2 (95 % CI, 1.6–3.0) for males and 2.4 (95 % CI, 1.6–3.0) for females [67].

Collectively, these findings suggest that childhood cancer survivors would benefit from dietary interventions that match caloric intake with physical activity, optimize calcium and other nutrients needed for bone accretion, and reduce dietary fat. Adherence to a healthful diet and regular physical activity has been shown to reduce the risk of cancer, cardiovascular disease, and other chronic illnesses [98, 99]. The American Cancer Society outlined nutrition and physical activity guidelines that aim to reduce cancer and cardiovascular disease risk [100]; similar recommendations have been endorsed by the American Heart Association and the Department of Health and Human Services [101, 102]. Briefly summarized in Table 29.2, these guidelines promote balancing fat, protein, and carbohydrate intake to assure nutrient adequacy and maintain health. The benefits of healthful dietary practices should be emphasized during counseling sessions with survivors: higher consumption of vegetables and fruits may be associated with a lower incidence of lung, colorectal, and other gastrointestinal cancers. Eating foods rich in monounsaturated and omega-3 fatty acids (e.g., fish, walnuts) is

Table 29.2 American Cancer Society (ACS) individual guidelines on nutrition and physical activity for cancer prevention

Achieve and maintain a healthy weight throughout life.
Be as lean as possible throughout life without being underweight.
Avoid excess weight gain at all ages. For those who are overweight or obese, losing even a small amount of weight has health benefits and is a good place to start.
Get regular physical activity and limit intake of high-calorie foods and drinks as keys to help maintain a healthy weight.
Be physically active.
Adults: get at least 150 min of moderate-intensity or 75 min of vigorous-intensity activity each week (or a combination of these), preferably spread throughout the week.
Children and teens: get at least 1 h of moderate- or vigorous-intensity activity each day, with vigorous activity on at least 3 days each week.
Limit sedentary behavior such as sitting, lying down, watching TV, and other forms of screen-based entertainment.
Doing some physical activity above usual activities, no matter what one's level of activity, can have many health benefits.
Eat a healthy diet, with an emphasis on plant foods.
Choose foods and drinks in amounts that help you get to and maintain a healthy weight.
Limit how much processed meat and red meat you eat.
Eat at least 2½ cups of vegetables and fruits each day.
Choose whole grains instead of refined grain products.
If you drink alcohol, limit your intake.
Drink no more than 1 drink per day for women or 2 per day for men.

Adapted from Kushi et al. [100]

associated with a lower risk for cardiovascular diseases. Ingestion of healthful carbohydrates like whole grains provides many vitamins and minerals, such as folate, vitamin E, and selenium, which have been associated with a lower risk of colon cancer [103]. Similarly, misperceptions regarding micro- and macronutrients should be corrected: ingestion of specific nutrients in pharmacologic doses does not provide the same benefit of eating a variety of fruits and vegetables, which provide fiber, vitamins, minerals, and phytochemicals that work synergistically to reduce cancer risk. The consequences of health-risking dietary practices should be explored in the context of the risks conferred by survivor's cancer treatment and family history: consumption of a high-fat diet may increase the risk of coronary artery disease in a survivor predisposed to cardiac dysfunction following anthracycline chemotherapy or chest radiation.

The American Cancer Society guidelines also provide recommendations regarding regular physical activity, which has been associated with reduced risks of breast, colon, and other cancers, as well as cardiovascular health risks [104–106]. Moderate-to-vigorous physical activity produces beneficial effects on metabolism of stored body fat and physiological functions affecting insulin, estrogen, androgen, prostaglandins, and immune function [98, 107]. The ACS recommends that adults should get at least 150 min per week of moderate-intensity activity or 75 min per week of vigorous-intensity activity or an equal combination, in addition to normal activities of daily living. Individuals who are sedentary or just beginning an exercise program are advised to slowly increase the amount and intensity of activity over time [100]. Importantly, due to the growing evidence linking the amount of time spent sitting with the risks of obesity, type 2 diabetes, heart disease, and some types of cancer, the ACS recommends limiting sedentary time.

Despite the documented benefits of regular physical activity, AYA survivors who previously received cardiotoxic cancer therapy but are interested in sports sometimes report hearing a "mixed message" about staying active yet nonspecifically limiting strenuous exercise. Complementing the aforementioned COG LTFU guidelines, institutional recommendations have been published to assist clinicians with providing specific, treatment-dependent patient information for optimizing

exercise after anthracycline chemotherapy and/or cardiac irradiation [108]. Similarly, athletically minded AYA survivors with a single kidney have been counseled historically against participation in active sports involving potential physical contact, though abundant trauma registry data describing kidney injuries do not support this practice. With this in mind, the COG LTFU guidelines were recently revised to endorse no categorical restriction on sports participation for mononephric childhood cancer survivors [109].

29.5.3 Tobacco Use

In contrast to earlier studies describing tobacco use in childhood cancer survivors [110, 111], contemporary investigations indicate positive trends in reduction of smoking initiation and an increase in cessation in childhood cancer survivors, suggesting an increased awareness about tobacco-related health risks associated with public health education efforts [112–115]. Children's Cancer Group investigators compared the smoking habits of 592 survivors of acute lymphoblastic leukemia diagnosed between 1970 and 1987 to those of 409 sibling controls [115]. Compared to sibling controls, survivors were significantly less likely to have ever smoked (23 % vs. 36 %) and less likely to be current smokers (14 % vs. 20 %). Emmons et al. reported similar results in a CCSS investigation examining the smoking behaviors of over 9,000 adult study participants surviving a childhood cancer diagnosed between 1970 and 1986 [112]. Rates of ever smoking (28 %) and currently smoking (17 %) reported by survivors were significantly lower than population prevalence rates for both male and female survivors. Other positive findings included evidence that male and female survivors who smoked were also significantly more likely to quit. Likewise, in a population-based study evaluating smoking practices of 10,326 participants in the British CCSS, 20.0 % reported to be current regular smokers and 29.8 % ever regular smokers, compared to 28.1 % and 48.8 %, respectively, in the general population [116]. Endorsing a current regular smoking status was more prevalent among survivors of Wilms tumor or Hodgkin lymphoma than survivors of a central nervous system (CNS) neoplasm and among those older (aged 10–14 years) versus younger (aged 0–4 years) at diagnosis. Overall rates of smoking initiation were lower in women and in those treated with chemotherapy or radiotherapy. Finally, in a CCSS investigation comparing smoking rates among 307 adolescent cancer survivors and 97 healthy sibling controls, self-reported smoking rates did not differ significantly between adolescent survivor and sibling groups (ever smokers, 28 % vs. 33 %; recent smokers, 10 % vs. 9 %, respectively) [117]. Adolescents endorsing recent smoking were more likely to have other smokers in household (RR = 2.24, CI ¼ 1.21–4.16), past history of suicidality (RR = 1.89, CI ¼ 1.00–3.56), and no previous treatment with cranial irradiation (RR = 2.40, CI ¼ 1.12–5.17).

These trends provide support for the potential benefits of health education that should continue as long as investigations indicate that childhood cancer survivors continue to compromise their health by smoking or using any form of tobacco. Cigarette smoking has been linked to an increased risk of cardiopulmonary disease including hypertension, emphysema, and stroke. In addition, tobacco use is the most important preventable cause of cancer in adulthood and has been linked to 90 % of cases of lung cancer and one-third of all other cancers including cancers of the mouth, larynx, pharynx, liver, colon, rectum, kidneys, urinary tract, prostate, and cervix. Investigations of adult cancer patients demonstrate additive risks of lung cancer when tobacco carcinogens are combined with thoracic radiation and specific chemotherapeutic agents [118–120]. Although the additional risks conferred by tobacco use to the development of cancer and cardiovascular disease in survivors of cancers presenting during adolescence and young adulthood have not been well studied, an excess risk is anticipated in survivors treated with the antineoplastic modalities with established risks for carcinogenesis and cardiopulmonary dysfunction. Therefore, survivors at risk should be reminded of their increased vulnerability to tobacco-related health problems. Likewise, counseling regarding secondhand smoke seems prudent, despite

the lack of demonstrating excess risk of adverse tobacco-related health outcomes in cancer survivors exposed to environmental tobacco smoke.

29.5.4 Alcohol

Investigations evaluating the practice of health-risking behaviors in adolescent and young adult cancer survivors largely indicate rates of alcohol consumption lower or comparable to those of their peers without cancer [121–124]. Only one European population-based study reported a higher prevalence of frequent alcohol consumption and binge drinking among adults childhood cancer survivors compared to age- and sex-matched population controls [125]. In this cohort, sociodemographic factors, e.g., male gender, associated with alcohol consumption patterns were similar among survivors and controls. These data are concerning considering that some cancer treatments and complications predispose the long-term survivor to an increased risk of hepatic dysfunction. Most contemporary hepatotoxic antineoplastic therapies are associated with acute toxicity, from which the majority of patients recover without apparent long-term sequelae [126]. Conditions reported to exacerbate hepatic dysfunction include chronic hepatitis, particularly chronic hepatitis C (HCV), and hepatic graft-versus-host-disease (GVHD). HCV is the most common etiology of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in the United States. The prevalence of chronic HCV ranges from 6.6 % to 49 % of childhood cancer survivors who were transfused before contemporary screening of blood donors [127–133]. Contrary to earlier reports demonstrating a mild clinical course in childhood cancer survivors with chronic HCV, we now recognize that a significant number of these patients are at risk for adverse outcomes including impaired quality of life, cirrhosis, hepatic failure, and hepatocellular carcinoma [127, 128, 130]. Although the transmission of HCV has declined since the development of blood donor screening tests for the virus, there are many patients surviving with chronic transfusion-acquired infection and many childhood cancer survivors untested and likely unaware of their risk of chronic infection and its implications for future liver health. Because of the high incidence of chronic infection in the majority of individuals exposed to HCV, the potential adverse outcomes associated with chronic infection including liver failure, and the availability of antiviral therapy that significantly reduce this risk, the Centers for Disease Control and Prevention recommend that all individuals at risk transfused before implementation of blood donor testing for HCV (July 1992) should be screened for the disease [134]. Survivors with chronic HCV infection confirmed by a polymerase chain reaction test for viral RNA should be counseled regarding transmission and treatment options. It is important to emphasize that chronic hepatic injury associated with chronic GVHD, chronic infection, nodular regenerative hyperplasia from cytoreductive therapy, or drug-related liver injury may accelerate the course of liver disease in survivors treated with hematopoietic stem-cell transplantation [135].

Liver injury related to treatment for childhood cancer is most often subclinical and may develop without a history of prior acute toxicity; thus it is important for clinicians to obtain a baseline screening of serum transaminases (alanine aminotransferase and aspartate aminotransferase) in asymptomatic survivors. In survivors with cancer-related hepatic dysfunction, preservation of residual hepatocyte function is critical since therapy is not available to reverse hepatic fibrosis. A more recently described and treatable form of hepatic dysfunction found in childhood cancer survivors is transfusion-acquired iron overload (hepatic siderosis) [136, 137]. In a recent cohort study of childhood cancer survivors ages 1.8–20.2 years at diagnosis, 36/73 (49.3 %) demonstrated elevated liver iron concentration, which was significantly associated with older age at treatment [137]. In addition to referral for antiviral therapy in cases with chronic HCV, standard recommendations to maintain liver health include abstinence from alcohol use and immunization against hepatitis A and B in patients who have not established immunity to these hepatotrophic viruses. Weight reduction in overweight/obese

survivors is also prudent to reduce the risk of hepatic injury from fatty liver hepatitis (steatohepatitis) [138, 139].

In addition to its direct hepatotoxic effects, consumption of alcoholic beverages, particularly in combination with tobacco products, increases the risk of cancers involving the oral cavity, larynx, esophagus, and possibly colon [140]. Cancer risk increases in direct proportion to alcohol intake and rises with regular consumption of as few as two drinks per day, with a drink defined as 12 fluid ounces (approx. 355 ml) of beer, 5 fluid ounces of wine (approx. 148 ml), and 1.5 fluid ounces (approx. 44 ml) of 80-proof distilled spirits [140]. Alcohol consumption has also been associated with a linear increase in breast cancer incidence in women over the range of consumption reported by most women [140]. To avoid alcohol-related carcinogenesis, people who drink alcohol should limit intake to no more than two drinks per day for men and one drink per day for women. Because population studies indicate that modest [141] alcohol intake of one to two drinks per day is associated with a lower risk for cardiovascular disease, the potential hepatotoxic and carcinogenic risks conferred by regular alcohol consumption must be weighed against its potential cardiovascular benefits.

29.5.5 Sun Protection

The use of sun protection measures is another understudied area of adolescent and young adult cancer-survivor health behavior. Recreational and lifestyle preferences have resulted in a steady increase in the incidence of skin cancers [142]. Melanoma and non-melanoma skin cancers (basal cell and squamous cell carcinoma) have also been reported with increased frequency in survivors of childhood malignancy treated with radiation therapy [7, 143–145]. Non-melanoma skin cancers are low-grade lesions that typically develop in skin included in radiation treatment fields, which may be in an unusual or non-sun-exposed part of the body. It is not known if sun protection will reduce the risk of radiation-associated non-melanoma skin cancer in childhood cancer survivors. However, public education regarding sun protection and self-examination has been associated with earlier diagnosis and treatment of melanoma in the general population [146, 147]. Therefore, it seems prudent to counsel survivors regarding methods of sun protection, the risk factors and symptoms of skin cancer, and the importance of periodic examination of the skin in and around the radiation field. Adherence to skin cancer prevention measures recommended for healthy populations are especially important for childhood and AYA cancer survivors [148]. These recommendations include: (1) Stay in the shade, especially during midday hours; (2) wear clothing that covers your arms and legs; (3) wear a hat with a wide brim to shade your face, head, ears, and neck; (4) wear sunglasses that wrap around and block both UVA and UVB rays; (5) use sunscreen with sun protection factor (SPF) 15 or higher and both UVA and UVB protection; and (6) avoid indoor tanning.

29.5.6 Dental Care

AYAs surviving cancer are at risk for oral health problems including salivary gland dysfunction, accelerated dental decay, chronic gingivitis, periodontal disease, and a variety of developmental abnormalities adversely affecting enamel and tooth development [149–153]. Consequently, routine dental care is important for early detection and institution of ameliorative interventions. To date, the only study reporting dental utilization practices in long-term childhood cancer survivors was organized through the CCSS [154]. Dental utilization practices in a CCSS cohort of over 9,000 adult survivors of pediatric malignancies were below recommended levels, even in patients at highest risk for dental abnormalities. Minority status, low educational attainment, annual household income below $20,000 (€18,500), and lack of health insurance were positive predictors for lack of dental follow-up, which are demographic factors associated with inadequate dental utilization in the general population [154]. Clinicians should emphasize that annual dental follow-up is important for all

survivors to maintain oral health. Survivors treated with head and neck radiation involving oral cavity structures may require more frequent dental monitoring and intervention to preserve dentition.

29.6 Summary

The achievement of long-term survival in the majority of adolescent and young adults diagnosed with cancer has appropriately focused efforts on maintenance of future health in this growing population. Following the cancer experience, a large proportion of these young men and women will experience some adverse effect on their health [3, 6, 12, 49]. Through risk-based care and education about the health risks conferred by the cancer experience, clinicians caring for long-term survivors play a critical role in the prevention, diagnosis, and rehabilitation of cancer-related complications and adjustment to chronic health conditions predisposed or exacerbated by cancer. Consequently, health professionals caring for adolescent and young adult cancer survivors may positively influence the future health of this vulnerable group by correcting knowledge deficits, addressing factors that enhance the survivor's vulnerability to health problems, and providing personalized health counseling that promotes the practice of health-promoting behaviors.

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Health-Related Quality of Life

30

Anne Klassen, Natasha Wickert, Elena Tsangaris, Robert Klaassen, and Samantha Anthony

Abstract

The adolescent and young adult (AYA) period is unique; individuals are faced with personal and developmental challenges, which are amplified by having a diagnosis of cancer. Understanding the unique challenges of AYA is critical and may be assessed through the use of clinically meaningful and psychometrically sound scales measuring the impact of cancer on health-related quality of life (HRQL). The purpose of this chapter is to identify patient-reported outcome (PRO) instruments used with AYA with cancer to develop a preliminary conceptual framework of the HRQL content deemed important for AYA. Findings from two previous systematic reviews and a search of Medline, PsycINFO, EMBASE, and CINAHL from January 2008 to December 2014 were conducted by our team to identify self-report cancer-specific PRO instruments for AYA. Twelve instruments developed for cancer patients and survivors were identified. A content analysis of 418 items from these instruments led to the identification of six major domains as follows: psychological, social, physical, general, sexual, and spiritual. Important differences in content were noted between PRO instruments designed for pediatric patients versus young adults. Specifically, pediatric tools lacked items to measure spirituality,

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goal setting/future plans, and sexual and reproductive health, while instruments designed specifically for AYA tended to measure the breadth of concerns of AYA. Using the most appropriate PRO instrument in clinical research and/or practice is crucial. Therefore, in selecting a PRO instrument to measure the HRQL of AYA, it is important to carefully consider how an instrument was developed and whether its content will appropriately answer the research question or clinical evaluative purpose.

30.1 Introduction

The cancer experience of adolescents and young adults (AYA) is unique [1]. The AYA period is a distinct developmental stage that is characterized by social, emotional, physical, and neuropsychological development [2]. During this time, AYA are faced with the challenges of gaining autonomy from parents, building personal values and identity, developing strong peer relationships (including intimate and sexual relationships), pursuing further education at college or university, and joining the workforce to become financially independent [3]. Cancer-specific issues, such as premature confrontation with mortality, changes in physical appearance, increased dependence on parents, disruptions in social life, education or employment due to treatment, loss of reproductive capacity, and health-related concerns about the future, may be particularly distressing for AYA [4]. Such concerns can have an important impact on the health-related quality of life (HRQL) of patients during active treatment and during survivorship [4]. As evidence-based medicine is rapidly setting a standard for clinical decision-making in the care of AYA cancer patients, the availability of clinically meaningful and psychometrically sound tools to measure the impact of cancer on HRQL is essential.

30.1.1 Definitions of HRQL

The World Health Organization's (WHO) definition of health "a state of complete physical, mental, and social well-being…" [5] has been the cornerstone for the definition of HRQL for many years. Beyond this definition, which categorizes health into three broad aspects (physical, social, and psychological), there is a lack of consensus on what constitutes HRQL, and more than 100 definitions have been proposed, with a variety of terms (e.g., quality of life (QOL), functional status, health status) sometimes used interchangeably [5–7]. A helpful definition of HRQL by the USA Food and Drug Administration (FDA) is as follows: "HRQL is a multi-domain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life" [8].

Fayed and colleagues performed content analyses of the most common patient-reported outcome (PRO) instruments measuring health outcomes of children and adolescents (generic [9] and cancer-specific [10]). They found that the content of instruments that purport to measure HRQL, or the broader notion of QOL, is weighted toward measuring performance, capacity, frequency, severity, and presence or absence of life and/or health domains, rather than targeting enjoyment, satisfaction, expectations, standards, or concerns about life and/or health domains [9, 10]. Given the lack of conceptual consistency among instruments, these authors advise that, in choosing an instrument, the content of potentially relevant scales should be considered carefully relative to one's research or clinical evaluative purpose.

30.1.2 Increase in Publications About QOL in AYA

Studies of QOL in AYA with cancer have increased dramatically over the past two decades. Figure 30.1 shows the yearly number of

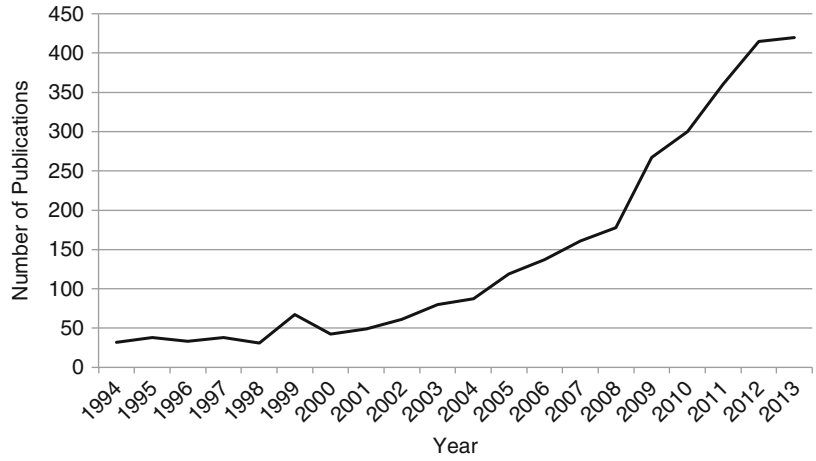

Fig. 30.1 Number of publications per year from January 1994 to December 2013

publications indexed in PUBMED from the following search: "Neoplasms" [MeSH] and "Quality of Life" [MeSH], with age limited to adolescents (13–18 years) and young adults (19–24 years). A total of 2,915 articles (of 22,670 without an age limitation) were retrieved through this search.

30.1.3 Patient-Reported Outcome Instruments

HRQL is typically measured using Clinical Outcome Assessment (COA) tools, i.e., instruments designed to measure concepts that include symptoms, overall mental state, or the effects of a disease or condition on how the patient functions and feels in their daily life [8]. The USA FDA has classified COA tools into four types: (1) clinician reported, (2) observer reported, (3) performance, and (4) patient reported [8]. PRO instruments are based on a report that comes from the patient about the status of his/her health condition without amendment or interpretation by a healthcare professional or anyone else [8]. The focus in this chapter is on PRO instruments developed for use with AYA cancer patients and survivors. We are particularly interested in self-report tools, as these are generally considered to be the preferred method for assessing a patient's experience of a construct [11].

30.1.4 Generic Versus Cancer-Specific PRO Instruments

PRO instruments that measure HRQL can be generic or condition/disease specific. Generic instruments are those designed for use across many types of diseases, treatments, and populations [12]. Such broad-based tools can lack content validity for particular patient populations, e.g., fail to measure issues that matter [12]. Content validity is the measurement property that assesses whether items are comprehensive and adequately reflect the patient's perspective for the concept of interest (COI) [13]. A range of generic instruments have been used with AYA cancer patients [14]. For example, in the younger cohort of AYA, our team conducted a systematic literature review valid through May 2011 and found that ten generic HRQL instruments had been used in 148 publications involving patients and survivors up to 25 years of age [14]. In the 148 publications, the most common measure used was the Pediatric Quality of Life Inventory (PedsQL) [15], which appeared in 58 publications [14]. The PedsQL is a 23-item PRO instrument that measures health problems within the following four domains: physical, emotional, social and school function [15]. The Health Utilities Index (HUI) [16, 17] (used in 26 publications) and the Child Health Questionnaire (CHQ) [18] (used in 25 publications) were the second and third most common generic HRQL instruments [14].

Another approach is the use of cancer-specific PRO instruments that were designed for use with various cancer subtypes. Since disease-specific PRO instruments address aspects specific to one disease (e.g., cancer), they may be more responsive to changes in health status [19]. The most common examples of such scales for cancer patients include the Functional Assessment of Cancer Therapy Scale (FACT-G) [20] and The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [21]. Both of these instruments, which were designed for adults (age range 27–89), also include a suite of scales for particular cancer subtypes. The FACT-G measures a range of domains, including physical, social, emotional, and functional well-being and relationship with doctor [20]. There are separate versions for certain cancer types prevalent among AYA (e.g., lymphoma, leukemia, and central nervous system (CNS) tumors) [20]. The EORTC QLQ-C30 measures a range of constructs, including function (physical, role, cognitive, emotional, and social), symptoms (fatigue, pain, and nausea/vomiting), global health, and QOL [21].

30.1.5 Longitudinal Follow-Up of QOL

To understand the impact of childhood cancer on HRQOL, a longitudinal frame of reference is often necessary [22]. HRQOL effects may change substantially throughout the course of the illness. Unfortunately, our systematic review primarily identified cross-sectional studies, which cannot detect the effects of illness that evolve with time. The QOL for AYA patients can change dramatically during their treatment course. For example, teenagers with Hodgkin disease had a significant improvement in their PedsQL of more than ten points when compared between the radiation and chemotherapy phase of treatment, which further improved off treatment [23]. In general, only short-term follow-up studies have been done in these patients, with long-term studies sorely needed. Future research should seek to incorporate longitudinal assessments of HRQOL in order to capture the evolving effects of childhood cancer for AYAs.

30.1.6 The Call for an AYA Cancer-Specific PRO Instrument

In order to include the voice of AYA in the assessment of treatment outcome, well-defined, valid, reliable and responsive PRO instruments that measure the concepts of importance to AYA are needed. The choice of which PRO instrument to use in clinical research or clinical practice is a crucial decision. If the wrong scale is used, it may appear that an effective treatment has little or no benefit. The use of a generic or even cancer-specific scale that was not designed specifically for the AYA population may not provide evidence that a treatment works or may not adequately assess HRQL. The right scale to use in a clinical trial is the one that has content validity for the context of use [8, 13, 24].

There have been recent calls for the development of AYA-specific tools. Nightingale and colleagues reviewed 16 qualitative studies of young adult survivors of childhood cancer and suggested that existing HRQL instruments do not comprehensively cover the concerns of AYA, which they found to include the following six domains: physical, social, psychological, spiritual, fertility/sexual, resilience, and body appearance [25]. Quinn et al. took a different approach by interviewing 30 young adult survivors of childhood cancer to identify content limitations in two adult-onset cancer survivor-specific HRQL instruments, i.e., Quality of Life in Adult Cancer Survivors (QLACS), Quality of Life – Cancer Survivors (QOL-CS), and a generic HRQL instrument (SF-36) [26]. The authors report three areas where content was lacking, including perceived sense of self, relationships, and parenthood [24]. Kuhlthau and colleagues [27] conducted focus groups with 19 AYA survivors of CNS tumors and identified the following seven key survivorship domains: physical health and well-being, mental health and well-being, cognitive functioning, social health and well-being, health behaviors, sexual and reproductive health, and support systems. These authors suggest that there are aspects of HRQL important to patients that are not covered by currently available HRQL tools [27]. The

common theme across these three qualitative studies is that HRQL tools not developed specifically for AYA may lack content validity [25–27].

30.1.7 Study Aim

In order to conceptualize the most important health concerns of AYA patients with cancer and survivors, our team performed a content analysis of HRQL instruments used with AYA to date. Our specific aims were as follows: (1) to identify cancer-specific PRO instruments measuring the HRQL concerns of AYA and (2) to perform a content analysis that involved coding and categorizing the items of each identified PRO instrument. Our overall goal was to develop a preliminary conceptual framework of HRQL content deemed important to AYA by PRO instrument developers.

30.2 Methods

We aimed to identify self-report cancer-specific PRO instruments for AYA, which were available in English and have published evidence of a development and/or validation process. We used the findings from two previous systematic reviews [14, 28] and performed an additional literature search of our own. In the first review, Anthony et al. sought to identify generic and cancer-specific PRO instruments that measured HRQL in cancer patients and/or survivors aged up to 25 years. The methods and results are described in detail elsewhere [14]. In the second review, Clinton-McHarg et al. [28] sought to identify cancer-specific multidimensional PRO instruments that measure psychosocial outcomes, including HRQL, in AYA cancer survivors. Finally, to ensure all possible HRQL instruments were identified, we performed an updated search of Medline, PsycINFO, EMBASE, and CINAHL databases from January 2008 to December 2014 for English language articles, replicating the search strategy outlined by Clinton-McHarg et al. [28]. For all PRO instruments identified, we obtained a paper copy and transferred the content into an Excel spreadsheet for coding. We then used the content analysis method described by Anthony et al. [14], which classified content according to the broad structure of the Patient-Reported Outcomes Measurement Information Systems (PROMIS), a health framework consisting of domains, subdomains, and identifying concepts [14].

30.3 Results

Our search identified a total of 12 instruments for use with AYA cancer patients and survivors. Table 30.1 outlines the characteristics of each instrument. The age range of participants for whom the scales were developed ranges from 8 to 39 years. The number of items included in each instrument varied ranging from 16 to 90, and the number of domains ranged between four and nine. Seven instruments were designed for use with cancer patients both on and off treatment, and five were designed for childhood cancer survivors.

30.3.1 Brief Description of PRO Instruments for AYA

30.3.1.1 Adolescent Quality of Life Instrument (AQoL)

The AQoL [29, 30] is a 16-item instrument for assessment of HRQL in adolescents with cancer. Items for this measure were generated from previously established QOL instruments and did not involve patient, parent, or expert opinion. High scores on the AQoL are associated with better QoL. Item reduction was conducted using feedback from researchers and by piloting the survey with seven volunteers who highlighted the items of most and least concern. Acceptable reliability was reported in a population of 75 participants with cancer aged 9–20 years [29], and test–retest reliability was adequate with overall scores ranged from 0.75 to 0.90 in three administrations [30]. No other psychometric results for the AQoL were described.

Table 30.1 PRO instruments used to measure HRQL in AYA cancer patients

Measure	Patient group	Versions	Age range (years)	No. items	Domains
Adolescent Quality of Life instrument (AQoL)	On and off treatment	Child and adolescent	9–20	16	Normal activities, social/family interactions, health status, mood, and meaning of being ill
Bone tumor DUX (Bt-DUX)	On and off treatment	Child and young adults	8–25	20	Social, emotional, cosmetic, physical
Cancer Assessment for Young Adults – Testicular (CAYA-T)	On and off treatment	Young adults	18–29	90	Physical, sexual, intrapersonal, social-relational, educational/ vocational/ avocational, spiritual
Impact of Cancer for Childhood Cancer Survivors (IOC-CS)	Survivors	Young adults	18–39	45	Life challenges, body/health, talking with parents, personal growth, thinking/memory problems, health literacy, socializing, financial problems
Minneapolis–Manchester Quality of Life Instrument – Adolescent Form (MMQL)	Survivors	Adolescent	13–20	46	Physical functioning, cognitive functioning, psychological functioning, social functioning, body image, outlook on life, intimate relations
Pediatric Functional Assessment of Cancer Therapy – Childhood Brain Tumor Survivor (Peds-FACT-Brs)	Survivors	Adolescent	13–18	37	Physical well-being, emotional well-being and illness experience, social/family well-being, survivor-specific concerns
Pediatric Quality of Life Brain Tumor Module (PedsQL-BT)	On and off treatment	Adolescent	13–18	24	Cognitive problems, pain and hurt, movement and balance, procedural anxiety, nausea, and worry
Pediatric Quality of Life Cancer Module (PedsQL-C)	On and off treatment	Adolescent	13–18	27	Pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance, communication
Quality of Life – Cancer Survivors (QOL-CS)	Survivors	Adolescents and young adults	16–29	41	Physical well-being, psychological well-being (distress and fear), social well-being, spiritual well-being
Quality of Life for Children with Cancer Scale (QOLCC)	On and off treatment	Adolescent	13–18	34	Physical function, psychological function, peer/school function, treatment/disease symptoms, cognitive function, plus 2 subscales of communication and understanding
Quality of Life in Children and Adolescents with Cancer (PEDQOL)	Survivors	Child	8–18	34	Physical functioning, autonomy, emotional functioning, cognitive functioning, social functioning peers/family, body image
Perceived Illness Experience Scale (PIE)	On and off treatment	Child and young adults	8–24	34	Interference with activity, disclosure of illness, school/work, peer rejection, parental behavior, manipulation, preoccupation with illness, treatment, physical appearance

30.3.1.2 Bone Tumor DUX (Bt-DUX)

The Bt-DUX [31] is a 20-item HRQL measure for children and young adults aged 8–25 years with malignant bone tumors. The Bt-DUX was created from the generic DUX-25 QOL questionnaire, which is a short form of the Dutch Children TNO-AZL Quality of Life Questionnaire. The DUX-25 contains 25 items that measure four domains, i.e., emotional, social, familiar, and physical. Ten items for the Bt-DUX were taken directly from the DUX-25, with the remaining items generated from interviews with ten patients and four healthcare experts. Item reduction involved input from four experts. Psychometric validation revealed good internal consistency reliability for all domains and the total score (Cronbach's $\alpha \geq 0.73$).

30.3.1.3 Cancer Assessment for Young Adults: Testicular (CAYA-T)

The CAYA-T [32] is a 90-item measure used to assess HRQL in young adults with testicular cancer, aged 18–29 years. Items for this measure were generated from a literature review, 21 patient interviews, and input from healthcare providers. Items were refined according to participant feedback and clinical applicability. A modern psychometric approach called Rasch Measurement Theory (RMT) analysis was used for item reduction to ensure that the observed data fit the responses of the predicted Rasch model. Psychometric validation showed adequate internal consistency reliability and test–retest reliability, with a Cronbach's $\alpha \geq 0.70$ reported for all scales, and intraclass correlation coefficients that ranged from 0.49 to 0.91.

30.3.1.4 Impact of Cancer for Childhood Cancer Survivors (IOC-CS)

The IOC-CS [33, 34] is a 45-item HRQL instrument for childhood cancer survivors aged 18–39 years. Items were generated through 64 patient interviews and refined in a focus group with 13 healthcare professionals and researchers and 17 patient advocates. Item reduction involved cognitive interviews with 13 young adult survivors and factor analysis. Higher scores on this instrument indicate greater impact. The IOC-CS evidenced adequate internal consistency reliability, with Cronbach's $\alpha \geq 0.70$ for all scales. Test–retest reliability from 136 respondents was good, with an overall ICC of 0.75 [34]. The IOC-CS was able to differentiate between cancer types.

30.3.1.5 Minneapolis–Manchester Quality of Life Instrument: Adolescent Form (MMQL)

The MMQL-Adolescent Form [35, 36] is a 46-item HRQL instrument for adolescent survivors of cancer aged 13–20 years. Item generation involved input from patients (focus group), parents, and expert healthcare professionals. Higher scores on the MMQL indicate better HRQL. A psychometric analysis of the MMQL-Adolescent Form showed adequate overall internal consistency reliability (Cronbach's $\alpha = 0.92$, range 0.67–0.89), with a test–retest reliability of 0.71 (ranged from 0.60 to 0.90) [35].

30.3.1.6 Pediatric Functional Assessment of Cancer Therapy: Childhood Brain Tumor Survivor (Peds-FACT-Brs)

The Peds-FACT-Brs [37] is a 37-item HRQL instrument for survivors of brain tumors. Item generation involved interviews with 20 survivors, 20 parents, 5 clinicians, and 7 teachers. Input from clinicians, QOL researchers, and children aged 7–15 years was used to refine a set of items, and the instrument was tested in 46 brain tumor survivors. RMT analysis was used to ensure that all items within the domains could be scaled together. Adequate internal consistency reliability was reported for three of four domains (Cronbach's α ranged from 0.51 to 0.82). No further psychometric analyses were reported.

30.3.1.7 Pediatric Quality of Life Brain Tumor Module (PedsQL™-BT)

The PedsQL™-BT [38] is a 24-item instrument that measures HRQL in children aged 2–18 years on or off treatment for a brain tumor.

Item generation for this instrument was developed from focus groups with patients, parents, and healthcare professionals. This module is identical to the PedsQL™ Cancer Module in the layout and instructions. Higher scores indicate better HRQL. A psychometric analysis of the PedsQL™-BT in adolescents aged 13–18 years showed adequate internal consistency reliability (Cronbach's $\alpha \geq 0.70$, ranged from 0.69 to 0.93).

30.3.1.8 Pediatric Quality of Life Cancer Module (PedsQL™-C)

The PedsQL™-C [39] is a 27-item instrument of HRQL for children aged 2–18 years on or off treatment for cancer. The PedsQL™-C was derived from an earlier instrument called the Pediatric Cancer Quality of Life Inventory (PCQL) [40–42]. Item generation and reduction techniques for the PCQL are described by the authors; however it is unclear how these data were used to develop the eight domains that comprise the PedsQL™-C. Specifically, it is not clear whether literature review, patient interviews, or parent input were used to develop the PedsQL™-C. Higher scores on this instrument indicate better HRQL. Psychometric analysis for the PedsQL™-C demonstrated adequate internal consistency reliability for all domains (Cronbach's $\alpha \geq 0.70$) in individuals aged 13–18 years. Construct validity was also established [43].

30.3.1.9 Quality of Life: Cancer Survivors (QOL-CS)

The QOL-CS [44] is a 41-item HRQL instrument for cancer survivors aged 16–29 years. Items for the QOL-CS were derived from a literature review and qualitative interviews with five cancer survivors. The authors do not report how many participants were young adults, and thus it is unclear whether there was any input from this patient age group. Factor analysis was conducted to inform item reduction. Other psychometric analysis revealed adequate internal consistency reliability, with Cronbach's $\alpha \geq 0.76$ for five of six scales (with the exception of the distress scale with a Cronbach's $\alpha = 0.54$), and test–retest reliability ($r \geq 0.81$) high for all domains. Zebrack and colleagues [45] later undertook a validation study of the QOL-CS in a childhood cancer survivor population.

30.3.1.10 Quality of Life for Children with Cancer Scale (QOLCC)

The QOLCC [46–48] is a 34-item HRQL instrument for adolescents aged 13–18 years on or off treatment. Items were generated through a literature review and interviews with patients and their caregivers. Higher scores represent poorer HRQL. Psychometric analysis revealed adequate internal consistency reliability, with Cronbach's $\alpha \geq 0.74$ for four of five domains. The QOLCC appears to differentiate well between patients on versus off treatment in three of five domains.

30.3.1.11 Quality of Life in Children and Adolescents with Cancer (PEDQOL)

The PEDQOL [49] is a 34-item HRQL measure for children aged 8–18 years who have completed cancer treatment. Items were generated from existing HRQL measures for children and expert opinion. Item reduction involved a factor analysis. Further psychometric analysis highlighted problems with internal consistency reliability, i.e., Cronbach's $\alpha \leq 0.64$ for six of seven domains. This instrument does not appear to discriminate well between children with cancer and healthy controls.

30.3.1.12 Perceived Illness Experience Scale (PIE)

The PIE Scale [50] is a 34-item measure of perceived illness experience in children with cancer and long-term survivors aged 8–24 years. Item generation for the PIE involved input from 15 children and adolescents who had undergone or recently completed cancer treatment. Formal item reduction strategies were not described. Higher scores on the PIE indicate more negative illness experience. Psychometric analysis highlighted problems with internal consistency reliability, with Cronbach's $\alpha \leq 0.68$ for six of nine domains. Test–retest reliability was acceptable for the total score ($r = 0.92$).

30.3.2 Content Analysis

The 12 instruments reviewed above provided a total of 489 items that we included in our concept sort. A total of 71 items (14.5 %) were deemed to be a determinant, rather than an outcome (e.g., family social support or techniques for coping with illness). The remaining 418 items were classified as outcomes and were assigned a major domain, a subdomain, and (if relevant) an identifying concept. A total of six major domains were identified as follows: Psychological (207 items), Social (88 items), Physical (76 items), General (23 items), Sexual (18 items), and Spiritual (6). We also identified 21 subdomains and 51 unique health concepts (see Fig. 30.2).

Of the 12 identified instruments, three (i.e., CAYA-T [32], IOC-CS [34], and QOL-CS [44]) had content that covered all six domains of our working framework. Two domains were measured by only a few instruments (e.g., spirituality and sexuality). Some subdomains were included in most instruments (e.g., emotional distress), while others were rare and were assessed by only a few instruments (e.g., behavior). Of the 51 unique health constructs pertaining to AYA cancer patients and survivors, the most commonly measured identifying concepts were anxiety/fear (22 items), worry (21 items), relationships with people (21 items), and relationships with peers (20 items).

An important difference in content was noted between the various PRO instruments designed for adolescents versus young adult patients and survivors. Specifically, the pediatric tools relevant to adolescents lacked items to measure spirituality, goal setting/future plans, and sexual and reproductive health. The PRO instruments designed specifically for AYA patients and survivors, on the other hand, were more likely to include the breadth of AYA-specific concerns.

30.4 Discussion

Though initially designed for use in academic and industry research, PRO instruments are increasingly being used in clinical care, patient/consumer education, benchmarking, and quality improvement. Such data facilitate comparative effectiveness research, inform discussions with regulatory bodies, and support an evidence-based approach to treatment [19, 51, 52]. It is thus important that clinically meaningful and psychometrically sound AYA-specific PRO instruments are available.

In order to carefully assess HRQL in AYA cancer patients, reliable, valid, and responsive PRO instruments are needed [8]. Best practice guidelines for PRO instrument development (e.g., those outlined by the USA FDA [8]) suggest that the combination of a literature review, qualitative interviews, and expert opinion together optimize the development of a comprehensive PRO instrument. This chapter outlined 12 unique PRO instruments designed to measure HRQL for adolescent and/or young adults. We found that interviews with AYA were part of the development in most of the identified instruments, with between 5 and 64 patients involved. Exceptions were the AQoL [29, 30] and PEDQOL [49], which did not involve any patient input, but were instead developed from existing HRQL instruments.

Most of the current PRO instruments were designed using a Classical Test Theory approach (CTT) [53]. Exceptions identified are the Peds-FACT-Brs [37], and the CAYA-T [32], which used RMT analysis, a modern psychometric method. Although CTT methods are widely used, they have limitations that have important consequences for the use of PRO instruments. These limitations include the following: (1) data generated are ordinal rather than interval; (2) scores for people and samples are scale dependent; (3) scale properties, such as reliability and validity, are sample dependent; and (4) data are suitable for group studies rather than individual patient assessment. The increasingly popular use of modern psychometric approaches in scale design offers certain advantages, including the possibility for item banking, scale equating, computerized scale administration, and methods for handling missing data [54, 55]. A modern psychometric approach can also provide scales that can be used with individual patients in clinical practice.

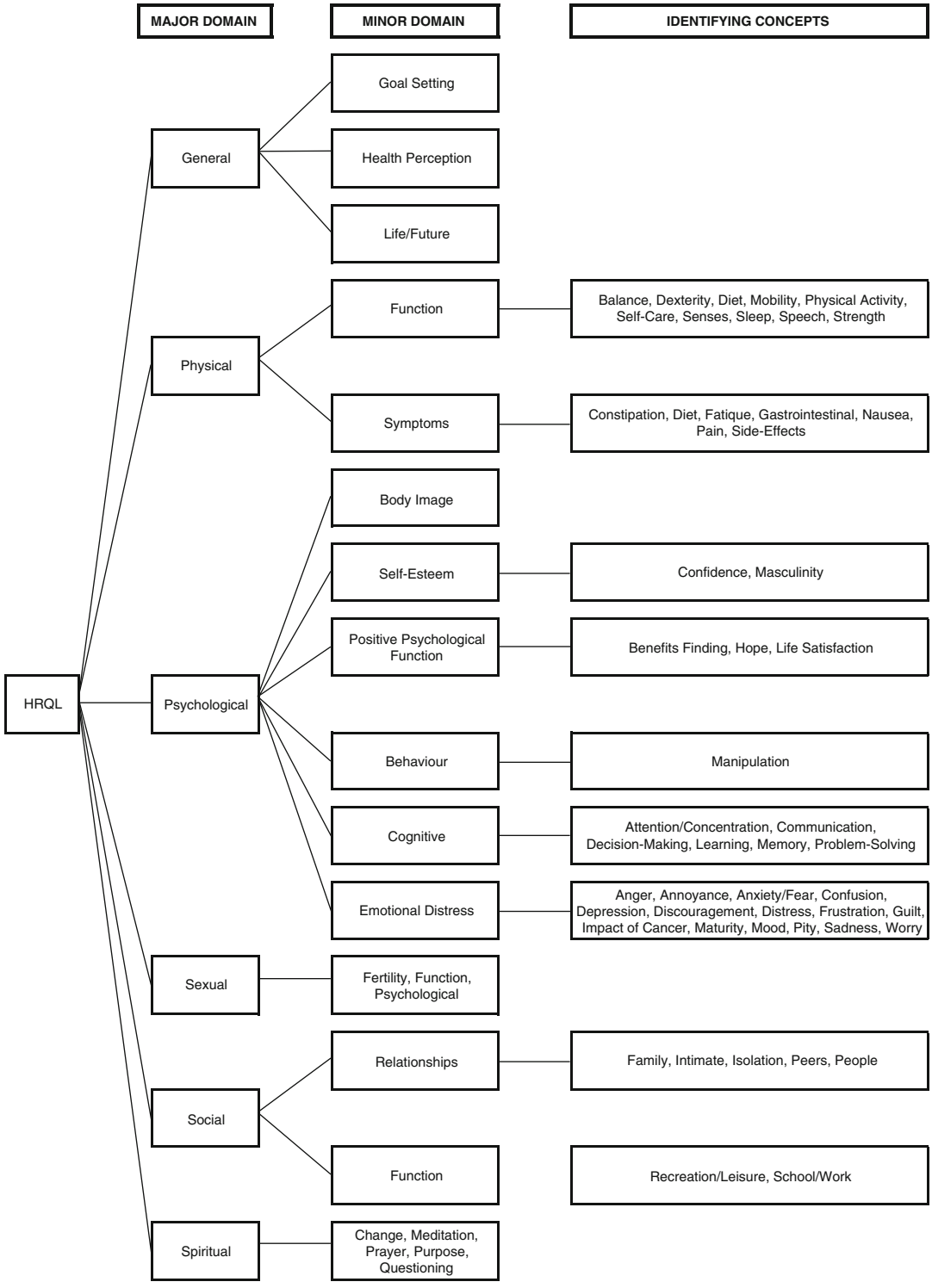

Fig. 30.2 Preliminary conceptual framework of HRQL in AYA

The AYA period of life is a unique stage, characterized by changes in many areas of development [1, 2]. AYA are faced with multiple transitions in this life stage, and challenges to this transition period arise as a result of having a cancer diagnosis [4]. Our team found that most of the identified HRQL instruments were developed for pediatric patients (that included adolescents), rather than AYA specifically, thus limiting their applicability to AYA as a distinct group. The pediatric measures fail to address some of the concepts important to AYA identified in recent qualitative studies [25, 27], including spirituality, sexual and reproductive health, goal setting, and body appearance. Newer measures such as the QOL-CS [44], IOC-CS [33, 34], and CAYA-T [32] were designed with AYA patients and cover their unique concerns, such as sexual and spiritual health needs. As these various PRO instruments are taken up and used in longitudinal studies and in clinical trials with AYA patients and survivors, we will begin to understand and interpret what the scores mean and to identify clinically important change.

Our team suggests that in choosing a PRO instrument to measure HRQL in AYA, one must consider the developers' approach (traditional versus modern) and adherence to international guidelines for PRO instrument development and validation. In addition, choosing the most appropriate PRO instrument for use in clinical research and/or practice is crucial, as results generated from an inappropriate scale may skew or provide false results, i.e., it may appear that an effective treatment has little or no benefit. Given the differences that exist between the 12 measures identified in our study, we highly recommend that, in addition to considering how an instrument was developed and validated, one must also closely consider the relevance of the content within the instrument in relation to the research question or clinical need. Finally, given that the conceptual framework of HRQL content, which we developed from AYA concerns by PRO instrument developers to date, is preliminary, future research in scale development for AYA cancer patients could build on this framework and enhance the validity of their importance to AYA.

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Palliative Care

31

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Abstract

Cancer is a leading cause of death in adolescents and young adults (AYAs) Wiener et al. (Pediatr Blood Cancer 60(5):715–718, 2013). Though most AYAs will survive, cancer will become incurable in 10–40 % Schrijvers and Meijnder (Cancer Treat Rev 33(7):616–621, 2007). Although the general philosophies of palliative care apply to AYAs, developmental considerations are unique to this group (Ferrari et al. J Clin Oncol Off J Am Soc Clin Oncol 28(32):4850–4857, 2010); Wein et al. J Clin Oncol Off J Am Soc Clin Oncol 28(32):4819–4824, 2010). The interaction of psychosocial, emotional, physical, and existential issues is essential to consider (Wein et al. J Clin Oncol Off J Am Soc Clin Oncol 28(32):4819–4824, 2010). The gaps in care experienced on both sides of the healthcare system between pediatric and adult medicine can be particularly impactful when delivering palliative care. The benefit of a multidisciplinary palliative care approach is widely appreciated as is the need to begin the process early in order to develop a trusting relationship (Wiener et al. Pediatr Blood Cancer 60(5):715–718, 2013; Baker et al. Pediatr Clin N Am 55(1):223–250, 2008; Ferris et al. J Clin Oncol Off J Am Soc Clin Oncol 27(18):3052–3058). Honest communication which supports autonomy is essential in discussions of their goals, worries, risks versus benefits of treatment, and advanced care planning (Clark and Fasciano Am J Hosp Palliat Care

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31.1 What Is Palliative Care?

The word "palliate" means to alleviate, to mitigate, or to make the effects of something less harsh or intense. Palliative care is a medical subspecialty that has arisen to care for patients with terminal illnesses which focuses on symptom control and psychosocial challenges of the patients and their families to alleviate suffering. The World Health Organization (WHO) defines palliative care as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [2–4, 6, 8–10]. The Center to Advance Palliative Care (CAPC) describes palliative care as "see[ing] the person beyond the disease" and as being "provided by a team of palliative care doctors, nurses and other specialists who work together with a patient's others doctors to provide an extra layer of support" [3–5, 7, 9–11]. This multidisciplinary approach to patient care addressing physical symptoms and psychological distress and helping to clarify the goals of care for the patient as well as supporting the patient's family is the core of the palliative care mission. Patients can benefit from palliative care at any stage of a terminal diagnosis, not necessarily only when there are no remaining treatments for the underlying condition. These services assist in affirming life by supporting the patient and family's goals including dignity throughout the course of their disease, dying process, and death [12].

31.2 The Palliative Care Team and Setting

Resources and availability of palliative care teams and services vary, as does the location of care. The gaps in care experienced on both sides of the healthcare system between pediatric and adult medicine throughout AYA oncology can be particularly impactful when delivering palliative care. It is well recognized that cultures differ between pediatric and medical oncology settings as do resources [13]. While pediatric care has been described as nurturing, family centered and often enriched with supportive care and centralized services, the availability of palliative care and multidisciplinary services can be more limited versus medical oncology. In addition, the family-centric pediatric approach can limit the autonomy needed by AYAs and offered within the adult-based system. Ideally adult and pediatric palliative care providers coordinate to provide care, especially for the younger or transitioning AYA. However, regardless of setting or resources, the benefit of a multidisciplinary palliative care approach is widely appreciated [1, 6, 7]. The team ideally includes nursing, medical staff (palliative medicine doctor, oncologist, advanced practice providers), social work, psychology, and spiritual support [5]. Other support team members such as music and art therapists and nutritionists are beneficial. In both the pediatric and adult settings, the inclusion of a child life specialist can be critical in communication and legacy building with the AYA patient or their children.

Though palliative care services can be delivered in multiple settings, most palliative care is currently administered in the hospital by a palliative care consultation team [14]. Many hospital intensive care units and oncology units, both adult and pediatric, now routinely integrate specialized palliative care to help with symptom management and addressing goals of care. When available, ambulatory palliative care clinics can also be integral in transitioning care for patients originally seen in the hospital and helping to support patients who are continuing treatment for their cancer despite a poor prognosis. And, as the home is often the preferred location for end-of-life care and death, the inpatient or outpatient

palliative care team can also help transition care directly to the patients in their homes or nursing homes often through hospice [15, 16]. Regardless of the members of the team or the location of care, a palliative care team taking care of AYA patients should be familiar with the specific developmental needs of AYAs.

31.3 Developmental Considerations of AYAs

While the Centers for Disease Control (CDC) defines adolescence as ages 10–19 and young adulthood as ages 20–24 years, AYA oncology defines the age range as 15–39 years, a span of three decades [9]. Although the general philosophies of palliative care apply to AYAs, developmental considerations are unique to this group which is also experiencing a multitude of "normal" life transitions [4, 5]. However, the interaction of psychosocial, emotional, physical, and existential issues is consistent and essential to consider in all AYAs [5]. What is also consistent is an "adult" understanding of death which can seem in direct conflict to the feeling of immortality often portrayed [5]. In fact, an adult understanding of death is usually achieved by age 9 [9]. Understanding, nurturing, and encouraging the normal development of AYAs while also acknowledging the abnormality of death at this age is the unique challenge of caring for this population [17].

31.3.1 The Younger AYA

Normal adolescent development includes physical changes with completion of puberty and physical maturation as well as psychosocial development marked by becoming independent, developing self-confidence, and exploring identity. Cognitively, adolescents gain the ability to think logically and abstractly. They begin questioning more as they develop their own values and beliefs [2]. This can be one of the most difficult times to encounter illness, especially terminal cancer [3]. Cancer and its treatment can delay pubertal development in the younger to mid-adolescent and alter both the physical appearance (hair loss, obesity, disfigurement) and capabilities (fatigue, weakness, sexual function) [3, 18]. Normal psychosocial development is compromised by an increased dependence on parents and others, physical changes that can interfere with self-confidence and intimacy, identity as a patient, and social isolation [2, 8].

In spite of this departure from normality, younger AYAs often have amazing insight into their disease, including their own mortality, and opinions and wishes for how they want to spend their remaining time [3]. While the experience of cancer at a young age can delay developmental milestones, other milestones can be reached more quickly due to the cancer experience [5]. Whereas in young children, decisions about end-of-life care, including do-not-resuscitate orders and sedation, are largely left to the parents, and the legal age of competency in the United States is age 18, adolescents often have the emotional and cognitive capacity to make these decisions starting around age 14 [5, 9]. Because of this dichotomy between capacity and legal competency, decision-making can be even more complex for adolescents versus young adults [18]. Shared decision-making with adolescents which supports autonomy should include discussions of their therapeutic goals, worries, risks versus benefits of treatment, and advanced care planning with both considerations and interventions based on their developmental needs [2, 9]. These discussions must be rooted in honesty as the development of trust and rapport is essential in communication. Especially within the pediatric setting, it can often be difficult to avoid paternalism, but treating the young AYA as an equal and providing advice or assistance for them to make their own decisions enable independence, self-confidence, and a sense of self [14].

Though family is not to be ignored in the delivery of palliative care at any age, it is an even more essential element in the care of an adolescent versus older AYA. According to the AAP Guideline on Pediatric Palliative Care and Hospice Care, it is important for care to be patient centered but "…with a constant commitment to providing the best possible care for that child in a manner that fully engages, respects, and partners

with the patient's family." This care should not only include partnering with the parents but supporting the siblings as well [19].

31.3.2 The Older AYA

Developmentally, transition from adolescence into adulthood is marked by an increased sense of self, awareness of others, development of meaningful relationships and family, an established sense of beliefs, and increasing adult responsibilities such as commitment to work and relationships, parenting, and even caring for one's own parents [2]. Younger adults in their late teens to early 20s are normally experiencing personal and spiritual growth and exploration of the adult world, but as young adults mature into their late 20s and 30s, they are often more settled in work, relationships, and their own lives.

A diagnosis of terminal cancer interferes with completing education, finding or keeping work, career planning, and relationships and can lead to loss of recently gained employment and financial independence. And, although the legal aspects of decision-making are more straightforward in young adults versus adolescents, there are unique challenges including disclosure of illness in the work setting as well as in new relationships [2]. Focus on family is still developmentally important; but whereas in younger AYAs, the family often includes the parents and siblings, in older AYAs, the role and needs of young spouses and children must be considered. The foundation of communication with healthcare providers must still include honesty and the development of trust, as in younger AYAs.

31.4 Introducing Palliative Care

Introducing palliative care to the AYA population carries with it unique challenges, in an already-challenging specialty. In general, palliative care is an often-misunderstood service confused with end-of-life care, with this misconception more prevalent in pediatric versus adult medicine [20]. While palliative care focuses on the relief of symptoms caused by a terminal illness, it is more accurately "the art and science of lessening physical, psychological, emotional, and existential suffering" [21]. This is a daunting yet crucial understanding in introducing care to the AYA oncology patient.

The adult literature has demonstrated the benefit of introducing palliative care early in the course of diagnosis and treatment [22, 23]. Early introduction of these services can result in increased quality of life, decreased anxiety and depression, and decreased utilization of hospital resources and chemotherapy at the end of life, and patients may actually live longer [22]. In 2011 the American Society of Clinical Oncology (ASCO) published a provisional clinical opinion recommending that both standard oncology care and palliative care be considered early for "any patient with metastatic cancer and/or high symptom burden" [24]. While this may be applicable for older patients or within the field of medical oncology, within pediatric oncology, the presence of metastatic disease is not necessarily predictive of risk for morbidity or mortality. In the same year, the CAPC published consensus guidelines to help identify hospitalized patients who could benefit from palliative care [25]. The first step is identifying patients who have a life-limiting condition. Patients who have frequent admissions for the same condition, an admission for difficult-to-control symptoms, complex care needs at home, or a decline in function at admission should prompt a palliative care consultation. In addition, patients who have a prolonged intensive care unit stay, have a lack of clarity in goals of care, or have challenges with consensus with family or staff regarding treatment decisions including resuscitation preferences, use of non-oral feeding or hydration, or other major medical treatment decisions are likely to benefit from a palliative care consultation. Providers caring for patients who may undergo a tracheostomy, feeding tube placement, initiation of dialysis, and other device placements may consider a palliative care consultation to help patients and their families with decision-making.

The unique challenges of the AYA population in regard to introducing palliative care include

their developmental stage, their physical differences from older adults, their psychosocial needs, and the need to care for their parental units, young spouses, and young children. However, within this span of these three decades (defined as ages 15–39), common threads of AYAs include a tremendous amount of life transition and that health, not morbidity and mortality, is the norm.

George suggests that the crux of the approach to the AYA must be rooted in autonomy and control for the AYA. He states: " Whilst it may sit uncomfortably, when facing the truth that a young person is dying, there is a strong case to make that observing autonomy, even when it is clearly not in the best interest of the patient may be more important than the consequence of a shorter life" [17]. Clearly, in the AYA population that is less than 18 years of age, this can be confounded by parental rights. However, regardless of age, the AYA must have autonomy and some control when treatment and palliative decisions are made. So when introducing the concept of palliative care and its team, it is imperative to allow the AYA the space to make decisions regarding how he/she will spend the remaining time they have.

The key tool in introducing palliative care to the AYA is honest communication [8]. Providers need to balance being realistic and devoid of false hope with being positive and hopeful. This dichotomy is hard and certainly changes as the disease marches on. This can be accomplished by developing a relationship with the AYA early in treatment and cultivating trust throughout various stages of the illness. There is also tremendous therapeutic power in the willingness to sit in loving silence, as uncomfortable as that may be to providers who are used to discussing interventions and plans. Sometimes inaction is preferable to action – "Don't just say something, stand there." Let the patient and family talk about what they think the plan and intervention should be.

The parent role, especially for adolescents, must be considered carefully when introducing palliative care. Evidence shows that how a child dies is of critical importance in the parents' further lives [26]. From the moment of diagnosis, there is bereavement; so, for the parent, palliative care starts at diagnosis. Throughout the illness trajectory, there are varied stages of bereavement: grieving what the young person is missing, grieving the loss of the family dynamic, and grieving the potential of life without their child. This is precisely why palliative care can be so helpful to the family from the time of diagnosis. If we refer back to the definition of palliative care as being the art and science of lessening suffering, then this is a desperate need families have as soon as their family member is diagnosed with a life-threatening illness.

Formal tools exist to aid in the introduction of palliative care. The Comfort Care Communication Tool (CCCT) was developed by the pediatric palliative care service at the Children's Hospital and Regional Medical Center in Seattle [8]. It is designed to be introduced by a multidisciplinary team and includes a four-quadrant design to document medical issues, quality of life, contextual issues, and patient preferences. An additional tool, *Voicing My CHOiCES*™ can be used to initiate communication regarding end-of-life care and is further described later in this chapter [27] (See Sect. 31.5 "End-of-Life Care").

When introducing palliative care to the AYA, it is imperative to begin the process early in order to develop a trusting relationship. It is equally imperative to allow the AYA to be as autonomous as possible with respect to decision-making. Finally, truth-telling and transparency are paramount and the building block for all future goals. The most negligent thing that can be done as providers is refuse to engage the reality of death or wait until the patient is at the end stage of illness. We need to do better. By working as a team, introducing palliative care early, and listening to AYAs with cancer, suffering can be ameliorated and true palliation provided throughout their disease course.

31.5 End-of-Life Care

Every year, more than 11,000 AYAs, 15–34 years of age, die from cancer and other life-threatening conditions [27]. Unfortunately due to provider discomfort with approaching end-of-life

discussions, these conversations are often delayed in being initiated or avoided all together. Many healthcare providers feel uncomfortable, unprepared, and unskilled in having end-of-life discussions. AYAs can be perceived as not being competent to make such decisions, further adding to the exclusion in end-of-life planning [27]. Given the broad age range and developmental variability, end-of-life discussions present unique challenges because what is appropriate at one end of the continuum for an adolescent can be completely inappropriate for an adult in their 30s [27]. However, not approaching these topics risks contributing to emotional isolation during the dying process [28].

31.5.1 Advanced Care Planning

When to initiate end-of-life discussions is a critical moment for healthcare providers. As with the introduction of palliative care, most literature supports introducing end-of-life planning when the patient is clinically stable and not in crisis [1]. Waiting until a medical crisis occurs to initiate these discussions can leave the healthcare provider and family in the dark regarding the wishes of the AYA. Despite limited resources available to meet the unique needs of this population, two well-known documents exist to help AYAs with end-of-life planning: *Five Wishes* and *Voicing My CHOiCES*™. These documents are age-appropriate guides and can assist providers when initiating this difficult conversation. *Five Wishes* is an advance care document addressing comfort, future planning, spirituality, durable power of attorney, and life support options. This document served as the foundation for the most current resource for end-of-life planning, *Voicing My CHOiCES*™, which incorporated the feedback of AYAs.

> "While always heartbreaking, the most intimate and peaceful adolescent deaths are those where the AYA trust their choices are respected, believe that they made a footprint on others' lives, and are assured that they will be remembered" [1].

In 2008, Wiener et al. published a study assessing the value of using *Five Wishes* as a way to facilitate end-of-life discussions with AYAs [28]. The *Five Wishes* document is comprised of five sections addressing different aspects of the end-of-life process: person who will make healthcare decisions when they cannot, type of medical treatment they want or do not want, how comfortable they want to be, how they want to be treated, and what they want their loved ones to know. Of those surveyed, 95 % of AYAs reported that this document was helpful to them. They identified items concerning how they wanted to be remembered as more important than topics concerning specific medical decision-making. This same study also reported that avoiding the topic of end-of-life and dying created feelings of isolation, fear, and anxiety. *Five Wishes* is an advance directive that meets the legal requirements in most states, is appropriate for all adults, and is available in 26 different languages [29].

Voicing My CHOiCES™ became available in October 2012 and is specifically tailored to assist AYAs in end-of-life planning [28]. It uses developmentally appropriate language and detailed information and contains both open-ended and closed-choice questions. It addresses how the AYA wants to be treated, cared for, and supported during their illness and how they want to be remembered after death. This document can ensure that an AYA's wishes of how they die are honored. There are nine sections: comfort, support, medical care decisions, medical treatment, family/friends to know, spiritual thoughts, remembrance, belongings, and voice (letters). Completing this document is a process. It requires multiple discussions at various time points throughout treatment. It is recommended that the AYA and healthcare provider complete the section regarding life support decisions together. Unlike the *Five Wishes* document, *Voicing My CHOiCES*™ is not a legally binding document. However, it provides direction to parents, caregivers, and healthcare providers regarding the AYA's desires and wishes.

31.5.2 Location of End-of-Life Care

One of the important choices an AYA has is where to die. While in-home hospice and inpatient hospice services are widely available for adults in the United States, the availability of services in some areas for those under the age of 18 may be limited. While for AYAs with cancer, their parents, and providers, home is often the preferred location for end-of-life care and death, hospitals remain the most common place of death [14–16, 30]. Geographic location of services as well as diagnosis, symptoms, family, marital status, socioeconomics, and ethnicity may all play a role in where an AYA dies [15, 30, 31]. The location of death is not nearly as important as being given the choice and acknowledging that it is acceptable for that choice to change over time.

The challenge for healthcare providers is how to delicately balance being hopeful while also allowing for meaningful, honest conversations about death and choices. The likelihood of an ideal time to approach the subject is rare. However, not approaching these discussions and lack of communication can lead to emotional distance, leaving the AYA feeling alone, afraid, and without control during a critical time [28].

31.6 Symptom Management in End-of-Life Care

Palliative care provides comfort care for any individual who is experiencing a life-threatening illness from diagnosis to death [22, 32, 33]. Access to a multidisciplinary palliative care team is essential when managing the complex physical and emotional symptoms of AYAs living with cancer [1, 5–7]. These services assist in affirming life by supporting the patient and family's goals including dignity throughout the course of their disease, dying process, and death [12]. The symptoms of cancer, its treatment, and its progression are determined by the cancer type and location as in any other age group. In younger AYAs, distressing physical symptoms have been reported in 89 % of patients receiving palliative care [3, 5]. Most patients experience multiple symptoms. The most common symptoms during palliative care are fatigue (57–86 %), decreased mobility and paralysis (76 %), pain (73 %), poor appetite (71 %), and dyspnea (6–21 %) [3, 5], though in the last week of life, dyspnea and pain may become more common [14].

Dyspnea, the subjective feeling of difficulty breathing, can be experienced as increased work and effort, tightness of the chest, and air hunger [34]. Dyspnea can be caused by alterations in afferent information, inspiratory effort, and blood gas balances. Evaluation of the underlying cause can help determine management options including non-pharmacologic ones such as optimal positioning, providing oxygen for hypoxemia, or offering a fan to assist with the feeling of dyspnea [35]. Immediate-release opiates, steroids, and bronchodilators are useful pharmacologic methods in managing a patient's symptoms of shortness of breath.

Pain is reported as one of the most common and concerning symptoms that a patient may experience. Optimal pain management is crucial as uncontrolled pain not only worsens quality of life, but may worsen outcomes such as wound healing, infection, and time to death [36, 37]. The WHO cancer pain ladder for adults is used as a guide for pain management [38]. Toward the end-of-life, opioids are most commonly prescribed for pain management as well as dyspnea. Morphine remains the most commonly used drug, both orally and intravenously, though methadone and transdermal fentanyl as well as non-opioid drugs are also commonly used [14]. Even in young adolescents, no difference has been found in the pharmacodynamics of these drugs versus adults [5]. In addition, even though experimentation is developmentally normal in adolescence and young adulthood, there is no literature to support increased abuse of opioids or other drugs in AYAs receiving palliative care [5]. Even so, some families and healthcare providers may be hesitant to escalate the dose of opioids to appropriately treat symptoms, often leading to suboptimal control of pain and other symptoms [3]. In a survey of parents who had a child died of cancer, 87 % reported that they felt that their child had suffered from uncontrolled pain [37].

The palliative care team can assist the patient in balancing symptom management with quality of life and with educating staff and other healthcare providers. Advanced care planning can assure the goals of the patient for symptom management, including pain, are met including the role of sedation for refractory symptoms.

Non-opioid and adjuvant analgesics can also be used for pain and other symptoms at the end-of-life [3]. NSAIDS are particularly helpful in patients experiencing bone pain as they inhibit cyclooxygenase resulting in decreased production of prostaglandins. Acetaminophen, often utilized as an antipyretic, can be helpful in reducing musculoskeletal pain. Co-analgesics, medications that have a primary indication for a symptom other than pain, can be helpful for certain etiologies of pain. Examples include antidepressants, anticonvulsants, benzodiazepines, and corticosteroids. Neuropathic pain can be treated with opioids in conjunction with medications such as tricyclic antidepressants, serotonin reuptake inhibitors, topical lidocaine, and calcium channel ligands such as gabapentin [39]. Fatigue is a common, yet difficult to treat, symptom of cancer progression as well as pharmacologic management of pain and other symptoms [40]. Psychostimulants have been used, but the benefit remains unknown as research to date in adults with cancer has produced mixed results [41, 42].

Complementary therapies can help with pain and symptom control [43]. Physical and occupational therapy services can augment pain management with therapeutic exercise, massage, use of a TENS unit, and hot/cold therapy. Invasive interventions such as nerve blockade can provide temporary and focal relief for severe pain; however with such interventions, prognostic indicators such as the benefit and duration of effect need to be taken into account [44]. In patients in whom pain cannot be controlled with systemic medications and therapy, or the adverse effects are not acceptable from a quality-of-life perspective when dosed high enough for pain control, epidural or intrathecal administration of opioids or local anesthetics is an option where available. The catheters must be placed by experienced providers familiar with not only the technique but its aftercare, and placement must be balanced with the patients' desire to die at home and the feasibility of hospice to manage these catheters in the home setting.

Complementary and alternative medicine (CAM) is commonly used by patients in cancer treatment and may enhance pain and symptom management by improving overall well-being [43, 45, 46]. Though studies have not proven acupuncture to improve pain for cancer patients, it may play a role by improving nausea and vomiting [47, 48]. Aromatherapy and massage have been shown to have short-term benefits on the well-being of cancer patients, and hypnosis may also be beneficial for pain [45–48]. While minimal literature exists to demonstrate the benefit of herbal supplements for cancer pain management, much attention has been given to the role of cannabinoids [43]. While studies have shown benefit for nausea and vomiting as well as anorexia [49], determining further benefits versus risks will require clinical trials. In studies of cancer pain to date, the analgesic efficacy of cannabinoids was no better than codeine [49, 50].

However, as with other aspects of palliative care in AYAs, it is important to appreciate the physical symptoms within the context of the psychosocial factors and psychological symptoms. In a study by Cohen-Gogo et al. of 45 AYA patients receiving end-of-life care, 100 % experienced sadness, anxiety, fear of being alone, fear of death, fear of pain, and guilt within the last month of life [14]. It is important to screen for these symptoms either informally through discussion with the AYA or as a part of routine care using a screening tool such as the NIH-PROMIS Cancer Instruments (http://www.nihpromis.org). But it is also important to address the symptoms in a multidisciplinary way, not just through medication but by attending to the emotional and psychosocial needs of the patient [51].

31.7 Psychosocial Needs and Supports

AYAs facing life-limiting illness and end of life have unique psychosocial needs. Moreover, defining AYAs as patients ages 15–39 creates a

cohort that spans more than one developmental stage, each with its own psychosocial challenges. It is well established that the experience of illness and dying negatively impacts the developmental tasks that AYAs should be completing [52]. In order to provide competent palliative care to this population, it is essential to understand the normative development that dying precludes, the psychosocial needs that exist, and the interventions that can support patients and families during this challenging time.

31.7.1 Patients Ages 15–17

Middle adolescence, defined as between 15 and 17 [3], is often a time of school achievement and socialization. Adolescents at this age may finally feel settled in high school and be planning a future that includes college, vocational training, or military service. While no time is convenient for catastrophic illness, a diagnosis of cancer in this age group can be particularly difficult. Acceptance by one's peer group is of paramount importance during this stage of development [53]. The logistics of cancer, which include appearance-altering treatments and time away from school and peers, are often socially isolating. In addition, an adolescent grappling with progressive or recurrent cancer has vastly different concerns and priorities than his/her peers, which can further inhibit social relationships.

Patients in this age group are most often cared for at pediatric healthcare facilities. A pediatric setting provides an advantage in that most facilities place a high priority on psychosocial support services. Adolescent patients may be able to access the services of a social worker, child life specialist, chaplain, and psychologist. An emphasis on family-centered care suggests that parents and siblings will also receive support related to coping and adjustment. Conversely, pediatric settings may offer less-comprehensive palliative care services than their adult counterparts.

Providing palliative care to this age group may mean navigating unique psychosocial issues. These are typically patients with definitive thoughts and opinions, but without legal standing to make decisions. In the United States, patients less than age 18 are not typically afforded the legal right to dictate their own healthcare. In a family system with supportive caregivers and open communication, this lack of legal authority may pose no problems. However, in a family with strained relationships or poor conflict-resolution skills, a medical tug-of-war may ensue. Even in more functional family systems, parents may have a protective desire to shield their child from unfavorable test results or a poor prognosis. In addition, cultural beliefs can certainly compound concerns about what a child is told about illness, dying, and death [54]. Medical and psychosocial teams may struggle with ethical dilemmas related to withholding bad news or avoiding an adolescent's questions, as it is recognized that patients as young as 14 may be viewed as functionally competent to make healthcare decisions [3, 53].

While honest, open communication with adolescents is arguably always important, it is particularly important in the setting of palliative care. Effective communication can be facilitated by care conferences with the patient, family members, and the multidisciplinary team. The adolescent should be encouraged to ask questions and should be given the opportunity to speak with members of the multidisciplinary team in private. Moreover, the patient should be encouraged to voice his/her thoughts, feelings, and concerns regarding end-of-life issues and the dying process by using care planning guides such as *My Wishes* and *Voicing My CHOiCES*™ [28]. At the end of life, adolescents may find it therapeutic to participate in legacy-building activities such as writing letters to friends and family and making choices regarding their funeral or memorial services.

Adolescent patients should be encouraged to maintain peer networks and socialize with friends whenever possible. School attendance may be maintained for as long as the patient feels able. If social connections with friends in the community are not possible, patients may benefit from attending formal support programs with other adolescents facing illness or end of life [53].

To promote the development of autonomy and independence, often stunted by the disease

process, adolescent patients should be given choices whenever possible. Choices ranging from what medical information is shared outside the immediate family to who may visit the hospital are all ways for the adolescent to exert some control over his/her life and environment. An important choice that the patient should have input on is the location of death. Some adolescents prefer to die in the hospital, where staff is familiar and any necessary interventions are close at hand. Others choose to die at home, surrounded by familiar people and things. As pediatric hospice care is not as widely available as hospice care for adults, availability of home services should be confirmed prior to offering the choice to die at home.

31.7.2 Patients Ages 18–24

Late adolescence, defined as between 18 and 24 [3], encompasses years meant for growth and exploration of the adult world. Patients in this phase of life are typically attending college, beginning careers, and launching an independent life. Thus, a diagnosis of cancer and the need for palliative care seem all the more cruel when compared with what adolescents at this age are meant to accomplish. At a time when peers are often living away from home for the first time, the demands of medical care typically require patients to return to their families of origin for care and support. Regression in such situations is seen as normal, but normalcy does not make easier the internal conflict that late adolescents experience when forced to abandon work or education due to a terminal illness [5]. A significant developmental task for this age group is the development of intimate relationships, an undertaking often significantly compromised by the experience of illness and preparation for death [52].

Patients in this age group may be treated at either a pediatric or adult healthcare facility. As a result, the psychosocial support services available will likely vary depending on the setting. These patients, assuming competency, are able to direct all aspects of their healthcare. However, depending on where an individual is on the developmental spectrum, he/she may continue to look to parents for decision-making. For example, an 18-year-old college freshman may be more likely to defer to parents' wishes than a 24-year-old young professional who has lived independently.

All patients over the age of 18 should receive education regarding advance directives (healthcare power of attorney, living will). The *Five Wishes* care planning tool described previously is legally accepted as an advance directive in many states and provides a user-friendly approach to these decisions [55]. Patients may not feel the need to complete advance directives as parents are generally the default decision-makers for unmarried AYAs. Should a patient decline to complete an advance directive for whatever reason, it may be helpful to introduce the *Voicing My CHOiCES*™ tool which, although not legally binding, can stimulate important discussion about an adolescent's wishes regarding end-of-life care [28]. Parents called upon to make decisions for an incapacitated adolescent would appreciate the reassurance that they are making choices consistent with their child's values.

As patients in this age group are often on the cusp of independence from their families, a separation process obstructed by illness, it is important to encourage these adolescents to express their thoughts and feelings to the medical team. Patients should be reassured that their goals of care and quality-of-life priorities are paramount. As with younger adolescents, these patients should be encouraged to maintain autonomy whenever possible and to maintain connections with their friends and intimate relationships. Open communication between patients and the multidisciplinary team should be maintained throughout the illness trajectory. In addition, AYAs would benefit from receiving supportive counseling to grieve the life that was just beginning and all the losses inherent to this experience.

31.7.3 Patients Ages 25–39

AYAs in this age group are often more settled in work, relationships, and their own lives. Patients

may be completing postgraduate education or hitting their stride in a chosen career. They may be dating, in a committed relationship, working at marriage, or navigating divorce. AYAs may have their own children or they may have hoped to start a family. Palliative care for a diagnosis of cancer would test most intimate relationships and may extinguish all but the most steadfast partnerships. Moreover, facing end of life at this stage may necessitate juggling the feelings and wishes of the patient's family of origin, spouse, children, and in-laws.

These patients are treated at adult healthcare facilities, although those can range from private oncology practices to community cancer centers to academic medical centers. Availability of psychosocial practitioners and formal support programs can vary widely depending on the setting as can the availability of comprehensive palliative care services. One advantage is the typical ease in accessing home or inpatient hospice care.

Specific psychosocial needs of these AYAs depend on the unique circumstances of each. The patient receiving palliative care may have been the family breadwinner, and his/her spouse and children may be facing an interruption of the family's sole income. Or the patient may be the primary caregiver for the family's small children. A thorough assessment of the patient's psychosocial situation is an important first step in honing in on the specific supports a patient may require.

As with the younger AYAs, these patients should be encouraged to complete advance directives. Palliative care team members may need to help the patient navigate between their own wishes and the wishes of their spouse and/or parents. As AYAs receiving palliative care become necessarily more dependent on their families for care, this dependence might impact decision-making as patients strive to reduce any burden their families might experience. As appropriate, AYAs should be referred to resources that may be able to assist with any other estate planning needs such as wills, trusts, and guardianship for minor children.

These patients also benefit from open communication with the medical team, connection to peer support and intimate relationships, and actively participating in choices regarding their care. For AYAs with spouses or children, there exists a particularly poignant opportunity for legacy-building activities. Patients may wish to leave written, oral, or video messages for surviving partners or children. These AYAs would also benefit from supportive counseling regarding the multiple layers of loss they are experiencing.

Professionals who work with cancer patients at end of life understand what a privilege it is to enter a patient and family's life at this time and walk this journey with them. The unique psychosocial needs of AYAs require a comprehensive approach from a knowledgeable, multidisciplinary team. In the words of Isaac Asimov, "life is pleasant. Death is peaceful. It's the transition that's troublesome." AYAs deserve the very best psychosocial care as they navigate this transition.

31.8 Family and Bereavement in Adolescent and Young Adult Palliative Care

Death of any member of the family is a sad and frequently tragic event that exerts profound and sometimes devastating effects on surviving relatives. This is especially true when a young family member is dying. No one is immortal, and it is the rule of nature that older family members leave this world first, leaving children to cope with the ensuing situation. It is universally accepted that the death of a young person, someone's child, contradicts this natural law [5, 56]. When an adolescent or young adult dies, parents lose their son or daughter, siblings lose their brother or sister, spouses lose their partner in life, young children lose their mother or father, and peers lose their friends.

Death is the most powerful stressor in everyday life, causing both somatic and emotional distress in virtually everyone closely tied with the person who has died. The effects may be intense and long-lasting. It has been reflected in a multitude of literary sources including the works of Shakespeare and his contemporaries to

modern-day medical publications [57]. In general and professional literature, three discrete terms are used to talk about the loss of a close relationship:

1. Bereavement is the reaction to the loss of a close relationship.
2. Grief is the emotional response caused by a loss including pain, distress, and physical and emotional suffering.
3. Mourning refers to the psychological process through which the bereaved person makes readjustments to the new reality after the death of a loved one through undoing his or her bonds to the deceased.

In modern western society, the perception of death has become quite different from what existed several decades ago. Significant advances in diagnosis and treatment of cancer, especially in the young population, have improved survival and cure so that death itself may be seen as a biological accident, not a foregone conclusion. The mainstream modern medicine is primarily concerned less with the promotion of life as with the prevention of death [58, 59]. In such circumstances even well-predicted death of someone suffering from incurable cancer becomes less obvious and accepted [58–60].

Death resulting from cancer is often predictable and expected. The period of time when realistic prospects for cure no longer exist and knowledge of imminent death of a young family member becomes an inevitable reality poses significant challenges for parents, siblings, spouses, and other family members. Anticipatory grief develops, and when it is too strong for someone to bear, this grief may become pathologic. On the other hand, the fact that the illness is usually prolonged and debilitating may allow for an anticipatory acceptance of the loss even when the concurrent grief is intense. In most cases, despite the profoundness of loss and intensity of grief, parents of deceased AYAs find within themselves sufficient psychological resources to continue with their everyday obligations such as caring for other family members and performing their professional and social tasks. According to published data [61–64], only a minority of bereaving parents develop significant psychiatric disturbances after the death of their child. This is not to say that they are not permanently changed or that death of a child is not difficult. The period after the death of a loved one is difficult for survivors and usually accompanied by frequent flairs of emotional and psychological reactions such as anger at the person for dying, at God for seeming injustice, and at professional personnel for perceived non-adequate care at the end of life. Many somatic symptoms may arise during this period such as disturbances in sleep and appetite, agitation, chest tightness, exhaustion, and other somatic complaints. While these normal reactions are often self-limited, bereavement following the death of an adolescent or young adult can be associated with considerable psychiatric and somatic impairment.

Complicated grief is defined as a complex, enduring phenomenon, which is usually associated with lasting psychiatric disorders such as major depressive disorder (MDD), anxiety, and post-traumatic stress disorder (PTSD), and, sometimes, may lead to such social disorders as illicit drug and increased alcohol consumption [65, 66]. In one study performed in Sweden [67], investigators tried to determine what the impact of death of young persons aged 16–24 years was on the function of parents during the bereavement process. Parents of offspring had four to six times the risk for sick leave due to psychiatric diagnoses with the most common being stress-related disorders, unipolar depression, and anxiety. Complicated grief can also result in decreased social functioning and physical illness [62, 64] as well as a feeling of one's life being meaningless without the deceased. The probability of developing complicated grief increases with preexisting psychological problems and with longer periods of time during which the actual death of a young member of family is expected. Grief that is not subsiding within the reasonable time for a given circumstances and that

seriously disrupts normal life should be addressed with therapy. On the other hand, providing treatment to bereaved individuals who do not have complicated grief is not appropriate and may be detrimental to a normal grief process [68–70].

The natural wish of parents to spend as much time as possible with the dying adolescent may lead to frequent and sometimes prolonged absences from their work place, thus potentially decreasing the family income and jeopardizing their professional careers. Siblings may be frequently absent from school and suffer decreased academic performance during this difficult period. Though within certain families marital problems can increase after the loss of an AYA child, the presumption that parental divorce rate is increased is not supported by research results published in modern professional literature [71, 72].

Though frequently unnoticed, the grief of grandparents should not be ignored [73–75]. What for parents is tremendous tragedy, for grandparents may be even more difficult. They experience double tragedy: the loss of a dying grandchild and the suffering of their own child. Grandparents may be unable to effectively provide help and support due to geographic barriers or limitations of their own health. Striving to and not being able to support their own daughter or son may lead grandparents to feel helpless and useless. Some grandparents are prone to depression and other psychiatric disturbances in this critical period of time [75].

The death of an AYA may be very distressing not only for his or her parents and other family members but also for close friends of the deceased. Adolescence is the age when the first strong and frequently long-lasting relationships develop. Young people of this age spend significantly more time with their peers during this period of their life than with parents. Loss of a close friend may be very painful and not without consequences for surviving peers. This may be their first death experience, even earlier than the death of a grandparent. In one recent study [76], authors examined young adults who experienced the death of a close friend or sibling within the past 3 years compared to those who had not experienced a loss. Complicated grief and depression were quite common among bereaved young adults with 19 % of those who lost their friend showing evidence of complicated grief and 37 % experiencing mild to severe depression [53, 77].

Death of a young adult in their 20s or 30s can be even more complex. The dying young adult in some sense has two families: one their own and other that of their parents. Frequently, an older young adult occupies at the same time three positions: son/daughter, spouse, and parent. The children may still be too young to cope with the death of their parent effectively, the spouse is devastated with such a loss during the most productive years of life, and parents suddenly find themselves alone and without someone they may rely on in their old age. When a young adult dies from cancer, the ensuing grief and mourning will be different depending on the relation of a grieving person to the deceased. Grief of the widowed spouse is not the same as the grief of the parent [78] though both may experience the positive and negative effects of caring for and then losing a loved one to cancer [60, 79]. It is absolutely clear that responses to the death of a loved one will be different and modified by a multitude of factors such as age, gender, family relation, and many others.

Despite the profoundness of loss, research shows that this loss can actually lead to personal growth. In a study of parents of young adults who had died of cancer, over half of parents reported that they had a sense of personal growth, had become more expressive of feelings, were able to talk more about sensitive emotional issues, and felt more productive; nearly half felt more content and had become more religious. Nearly two-thirds of the parents had experienced an increased sense of spirituality. The death of the child had resulted for many parents in a greater closeness among the surviving members of the immediate family, including their spouses, their other children, their grandchildren, and their deceased child's spouse [60].

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Addressing the Ethical Challenges for Young Adults, from a Rights-Based Perspective

32

Faith Gibson and Imelda Coyne

Abstract

Healthcare professionals frequently encounter ethical situations in their daily practice while caring for and making decisions with patients and other family members. They may often experience moral uncertainty and dilemmas about the best or right approach to handle ethical concerns. Ethical conflict can sometimes occur particularly when there is a clash of values between individuals, concerning which of the possible options should be chosen: such conflict can be potentially harmful and adversely affect the dynamics within the caring team.

We sought to contribute to the narrative of real-world practice by drawing upon the experience of those delivering direct cancer care. We sought professional's views to present a contemporary perspective on the ethical challenges they encounter while caring for young people with cancer. The narrative that follows has been constructed around the central themes that professionals encounter, which we wove into relevant literature and some personal reflections. The themes include stopping or not stopping when treatment is futile; delaying or avoiding difficult conversations, about cancer, around poor prognosis or end-of-life care; caught between competing obligations between family- and young adult-centred care; patient choice, when faced with treatment options and place of care, access to clinical trials/research and fertility options or when refusing treatment; and tensions between a professional's personal moral compass, expectations attached to their role and conflict with team members.

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We argue here:

1. The need for models of care that are *person-centred* to promote positive and equitable engagement with patients, families and carers, empowering adolescents and young adults in making decisions and enabling them to actively influence their care.
2. The need for an *organisational culture* that has established processes and practices that facilitate and support team discussions about ethical issues and dilemmas that occur in everyday clinical care.
3. The need to create an effective *ethical climate*, where all perspectives are considered, shared decision-making is valued and open dialogue between team members is encouraged.

32.1 Introduction

There is no doubt that life trajectories and biographies are changed as a result of a cancer diagnosis [1, 2]. Stories of lives interrupted and disrupted are evidence of the impact felt, in both the short and long term: the impact being felt 'long after malignant cells have been controlled' [1, p. 279]. The literature suggests that a diagnosis of cancer results in a web of ongoing influences, arising from the disease, treatment and social and personal aftershocks. These influences require negotiation and renegotiation to accommodate the enforced change of personal identity, what some now refer to as 'biographical disruption' [1–4], but has also been referred to as the 'new normal' [5–7], and more recently 'negotiating the present and planning for the future' [8]. The energy and effort invested in creating this 'new normal' include continually visiting a history of a serious illness to make sense of current and possible health and psychosocial consequences and thereby accommodate cancer-related influences on a life course [8]. The 'disruptive force', that is, a cancer diagnosis [9, p. 3], can lead to a portion of a young adult's life 'lived in a state of suspension during treatment and recovery' while at the same time 'their lives were moving forward' [10, p. 383]. A consistent theme throughout the body of evidence about the experiences of young adults with cancer is the impact on daily life and the need to promote a sense of normalcy. Hinds [11] describes normalcy as adolescents looking to the future, of improved or recovered health and how they imagine being able to appear, do and feel like healthy others. That the patient is first a normal young adult who happens to have a diagnosis of cancer should be the foundation of any model of care we choose to implement [12]: models where creating an environment of flexibility is an essential characteristic, which enables us to deliver developmentally appropriate care [13], irrespective of the place of care, where knowledge of the 'International Charter of Rights for Young People with Cancer' [14] is guiding the principles of care.

This Charter was launched in 2011. It makes explicit nine rights and calls on the international community, 'to recognize that access to quality cancer care is a right, not a privilege, and to improve the services and support that young people diagnosed with cancer receive, regardless of geographical location' [14 p. 49]. Human rights are enshrined in the national constitutions and legislation of most countries. A rights-based approach needs to be underpinned by a values base for practice. A values base must reflect what patients, families and carers are asking for, and according to the PANEL principles (Scottish Human Rights Commission http://www.scottishhumanrights.com/careaboutrights/whatisahumanrightsbasedapproach) [15], this should consist of the following:

- *P*articipation: where everyone has a right to participate in decisions about them.
- *A*ccountability: effective monitoring of human rights standards is in place.
- *N*on-discrimination and equality: where all forms of discrimination are prohibited, prevented and eliminated.

- *E*mpowerment: individuals know their rights.
- *L*egality of rights: the recognition that rights are enforceable.

In essence, when thinking about clinical care, it is about empowering young people to know and claim their rights and increasing the ability and accountability of individuals and institutions who are responsible for respecting, protecting and fulfilling rights. Models of care that promote positive and equitable engagement with patients, families and carers must be a central focus for our rights-based practice [16].

We want to particularly highlight 'right number 6' of the International Charter of Rights for Young People with Cancer, which states: young people have the right to *empowerment in making decisions* supported by full and *detailed explanation* of all treatment options and long-term effects of the disease enabling them to *actively influence their care* (http://www.canteen.org.nz/get-involved/international-charter-of-rights-for--young-people-with-cancer) [17]. It is our intention, to examine further the terms in italics as we advocate for a person-centred approach to all ethical considerations faced by healthcare professionals when working with adolescents and young adults (AYA). Person-centred care aims to ensure a person is an equal partner in their healthcare: the individual and the health system benefit because the individual experiences greater satisfaction with their care and the health system is more cost-effective (Royal College of Nursing [RCN] ttp://www.rcn.org.uk/development/practice/cpd_online_learning/dignity_in_health_care/person-centred_care) [16]. The principles of person-centred care include:

- Treating people as individuals
- Respecting their rights as a person
- Building mutual trust and understanding
- Developing therapeutic relationships

McCormack and McCance [18] describe care processes and prerequisites of person-centred care that leads to better outcomes. These include satisfaction with care, involvement with care, feelings of well-being and creating a therapeutic culture. We argue here, for person, not patient, centred care, informed by a rights-based approach to all aspects of ethical care.

In this chapter, we first describe what we mean by ethical challenges. Our focus will be to present some of the ethical challenges faced by colleagues in the real world of practice and some of the strategies used by them to deal with these. As professionals we are not short of guidance, policies and in many cases 'heavy tomes' that guide us in terms of the practical use of ethics in practice [19–22]. A considerable amount has been written on ethical issues and ethical challenges, and therefore, it is not our intention to duplicate any of those influential and seminal pieces here, more to offer examples that will assist reflection on the reader's own experience. We then conclude, by considering these challenges, and offer our own reflections on the 'right number 6' of the Charter and how a rights-based approach can help us to both avoid and assist when dealing with ethical challenges in the AYA field.

32.2 What Do We Mean by Ethical Challenges?

Healthcare professionals encounter ethical questions in their daily practice and often experience moral uncertainty and dilemmas that accompany critical ethical concerns. Ethical conflict occurs when there is a clash of values between individuals, or within an individual, concerning which of the possible options should be chosen: such conflict can be potentially harmful and have far-reaching consequences [23]. Conflict usually begins as moral disagreements about an issue, the perception of unfairness in dealing with an issue or an emotional response to that situation [24]. Moral disagreements are expected to occur in practice. We work in a complex area of clinical care, often one that is emotionally charged. But when these disagreements progress to ethical conflict, care can become more complicated, and tensions can become high. Ethical conflicts are increasing, for a number of very obvious reasons, including extended life spans, increased technology, the public's ever-increasing expectations of medical care, greater cultural and religious diversity, shifts in healthcare financing and limited resources: where

caring within this context impacts on many factors and can cause ethically challenging situations that can compromise relationships and disrupt teamwork. Vivian-Bryne and Hunt [25 p. 1] argue that 'no action is free of ethical relevance'. They advocate for healthcare professionals to adopt the idea that decision-making is a social meaning-making activity and takes place within context. So, constructing ethics with others can help to maintain relationships and maximise teamwork and reduce ethics-related stress and moral distress [23]. Avoiding raising concerns and avoiding conflict by accommodating differences are described as the least helpful strategies. Organisational structures that support a culture where interdependence and shared decision-making are valued, moral differences are addressed, dialogue is encouraged and all voices of the caring team 'blend in' provide the best environment in which ethical challenges can be addressed [23]. Being on 'the same page', with patients and families, where care goals and treatment goals and their consequences are communicated effectively and in a timely way, ensures patient preferences are considered, and quality of care is maximised. The ethical climate in which ethical challenges occur must not be overlooked [26].

32.3 Why Ask Experts to Tell Us About Their Ethical Concerns and Management Strategies?

Throughout this textbook authors who are experts in their field have drawn extensively on evidence and examples from clinical care to support their writings. Much of this applies to the content of this chapter too. To contribute to the narrative of real-world practice, we have chosen to draw on the experience of those delivering direct cancer care. We have sought professional views to present a contemporary perspective on the challenges that they face, revealing experiences that might best illuminate current ethical issues facing those working with AYA. Our approach was to contact experienced individuals in the field by email to ask if they were able to contribute to this chapter by sharing what they thought were the main ethical challenges they encounter in everyday practice.

32.3.1 Our Approach

We approached individuals who represented different disciplines including medicine, nursing and psychology from countries in Europe, America and Australia. We used personal contact, conference proceedings and published papers to identify individuals working in the field. We received comments back from 12 individuals, from a total of 25 requests sent. The professionals who responded to our request are acknowledged at the end of this chapter. These individuals responded to a list of questions that were based on a questionnaire used by Cecilia Bartholdson and colleagues [27] to explore ethical issues faced by healthcare professionals in children's cancer care in Sweden. We adapted the questions with the permission of Bartholdson and colleagues.

We asked six key questions:

1. Please briefly describe the ethical issues that arise most frequently in your work.
2. Please list here factors that have prevented you from doing what you believe is right/best in relation to ethical issues in clinical care/treatment of patients.
3. Please briefly describe the ethical issues, which, in your experience, lead to the most frequent conflicts with your co-workers.
4. Please mention how you deal with ethical issues that commonly occur in your unit.
5. Have you any suggestions about what you could do to deal with ethical issues?
6. Please briefly describe your experiences of teamwork in dealing with ethical issues in healthcare/treatment of patients.

32.4 What Are Some of the Challenges Professionals in Our Field Face?

The narrative that follows has been constructed around the central reoccurring themes from the returned emails, which we have then woven into relevant literature and some personal reflections. These themes can by no means account for all the ethical challenges healthcare professionals might face nor indeed all that our respondents shared;

they are a perspective on a point in time by a selected group of individuals. But what they serve to do is to highlight the complexity and varied nature of these challenges which when viewed through the lens of ethical principles, we can begin to see how we might use rules to inform our discussions and focus our debate, as well as gathering and understanding the perspectives of all those involved, in order to resolve an ethical challenge.

We have grouped the topics highlighted by colleagues and these include (1) stopping or not stopping when treatment is futile; (2) delaying or avoiding difficult conversations, about cancer, around poor prognosis or end-of-life care; (3) caught between competing obligations between family- and young adult-centred care; (4) patient choice, when faced with treatment options and place of care, access to clinical trials/research and fertility options or when refusing treatment; and (5) tensions between a professional's personal moral compass, expectations attached to their role and conflict with team members. Where relevant we have drawn on their direct words, presented in italics, to really reflect the issues they so willingly shared.

32.5 Stopping or Not Stopping When Treatment Is Futile

With advances in treatment, the expectation is that most AYAs will survive cancer, but this is not the case, and outcomes are not so positive particularly for AYAs as demonstrated by Bleyer's work [28]. The decision to stop treatment is a very difficult one, and often there are conflicting perspectives on how the process should be handled. Our respondents noted that with good survival figures, it has become more difficult to know when to cease active treatment. Indeed, on first entering the environment of healthcare thinking that cancer means death, often their expectations change to think that cure is and in fact is always possible. When it is not possible, *someone must have made a mistake somewhere*, leaving families searching for *new answers*. Frequently all options are considered, and ensuring that *every stone is upturned* can lead to delays or lack of preparation for end-of-life care. Families expect a cure, and adapting to a change in this rule is very challenging for all involved, particularly if there was an expectation of cure from the outset.

Parents may exhort and pressurise healthcare professionals to continue all treatment even if the outcome is futile. This may lead to situations where professionals may continue exhausting all options, even though they may know that survival is unlikely and where quality of life could be affected significantly. Continuation of *pseudo curative treatment versus purely palliative approaches* presents its own challenges, *where clinician comfort, or lack of it, in offering palliative care early enough to allow the AYA and the family to prepare* is compromised. There are problems it would seem, with teams not stopping when treatment is futile, *because the parents are not yet on board*. A number of respondents mentioned differences between paediatric oncologists, haematologists and adult/AYA oncologists, where some are *better at pragmatism* than others. *Even when a clinician recognises that they went on treating for too long, it isn't always possible to say you would do something different next time*. A number of respondents mentioned how important it was that *a patient and their family need to feel that their wishes have been heard*.

The AYA may have strong feelings either way, but if not involved in the decision to stop or to continue with treatment, then their preferences are not heard and their right to participation not upheld, and they are disempowered. Making the decision to stop is a very difficult one for parents, AYA and professionals. Where there are disagreements, then conflict often ensues. Families may look to other countries, search the Internet, seek a second opinion and in general consult widely. Our respondents spoke of some of the challenges that result from this searching for hope, particularly where the AYA has been excluded from any discussion by their parents. Research indicates that open discussion in a supportive trusting environment coupled with information and recommendations can assist in decision-making about continuing care

[29, 30]. A dialogue that begins with the AYA and their family at diagnosis and continues, and where accurate perceptions of the prognosis is gained through such discussions in a trusting relationship, has been show to lead to less disagreements about continuing with cancer-directed treatment [31].

In cases where disagreements cannot be resolved, the Courts may be asked to intervene. In the UK the ability of AYA to refuse treatment before the age of 18 when it is held to be in their best interests is limited – in several cases the Courts have overridden an adolescent refusal of life-saving treatment. While a person aged 16 years and over is presumed to have capacity and their consent must be respected, the law regarding refusal of treatment between the age of 16 and 18 years is ambiguous. In some US states, the mature minor doctrine has permitted teenagers to refuse treatment and die (http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=692) [32], but states, where this does not apply, such as in Connecticut situations like that of Cassandra C, who was 17 at the time of discussions, show how overruling the decision of an AYA to refuse treatment presents both ethical and emotional issues http://www.theguardian.com/society/2015/mar/09/teen-battled-cancer-chemo-treament-remission [33]. Cassandra C was clearly able to articulate her views and understood the consequences of her decision, 'Whether I live 17 years or 100 years should not be anyone's choice but mine', she wrote in http://touch.courant.com/#section/-1/article/p2p-82494220/ [34]. 'How long is a person actually supposed to live and why? Who determines that? I care about the quality of my life, not just the quantity'. The issue of competence and the challenges faced when an AYA refuses life-sustaining treatment can be explored further in Ian McEwan's [35] most recent novel, *The Children Act*, or readers can listen to episode 4, series 11, of Radio 4 'Inside the Ethics Committee' on iPlayer http://www.bbc.co.uk/programmes/b0643x61 (these are archived so they can be listened to at any time) [36]. The perspective of the AYA, irrespective of the legal decisional authority in respective countries, is important and supports the need for effective communication, partnership and relationship-based decision-making best described by Hinds et al. [37].

32.6 Delaying or Avoiding Difficult Conversations, About Cancer, Around Poor Prognosis or End-of Life Care

Collusion between parents and healthcare professionals and exclusion of the AYA in discussions at the time of diagnosis, then later when facing end-of-life care, were described by some of our respondents. Open communication with AYA although believed to be a good thing, and enshrined in policy, can still, it would seem, not be taken for granted. The word cancer evokes strong feelings and there remains, despite the best efforts of some healthcare professionals and some organisations, two dominant themes in society: that AYA do not get cancer and that if they do they will die. So it is not surprising that some families, whether for cultural or religious reasons or simply to protect their child, will go to enormous lengths and cause themselves more anxiety and stress by excluding them from any decision-making based on the knowledge that they have cancer. Our respondent's spoke of the challenges this then creates. When parents say that, *they know them best and they won't be able to cope*, healthcare professionals are faced with either further colluding with parents; speaking out and expressing their views and views of the team, based on their experience of what has worked in the past; or placing the AYA central, respecting their rights as an individual and talking direct to the AYA.

The implication of not knowing, as highlighted by many of our respondents, is that AYAs are prevented from being involved in decisions that affect them, and they may be absent from treatment-related/end-of-life care discussions. In the short term, difficulties arise for healthcare professionals in knowing how best to prepare AYA for the journey they are to embark upon. Tensions can arise between professionals and family members, as well as between team members [38]. In the long term, lack of knowledge of what has

happened to them may prevent them from making wise health choices in the future or from being part of decisions about *what happens next*. Receiving clear information and support from the clinical team have been described by AYA as facilitating involvement in decision-making [37].

Mutual pretence and concealing information from AYA are now thought to be unhelpful. There is general agreement that the sharing of cancer-related information leads to improved knowledge and understanding of the illness [39]. Shared information has the potential to enable AYA to feel more in control of their treatment and illness and to participate more fully in their care and decision-making. However information that needs to be communicated is often very complex and can be quite uncertain and emotionally charged, setting the scene for miscommunication [40]. There is clear evidence that young people with cancer desire information about their illness and treatment [39, 41, 42]. Equally challenging is the situation where the AYA excludes their parents/family members from all discussions about their care. Thus a new challenge presents itself in terms of the triad of communication, managing expectations and offering support to all who need it. Some spoke about *parent-free-time* allowing the AYA to be alone and talk to healthcare professionals about what they are feeling and for parents to be able to do the same: together this explicit approach would work towards *creating a trustful and open communication* approach to caring [43].

Participating in end-of-life decisions is life altering for AYA with incurable cancer, their families and their healthcare providers [29, 44]. As Henry Marsh, in his book *Do No Harm*, said: 'the difficulties are all to do with the decision-making' [45]. Parents want to do what's in the best interest of the AYA which may lead parents to try to limit information with the AYA which is not conducive to planning end-of-life care [46]. Tomlinson and colleagues found that hope, increased survival time and child quality of life were more significant in parents' decision-making at end of life compared to professionals who viewed financial considerations as more important [47]. Healthcare professionals often experience difficulty reconciling parents' preferences to withhold distressing information and the AYA right to information and participation. To respect AYA right to participation, their preferences should be determined and information provided accordingly in a sensitive caring manner. The facilitation of shared decision-making requires active engagement with AYAs and their families, information sharing, clear communication and trusting relationships [48]. We might argue that there is a continuing need for professionals to undergo education and training to enhance their competence particularly with regard to palliative care and end-of-life care [49, 50]. The ability to work more openly, proactively and collaboratively with families, key messages from Coad et al. [51], are useful reminders to all members of the clinical team.

32.7 Caught Between Competing Obligations, Such as Family-Centred Care

Professionals are not working alone and alongside AYA; parents are also essential members of an effective multi-professional team. Thus we talk about a triad when we are referring to partnership working in our field: where partnership is both fluid and dynamic, with role boundaries between all three members of the triad changing over the course of a relationship [41]. Understanding this dyad, young person-parent roles, is essential for professionals to uphold the individuality of each partner and to respect their views and value their input into the multi-professional team. The shifting roles within families make this work more complex. Making a judgement of when discussions need to involve both the parents and the young person is less than straightforward. The need to ascertain values/wishes of the young person and their family is essential; we need to understand the complexities of each family, make no assumptions and be guided by the AYA in terms of how we might define and approach family-centred care for them. Conversations about sexuality and fertility, for example, *drug histories being discussed with minors when parents are present*, all present challenging situations, where there is an obligation to inform AYA about such health matters, irrespective

of how uncomfortable that makes a professional feel or how tricky it might be to orchestrate that meeting to meet different needs [52].

Family-centred care sets the parents at the centre of the child's care, with the young person taking a more passive role [53]. An alternative to family-centred care is however emerging: child-centred care has now been defined as a model where children and their interests need to be at the centre of our thinking and our practice [54]: here we can replace child with AYA in recognition of their agency and right to participate. An important premise in this further clarification of terminology that helps us in our field is the recognition that AYA views are not always the same as their parents or of their health carers, and when given the opportunity, they are able to represent themselves [55]. *Finding the right balance between informing adolescent patients about their disease*, *its treatment*, *and prognosis*, *respecting their need for the truth and a full awareness*, *while at the same time protecting their feelings and sustaining their hope is very challenging*: what Pavlish et al. [26 p. 595] refer to as 'navigating the intricacies of hope and honesty'. Add into this situation sensitivities regarding family-centred care, in the case of a minor or even a young adult, and the triad of communication can equally present emotional and ethical challenges. There is a danger in 'trying to keep everyone happy', that leads to uncertainty and inaction [23] while recognising still the impact cancer has on the whole family and how they negotiate roles within it [56].

32.8 Patient Choice and Shared Decision-Making, When Faced with Treatment Options and Place of Care, Access to Clinical Trials/ Research and Fertility Options or When Refusing Treatment

The empirical literature supports the position that many young people, especially those who are veterans of illness, can produce coherent and rational views relevant to decisions about their care [57]. This literature also reveals that there is no straightforward association between age and competence [58]: except that capability increases as young people grow towards adulthood resulting in increasing autonomy that shifts responsibility from the parent to the young person. Much of the new social studies literature has repeatedly argued to reposition 'children' as competent and rational [59], therefore deserving of the right to make autonomous decisions. Young people's ability and desire to be involved do of course vary. Respecting their differences means supporting them as far as they want to go, trying not to impose on them over-involvement or exclusion in decision-making [58, 60]. We would agree with Dixon-Woods and her colleagues [57] that most decisions in our field are made informally and are negotiated within particular forms of social relations, within which there are either shared decisions or situations where young people and parents defer to one another. Difficulties may arise, however, when young people are receiving their care within an adult setting, *where they tend to deal with the AYA on their own and may not recognise how much the AYA needs a parent with them*.

Patient choice and participating in decisions have been a focus for governments in the UK and elsewhere, with policy documents increasingly focusing on patients being central to decision-making in healthcare, for example, 'Giving people more choice and control over their treatment and services is one of our key priorities in the NHS…' [61]; 'Choice is fundamental to the delivery of a truly patient-centred NHS…' [62]; and 'No decision about me without me' [63]. But where upholding choice conflicts with going against medical advice, then challenges can result. *The young person not wanting chemotherapy because they do not want to lose their hair, and the young person who did not want a nasogastric tube passed because they don't like the look of them* were just a couple of examples that have posed challenges for our respondents. In situations such as these, tensions can be escalated, where members of the healthcare team as well as other family members may have a stake in decisions being made

by AYA [60]. In their review, Davies et al. [64] described several themes, which relate to decision-making in cancer, about whether to enter a clinical trial, around palliative and end-of-life care, fertility issues and risk-taking following completion of therapy. Other than risk-taking, all were mentioned by our respondents and indicate strength of consensus on the everyday decisions made by AYA. Clinical decisions are often complex and context dependent and should be based on best practice and individual patient needs. These are made more complex when many stakeholders are involved and the AYA wants to maintain their independence, but due to the complexities of treatment decision-making, they are forced to rely upon parents and healthcare professionals' support and expertise, thus creating a dependent or interdependent relationship. A young person may also feel pressurised and torn between their own wishes and those of their parents' or healthcare professionals. Hence the burdensome nature of some decision-making strengthens the case for shared decision-making.

Shared decision-making is an emerging strategy that focuses on strengthening the collaboration between clinician and patient, encouraging dialogue and discussion. Involvement in shared decision-making for AYAs means receiving information, being able to voice preferences, having a choice and negotiating and choosing how treatments are administered [65]. In prior research, these approaches to involvement have been reported by young people as being very important for them [66]. Furthermore loss of control can leave adolescents with feelings of inadequacy and anger, a sense of frustration, and potentially lead to non-adherence with treatment [67]. Professionals should adopt an individualised flexible approach so that AYAs can have an active, shared or passive role as and when they prefer [48]. Where potential discrimination may occur when a young person is unable to participate fully, such as in the case of those with cognitive disabilities, then healthcare professionals will need to work even closer with families to understand their preferred approach to communication and shared decision-making.

32.9 Tensions Between a Professional's Personal Moral Compass, Expectations Attached to Their Role and Conflict with Team Members

Practices within our field require multi-professional working, within and across disciplines and also across into other specialities. Thus we may find ourselves working alongside professionals with different values and views to those we uphold, as well as *different philosophies of care*, *paediatric versus adult*. Here again there is the potential for ethical conflict, where *we don't always come up with a unanimous decision*, *but usually one that can be accepted by all*. Probably because decisions are never *black and white……should go with the majority expert opinion*. This indicates the importance of each discipline respecting each other's expertise, listening closely to what others have to say and allowing time for discussion of viewpoints. Viewing an ethical issue through a different disciplinary lens will contribute to a fuller discussion and may raise awareness of different issues that need to be considered within a respectful environment. Interprofessional differences that emerge through different experiences, education, culture, personal values and moral beliefs cannot be avoided and probably align closely with different perspectives of 'in the child's best interest' [27]. Creating the right environment would seem to be key, one that prevents conflicts from occurring or has robust structures in place to manage them, should they occur. Pavlish et al. [23] refer to a 'moral community', the characteristics of which include:

1. Open, respectful team relationships
2. Processes for timely, honest planned communication
3. Accessible, strong, ethics-minded leadership
4. Routine, readily available, system-wide ethics resource
5. Provider awareness and willingness to use ethics resources

The implicit notion of accountability within this moral community is to be welcomed, where

a 'shared commitment to the moral good of high-quality patient-centred care is system-wide' [23 p. 138].

32.10 How Might We Deal with Ethical Challenges?

Many respondents spoke about the strategies they used, such as multi-professional forums, where clinical cases can be discussed and where there is open and frank discussion about clinical decisions, particularly difficult ones. Clinical ethics meetings were also commonplace, where healthcare professionals were able to draw on the expertise of a range of professionals. Some clinical ethics meetings would draw upon the expertise of ethical experts or other personnel, such as the chaplain, that can help provide a fresh or different perspective, particularly if emotions are high and there has not been a resolution of differences of opinions on the best way forward. An *open and allowing climate that permits everyone to raise his/her concerns* was championed by many of our respondents. In contrast, *lots of talk in the lunchroom and during coffee breaks or between colleagues* was thought to give only *a narrow picture of the situation*. Bringing professionals together in a more formalised approach or even in an *ad hoc emergency type meeting* was thought more helpful: *teamwork is more effective than one person trying to sort it out*: where involving the patient, *or at least give them an opportunity to have involvement if they want it*, was more commonplace. We heard about good examples of creative ways for AYA to tell their story and hence have the opportunity for greater involvement in all aspects of their care [68].

Having good team cohesion, respect for different experiences and clear communication were all described as essential factors in clinical ethics meetings. Trust, respect and open communication are essential elements of an effective team and are crucial when a team is faced with an ethical dilemma. Shared communication and an open dialogue were seen by all as the cornerstone of multi-professional working. Multi-professional working is the cornerstone of care delivery, within which professional roles should be clearly defined so that individual roles complement one another [69]. So that, "*it feels difficult to contradict a consultant who has led a discussion*" no longer presents a challenge to team members who *want to do the right thing*: what Pavlish et al. [23 p. 595] refer to as 'weighing risks of speaking up in hierarchal structures'. The importance of open dialogue within the clinical team was emphasised, where professionals from different disciplinary backgrounds can share their understandings of the family situation and contribute their opinions and have those opinions heard and respected in order to reach *interprofessional consensus decisions*.

A review of ethics consultations at St Jude Children's Hospital in the USA revealed religious concerns including refusal of care based on religious beliefs were more common when compared to similar reviews with adults [70]. In addition, consultations were more often prompted by distress arising from disagreements about a treatment plan or from inadequate clinician-family communication. Clinicians in this study frequently consulted on two main issues, when deliberating whether potentially burdensome treatments were truly in the patient's best interest and when deciding how to clarify the goals of care with a family when the prognosis was poor; these same issues were also mentioned by our respondents. A strong professional duty, similar to our respondents, was noted, to advocate for care goals that align most with the clinician's sense of what would be in the child's best interest [70]. Such reviews are helpful in understanding the purpose of ethics consultations, and confirming the reason for consultation depends on one's point of view and may be viewed quite differently by others involved [71]. A typology of case consultations developed by Gillam et al. [72] is helpful in informing our own reflections on what we might seek to take to an ethics consultation and certainly provides a summary on many of the themes examined in this chapter (see Box 32.1).

Box 32.1: Typology of Ethics Case Consultations

1. Parents disagree with recommendations of the treating team.
2. Adolescent/potential mature minor disagrees with recommendations of the treating team.
3. Child is resisting treatment.
4. Parents disagree with one another about treatment or management options.
5. Clinician is uncertain about the appropriateness of offering a particular treatment.
6. Clinicians and parents are both uncertain about the best way to proceed when a variety of options are available.

32.11 Reflections and Concluding Thoughts

Over the past several decades, changes have occurred that have altered the way that healthcare is both perceived and delivered. The availability of new health technologies, the increased consumer demand, cost improvement, cost efficiency, limited resources in healthcare, reconfiguration of services and the improved professional skill and knowledge competencies have all played their part in creating the complex and demanding workplace we work in today. The nature of AYA cancer care will continue to evolve; future challenges of technology, limited resources and service reconfiguration, although not known in detail, can be anticipated. Thus the clinical speciality will evolve and healthcare professionals will continue to specialise and narrow their field of practice to meet these ongoing demands. Ethical situations and conflicts will continue to arise as we are challenged to deliver individualised care in an increasingly complex environment.

It has been suggested that caring in ethically demanding situations can be facilitated through *presence*, *atmosphere*, *self-knowledge* and *time* [73]. Creating an effective ethical climate must include the availability of appropriate 'tools' and resources, such as formal or even informal ethics consultations and training [23]. The centrality of relationships between healthcare professionals was a theme running through the comments of all of our respondents. Specifically mentioned as facilitators to this were trust, mutual respect, open dialogue, professional competence in AYA care and intentional collaborations with AYA and their family members. Barriers were also mentioned, and in addition to the opposite of all the listed facilitators, we draw attention to understanding the shifting roles within families, professional differences within clinical teams and the often ambiguous interpretation of the law regarding those considered a minor (where age varies in different countries). Accommodating expertise of the multi-professional team, parental decisional authority and AYA emerging maturity and competence in decision-making would seem to be the key elements in any model of decision-making in AYA cancer care [74] that could mitigate ethical conflicts.

We all have a responsibility to ensure our own organisations seek ways to both document and improve how we promote the use of ethical principles in our decision-making and to facilitate team-based discussions on ethical dilemmas. Teamwork and recognition of when an impartial expert view might be required are essential, but ultimately we all require openness and the ability to value everyone's contributions to decisions. Young people have the right to *empowerment in making decisions* supported by full and *detailed explanation* of all treatment options and long-term effects of the disease enabling them to *actively influence their care* (http://www.canteen.org.nz/get-involved/international-charter-of-rights-for-young-people-with-cancer) [13]. We hope that with the help of our respondents, we have provided evidence of how we can uphold this right and provide equitable care to young people.

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33 Economic Evaluation in Adolescent and Young Adult Cancer: Methodological Considerations and the State of the Science

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Abstract

Despite the considerable prevalence and incidence of cancer cases among adolescents and young adults (AYAs) and a growing attention to the economics of cancer care, few studies have addressed the economic impact of cancer in AYAs. In this chapter we discuss four important aspects of cancer care economics as they pertain to the AYA population. We begin with an overview of the unique factors that contribute to cost and disease burden in cancer. This is followed by a discussion of health-related quality of life (HRQL) considerations in relation to economic analysis. We then describe types of economic analyses that provide estimates of costs and benefits, with benefits defined as improved survival and/or improved quality-adjusted survival. In the final section, we discuss how HRQL can be used to predict future clinical outcomes and healthcare utilization and, thus, expenditures. In the absence of a rich evidence base, we instead provide a guide to the reader as to how to create the data to support future science in this area.

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Adolescent and young adult (AYA) cancer patients and survivors – those who were between the ages of 15 and 39 at the time of their first cancer diagnosis – often experience substantial health and economic challenges. However, to date there is limited literature available concerning the health and economic impact of AYA cancer. Health challenges may stretch well beyond the initial phase of cancer treatment, with many survivors experiencing lasting and late effects of treatment and a range of other health conditions. The economic impact of cancer diagnosed in adolescence and young adulthood stretches beyond the healthcare system, impacting patients and their families, as well as their attainment of educational and vocational pursuits. As compared to adults without a history of cancer, patients and survivors are at risk for higher healthcare expenditures and greater productivity loss. Given developmental transitions during adolescence and young adulthood, a cancer diagnosis and its treatment could also have substantial effects on educational attainment and labor-force participation [1, 2]. However, AYAs have been underrepresented in the cancer treatment and survivorship literature, and as a result, substantial gaps remain in understanding the long-term consequences of cancer in this age group [3].

The main empirical study on the health and economic burden of AYA cancer was based on United States (US) national survey data by Guy et al. [4] which we draw on below. Guy et al. [4] used the 2008–2011 Medical Expenditure Panel Survey (MEPS), a nationally representative household survey that collects detailed information on demographic characteristics, healthcare expenditures, employment characteristics, and cancer diagnosis information including age at diagnosis. This compiled information allows for a comprehensive analysis of the economic burden of AYA cancer [5].

33.1 Burden of Illness

In 2011, 69,310 AYAs were diagnosed with cancer in the US [6]. Progress in recent decades has led to significant improvement in overall cancer survival rates, although the AYA population has experienced improvement to a much lesser degree than other age groups [7, 8]. Nevertheless, the population of AYA cancer survivors is growing. An estimated 634,000 AYA cancer survivors were alive in the United States in 2014 [9]. All cancer survivors are at risk for developing chronic health conditions from the chemotherapy, radiation, and surgery they received during treatment. However, given the timing of their diagnosis and treatment and the possible interruption of normal developmental processes, AYA cancer survivors also face unique medical, psychosocial, financial, and occupational challenges [1, 7, 10–12]. Medical care in the years following cancer treatment is particularly important: survivors need to be screened for late effects, such as secondary cancers, infertility, and cardiac conditions, so that these conditions can be detected and managed [13].

33.2 Medical Costs of Care

Medical costs of care are the costs associated with the medical care received, including physician visits, hospitalizations, surgery, radiation therapy, and chemotherapy. Costs are typically measured by examining the payments made to providers. The direct medical costs of AYA cancer include not only the costs of diagnosis and treatment of the disease, but also those associated with the treatment of cancer- and treatment-related lasting and late effects. For example, cost calculations include physician, nurse, and other staff salaries or fees, operating room time, equipment, pharmaceuticals, laboratory testing, laboratory staffing, other materials, and administration (operations, human resources, finance, etc.), among other things.

Cancer costs are typically reported as either *incidence costs* or *prevalence costs*. Incidence costs refer to costs for cancer patients diagnosed in a specific time period, while prevalence costs pertain to the cost for all individuals with a history of cancer in a specific year, regardless of when the initial diagnosis occurred [14]. For

example, an incidence cost estimate in 2014–2015 would only include individuals diagnosed within this period, while a prevalence cost estimate would include all individuals ever diagnosed and alive during 2014–2015 and include costs incurred during this period. From the perspective of measuring the overall burden of AYA cancer, prevalence costs are more useful. Alternatively, measurement of incidence cost can be used as a method to examine the economic burden of AYA cancer among newly diagnosed patients. An additional approach of cost assessment is known as the *phase-of-care* method. Phase-of-care cost analysis divides costs into clinically relevant periods or phases in relation to diagnosis and death (i.e., initial, continuing, and last year-of-life phases) [14]. Examining costs in the continuing phase could help identify costs associated with the lasting and late effects of treatment as well as costs of additional care for recurrent disease [14]. The identification of specific health services which are directly attributable to cancer or one of its myriad late effects can be very complex. For this reason, health service utilization (and associated costs) for individuals who have had cancer is commonly compared to age- and sex-matched individuals who have not had a cancer diagnosis.

Guy et al. [4] estimated direct medical costs among AYA cancer survivors using a prevalence-based approach. The study compared the annual medical expenditures among survivors of AYA cancers against those of individuals without a history of cancer, reporting overall expenditures and expenditures grouped by source of payment and service type. Survivors of AYA cancers had higher mean annual medical expenditures than individuals without a history of cancer. The per-person annual medical expenditures were $7,417 for AYA cancer survivors versus $4,247 for individuals without a history of cancer (Table 33.1). The largest sources of payment among survivors and individuals without a history of cancer were private health insurance and Medicare. Among survivors of AYA cancers, ambulatory care and inpatient care accounted for the largest share of medical expenditures.

33.2.1 Nonmedical Costs of Care

Nonmedical costs of care for AYA cancer patients include monetary losses associated with lost productivity from premature death (known as mortality costs), time lost from work due to long-term cancer- or treatment-related morbidity (known as morbidity costs), and time spent receiving cancer

Table 33.1 Per-person medical expenditures among survivors of AYA cancer and individuals without a history of cancer, the United States, 2008–2011

	Survivors of AYA cancer	No history of cancer	
	Adjusted expenditures [95% CI]	Adjusted expenditures [95% CI]	*p*-value
All sources of payment	$7,417 [6,133, 8,700]	$4,247 [4,142, 4,352]	<0.001
Source of payment			
Out of pocket	$765 [684, 846]	$686 [670, 701]	0.044
Private health insurance	$3,083 [2,312, 3,854]	$1,825 [1,758, 1,892]	<0.001
Medicare	$1,246 [898, 1,594]	$948 [901, 996]	0.051
Medicaid	$541 [361, 721]	$380 [342, 418]	0.056
Other	$876 [578, 1,174]	$411 [387, 435]	<0.001
Service type			
Ambulatory care	$2,409 [1,851, 2,968]	$1,376 [1,335, 1,417]	<0.001
Inpatient care	$1,605 [1,115, 2,096]	$1,169 [1,116, 1,221]	0.043
Prescription medications	$1,466 [1,241, 1,691]	$1,034 [970, 1,099]	<0.001
Other services	$820 [694, 946]	$686 [658, 714]	0.026

Adapted from: Guy et al. [4]

treatment [14]. Mortality costs evaluate the potential dollar value lost to society when an individual dies prematurely based on their age and projected income. It is important to note that mortality cost estimates are highly dependent on the approach used to quantify lost productivity after death. In contrast, morbidity cost can be appreciated as lost productivity due to disease, treatment, or late effects. To calculate morbidity costs, absences from work can be assigned dollar figures based on projected income. Morbidity cost may also be influenced by diminished volume or quality of work and reduced participation in household or educational endeavors. Finally, patients are burdened by time costs which may be highly variable as they account for the time allocated to care.

33.3 Mortality Costs

Mortality costs assess the potential dollar value lost to society when an individual dies prematurely. There are two common approaches for assessing the economic value of mortality loss. The *human capital* approach gives annual age- and sex-specific earnings data for each year of life lost, representing a figure that reflects loss of projected income. This creates an approach that directly applies more weight to higher earning years of life. The *willingness-to-pay* (WTP) approach, in contrast, uses survey data that assesses how much individuals would be willing to pay for an extra year of life at different ages and health states [15, 16]. A third, less commonly used approach, is the *friction cost method*, which takes the employer's (rather than the patient's) perspective on lost productivity. Using this method, time is only counted as lost until another employee takes over the patient's work [17]. These three methods can produce quite different results. The friction cost method will often result in a lower cost. The human capital and willingness-to-pay approaches will typically produce similar results in a young adult population, but tend to diverge (with the human capital approach producing lower costs) toward the end of adulthood [15]. Limited information exists on the mortality cost of AYA cancer.

33.4 Morbidity Costs

Cancer-related long-term morbidity can cause varying degrees of productivity loss. Also, depending on the type and severity of cancer-related morbidities, the economic implications may manifest in different ways. This logic justifies the broad array of existing metrics that economists may use to calculate the morbidity cost. While morbidity cost assessments are derived at least partially from estimates of lost work, morbidity cost analyses of wider breadth can also incorporate productivity loss in other realms, including education losses or inability to participate in household or routine practices.

33.4.1 Employment

There are several measures and indicators related to workplace productivity that can be useful in measuring the impact of AYA cancer and its treatment. At the simplest level, *rates of employment and unemployment* can be compared for survivors of cancer diagnosed in adolescence and young adulthood over time, relative to a population of individuals without a history of cancer. A meta-analysis of 36 studies found that cancer survivors were more likely than healthy control participants to be unemployed (33.8% vs. 15.2%; pooled relative risk [RR], 1.37; 95% confidence interval [CI], 1.21–1.55) [18].

Employment metrics can also address alternate measures of productivity loss that may offer the benefit of increased sensitivity to detect otherwise unappreciable outcomes. A simple example of this is evaluating work intensity, either by examining the proportion of the employed population who work *full time* versus *part time* or calculating and comparing *average hours worked per week* [19]. Another commonly used measure is *employment disability* (being unable to work due to health limitations).

Some of the more granular metrics used to evaluate productivity loss in the workplace account for changes that are not outwardly reflected in employment status. A particularly useful example of these measures is *absenteeism* (missed time from work). Cancer has also been reported as a causative factor in *presenteeism* – working while disabled from a mental or physical illness [20]. The economic consequences of presenteeism have been reported as being even greater than those attributed to absenteeism [21]. In their review on the impact of cancer on employment, Steiner et al. also suggest examining changes to work role and content that may occur as a result of cancer and its treatment [19]. Metrics that have been used to assess this outcome include *change in employer*; *change in work type*, *duties*, *or skill*; *and change in work productivity*, among others.

In the most comprehensive empirical study on the health and economic burden of AYA cancer to date, Guy et al. (2014) measured morbidity costs among AYA cancer survivors [4]. Among survivors of AYA cancers, total annual per capita lost productivity was $4,564, compared with $2,314 among individuals without a history of cancer (Table 33.2). Productivity loss resulting from employment disability accounted for the largest portion of total productivity loss. Survivors of AYA cancers were more likely to report employment disability and an increased number of missed work days as a result of illness or injury.

33.4.2 Education

Educational metrics can be valuable tools for examining the economic burden of AYA cancer, as they can be directly indicative of economic well-being. The most commonly used (and accessible) metrics in this class are *educational enrollment* and *completion rates*: rates of enrollment and completion of high school, college, university (including advanced degrees), and vocational and technical schooling. The literature to date reveals limited analyses of educational outcomes in patients afflicted by a cancer diagnosis between the ages of 18 and 39. Dieluweit et al. in a German study reported that survivors of adolescent cancers generally achieve higher educational and vocational levels than individuals who do not have a history of cancer; however, those survivors who have neurophysiological late effects are at heightened risk for failing to graduate from college [22]. There are several studies that have examined similar outcomes in childhood cancer survivors (e.g., [23, 24]). Most of these studies conclude that specific subsets of the childhood cancer population (typically those with tumors or treatment affecting the central nervous system) are at heightened risk for failing to graduate from high school and have lower rates of postsecondary school entrance and employment [24].

33.4.3 Other Morbidity Costs

Burdens faced by AYA patients are not isolated to educational and employment domains. Risk of acute or late effects of treatment and continued long-term surveillance can cause strain in other dimensions of daily living that may reduce economic potential. It is easy to conceptualize the ability of a cancer diagnosis in the AYA age range to yield a breadth of economic consequences, but again, literature is sparse to date. Guy et al. [4], referenced above, demonstrated that survivors of AYA cancers were more likely to report increased *lost household productivity* (inability to complete household work due to health limitations) when compared to individuals without a history of cancer. The increased loss of household productivity contributed significantly to total per capita productivity loss, along with employment disability and absenteeism (Table 33.2).

In the same study, Guy and colleagues examined a variety of measures to evaluate limitations among AYA cancer survivors relative to a population without a history of cancer. Measures included limitations in work, housework, or school, being completely unable to do activities (work at a job, do housework, or go to school), cognitive limitations, and limitations in physical functioning [4]. Survivors of AYA cancers were

Table 33.2 Adjusted per-person lost productivity among survivors of AYA cancer and individuals without a history of cancer, United States, 2008–2011

	Survivors of AYA cancer	No history of cancer	
	Adjusted productivity loss [95 % CI]	Adjusted productivity loss [95 % CI]	*p*-value
Total per capita total productivity loss	$4,564 [3,740, 5,387]	$2,314 [2,196, 2,432]	<0.001
Employment disability	$3,645 [3,051, 4,238]	$1,828 [1,735, 1,921]	<0.001
Absenteeism	$500 [398, 603]	$329 [316, 342]	<0.001
Lost household productivity	$419 [291, 546]	$157 [145, 169]	<0.001

Adapted from: Guy et al. [4]

less likely to be employed and more likely to report limitations in work, housework, or school, cognitive limitations, limitations in physical functioning, and being completely unable to do activities compared to individuals without a history of cancer (Table 33.3). Among individuals not working, survivors of AYA cancers were more likely to report being unable to work because of illness or disability.

33.5 Time Costs

Patient and caregiver time costs account for the time spent by patients and caregivers traveling to and from treatment and follow-up care and time spent waiting for and receiving care. However, this information is not routinely collected. Time cost estimates can be calculated among patients and caregivers by combining the time spent receiving care or providing assistance with the human capita approach, willingness-to-pay method [14], or the friction cost [17] estimates of the value of that time. Although patient and caregiver time costs have been estimated among cancer survivors of all ages [25], limited information exists among AYA cancer survivors.

33.6 Methods for Economic Evaluation

The evaluation of medical interventions necessarily involves review of clinical outcomes and effectiveness. However, mounting healthcare costs and the associated strain imposed on patients, payers, and society has stimulated active consideration of the economic consequences of medical interventions. There is a range of economic evaluation tools for this purpose, each of which provides different types of information and requires different data and assumptions.

Economic evaluation of a healthcare intervention is founded on the premise that resources are finite and hence that using one diagnostic or therapeutic approach diverts resources away from others and perhaps from other health conditions. Each economic evaluation tool sheds light on whether diverting resources to the particular approach in question is, on balance, "efficient," meaning that it improves population health relative to targeting resources to an alternative therapy or strategy. Efficiency is, of course, only one consideration in healthcare decision-making. Other factors may include, for example, equity and budget impact (affordability). However, understanding how efficiently resources are being allocated is a primary element of any healthcare cost analysis.

The following discussion reviews three approaches to cost evaluation in medical interventions: cost minimization analysis, cost-effectiveness analysis, and cost-benefit analysis. A cost minimization analysis compares the cost of two interventions that confer the same clinical benefits (e.g., two programs that each prevents the same number of breast cancer cases in similar populations). A cost-effectiveness analysis relaxes the requirement that the compared interventions confer equivalent clinical benefits. Finally, cost-benefit analysis assesses an intervention's cost and clinical benefits, all measured

Table 33.3 Employment and functional limitations of survivors of AYA cancer and individuals without a history of cancer, United States, 2008–2011

	Survivors of AYA cancer	No history of cancer	
	%	%	*p*-value
Employment			
Not employed	33.4	27.4	<0.001
Reason for not working			
Could not find work	20.7	21.8	0.621
Retired	41.0	44.9	0.026
Unable to work because of illness/ disability	34.1	23.9	<0.001
Maternity/paternity leave	2.3	1.2	0.049
Going to school	7.6	9.2	0.237
Taking care of home or family	16.5	17.3	0.649
Other	6.3	6.1	0.904
Never worked for pay	7.5	8.4	0.389
Functional limitations			
Any limitation in work, housework, or school	17.0	10.5	<0.001
Completely unable to do activities	11.9	6.7	<0.001
Cognitive limitation	11.1	5.7	<0.001
Limitations in physical functioning	20.8	14.6	<0.001

Adapted from: Guy et al. [4]

in dollars, without reference to another health intervention. In short, cost-benefit analysis assesses the worth of a medical intervention relative to non-health alternative expenditure options.

In all cases, the analyst must select a perspective that determines which costs will be included. Common perspectives include (1) the patient and the patient's family (including patient co-payments, which can be substantial in the case of certain medications, and time spent by family members caring for the patient); (2) the healthcare system (including both health delivery institutions and healthcare payers, such as private insurance companies and public programs like Medicare and Medicaid); and (3) societal (all costs, including those just described, and others, such as productivity losses absorbed by employers and workers).

The perspective of an analysis can influence its results. For example, consider an intervention that shifts care away from formal institutions and increases the amount of care provided by a patient's family members. That intervention could appear to increase costs from the patient/patient family perspective, decrease costs from the healthcare system perspective, and perhaps show relatively little change in costs when assessed from the societal perspective.

Which perspective is most appropriate depends on the purpose of the analysis and its audience. Economists favor the societal perspective because it helps to identify interventions that are optimal in some global sense, whereas narrower perspectives are vulnerable to crediting interventions that merely shift costs away from one party to another. On the other hand, the societal perspective arguably suffers from a lack of relevance, at least in the US, because in this country, there is no "societal decision-maker" allocating all of society's healthcare resources. Instead, it may make sense to assess an intervention's impact from the healthcare perspective (e.g., if the analysis audience is payers) or from the patient/family perspective if the goal is to determine what burden alternatives impose on those most personally involved. Indeed all three perspectives have important roles to play, and the societal perspective has the potential to inform decisions made by agencies such as Medicare and Medicaid.

33.6.1 Cost Minimization Analysis

Because a cost minimization analysis limits attention to differences in cost among interventions, it is appropriate only when the decision-maker is not concerned with differences in clinical implications or when the differences in clinical impacts are minimal. For example, Green et al. [26] compared 6-month and 15-month treatments for children with Wilms tumor. The two groups did not differ significantly in terms of a 4-year relapse-free survival, the key clinical outcome. As a result, the relevant comparison was the difference in costs.

Drummond et al. [27] outline considerations for cost minimization analysis. A prime concern is cost assigned to medical services. That is because the amount charged may not correspond to the value of the resources consumed. One situation in which this occurs is when the difference between charges and costs is a monopoly profit for the provider of the services (i.e., a profit exceeding the normal rate of return earned in a competitive market). Whether the funds covering profit are a "cost" depends on the analytic perspective. From a societal perspective, monopoly profits represent a transfer, not an expenditure (and loss) of resources. That is because the cost imposed on the payer (in this case the patient) corresponds directly to the gain accrued by the service provider. Hence, the monopoly profit is a "wash." For an analysis conducted from the patient perspective, payment covering "profit" is properly considered a cost.

Several other considerations are particularly relevant for diseases that have long-term impacts, like cancers affecting AYAs. First, how the time of family and caregivers is valued can influence the results. Time can be valued based on wage rates or on the value people place on their leisure.

Second, cost estimates depend on the analytic "time horizon." Although clinical trial study outcomes may extend for a relatively limited period due to short-term follow-up, treatment impacts can extend for many years into the future. Such impacts can include morbidity associated with cancer treatments. It can also be reflected in reduced survival for cancer survivors. The analyst therefore faces a trade-off between limiting attention to empirically measured outcomes that omit relevant long-term impacts and estimating long-term impacts without the benefit of empirical data.

Whichever outcomes are included, future impacts should be discounted to reflect time preference. In brief, a cost incurred in the future has a lower "present value" than the same nominal cost incurred sooner. The present value of a cost C incurred n years in the future is $\frac{C}{(1+r)^n}$, where r is the annual discount rate (a value of 3 % is common) [28]. The impact of discounting can be substantial for analyses with time horizons of a decade or more, making this issue relevant in the case of AYAs. For example, at an annual rate of 3 %, discounting depresses the value of a cost incurred 30 years in the future by a factor of 2.4.

Third, the cost of a technology can change substantially over its life cycle because of rules governing patent protection [29]. In the US, manufacturers are often given a period during which they have the exclusive right to sell their product. That period is designed to allow manufacturers to recapture their research and development costs, but it means that drug prices are often substantially higher than they are following expiration of the patent and the introduction of competition by producers of generic versions of the drug. Hence, from the patient and healthcare payer perspectives, costs can change substantially over time. Average costs over a product's lifecycle are somewhere between these two extremes.

Finally, depending on the perspective, nonhealthcare costs can represent an important component of a disease's overall costs. In the context of diseases affecting AYAs, productivity losses associated with disease can be particularly salient.

Productivity costs are relevant for societal analyses. They can also be relevant to patients to the extent that individuals lose wages because they cannot work. Companies that self-insure and can therefore be classified as "payers" can also be affected by the health conditions that impinge on worker productivity.

33.6.2 Cost-Effectiveness Analysis

A cost-effectiveness analysis compares interventions in terms of the "cost-effectiveness ratio," which is the intervention's added costs divided by its added health benefits. Calculation of the cost-effectiveness ratio requires estimation of health benefits, but that added information means that cost-effectiveness analysis can compare interventions that differ not just in terms of cost but also in terms of health effects.

Cost-effectiveness analysis is subject to the following considerations. First, the ratio depends on the target intervention to which the intervention is compared. The comparator could be "no treatment" (which is typically of limited relevance), or it could be an existing standard of care regimen. Relative to no treatment, an intervention's incremental health benefits can be substantially greater than when the same intervention is compared to an existing treatment. Whether the incremental costs differ as much as the incremental benefits depends on how costly the standard of care is.

Second, it is possible for the incremental cost (the ratio's numerator) to be negative, implying that the intervention reduces costs. That can happen when an intervention reduces utilization of more expensive downstream services. It is also possible for incremental health to be negative, meaning that the intervention, on net, makes health worse. That can happen if, for example, the impact of an intervention's side effects exceeds its therapeutic benefits.

Finally, cost-effectiveness analysis can be customized to characterize value for a particular therapy by appropriately defining the health benefits. For example, for a cancer screening intervention, benefits might be defined as the number of cancer cases prevented. Tailoring the benefits to the disease and intervention under investigation helps to make the resulting ratio more salient and intuitive. Tailoring the outcome measure in this way, however, also limits the ratio's usefulness because it can make it impossible to compare directly interventions that have different effects. For example, it is not possible to compare an intervention that costs $100,000 per myocardial infarction prevented to another that costs $150,000 per case of leukemia prevented. Cost-utility analysis, which we now turn to, addresses this limitation.

33.6.3 Cost-Utility Analysis

Cost-utility analysis is best thought of as a cost-effectiveness analysis that quantifies benefits in terms of "quality-adjusted life years" (QALYs) saved. QALYs were developed to characterize health benefits in terms of a "common metric" [30]. QALYs reflect both longevity and health-related quality of life (HRQL), meaning freedom from pain and normal ability to engage in regular activities. Individuals gain one QALY for each year they live in a (hypothetical) state of "perfect health." They can also gain a QALY by living *more* than 1 year in less than perfect health. Hence, each year lived with an adverse health condition is worth less than one QALY. A health condition's "utility weight" refers to the annual QALY gain experienced by an individual living with that condition. More severe conditions have lower utility weights. Being dead has, by convention, a utility weight of zero. In short, a health intervention can save QALYs by extending survival, improving HRQL (and hence increasing QALYs accrued per year), or some combination of both.

Because utility weights can and have been estimated for a wide range of health conditions, cost-utility analysis can be used to evaluate and compare a large number of health interventions. Greenberg et al. [31] identified 242 cancer-focused cost-utility analyses published through 2008 and cataloged in the Tufts Medical Center Cost-Effectiveness Analysis Registry. The median cost-effectiveness ratios (2008 US dollars) by cancer category were $27,000/QALY (breast cancer), $22,000/QALY (colorectal cancer), $34,500/QALY (prostate cancer), $32,000/QALY (lung cancer), and $48,000 (hematologic cancers).

The QALY metric facilitates comparisons across disparate disease and health conditions, but it also necessitates additional assumptions – most notably, the estimated utility weight for each

health condition. Weights can be estimated by administering questionnaires to determine the trade-offs individuals are willing to make between longevity and diminished HRQL. QALYs can be estimated using those weights that reflect the preference of the population with the disease in question. But eliciting preferences from the affected population is not always feasible. Instead, preferences may be elicited from proxies (e.g., parents can serve as proxies to assess conditions affecting children), medical professionals, or the general population without the disease in question.

Alternatively, utility weights can be derived from standardized indexes that rate health conditions along several dimensions. For example, the EQ-5D measure has five dimensions (or domains) of health status – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each of which is rated as "no problems," "some problems," and "extreme problems." EQ-5D is used by the UK's National Health Service to derive utility weights for a wide range of conditions. Standardized indexes can be more readily used than direct elicitation approaches because they do not involve eliciting preferences from a sample of respondents. But these scales may not account for or be sensitive to the particular aspects of the health condition. The EQ-5D accounts for some of the condition attributes associated with cancer, but it may only indirectly address others, such as fatigue. Moreover, the 3-point rating scale may have insufficient granularity to characterize the impact of various therapies. EQ-5D is one of a family of generic preference-based measures that are frequently used to generate the utility scores used as weights in estimating QALYs. Other generic preference-based measures that are widely used in cost-utility studies include the Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3) [32, 33], the Quality of Well-Being Scale [34], and the Short-Form 6D based on the Short-Form 36 and Short-Form 12 Questionnaires [35, 36]. The scoring functions for each of these measures are based on preferences elicited from the general population, reflecting community values (societal viewpoint), an attribute favored by a number of regulatory authorities.

The 2010 review by Greenberg et al. [31] of 242 cancer cost-utility analyses published through 2008 and cataloged in the Tufts Cost-Effectiveness Analysis Registry identified six articles that evaluated interventions to address cervical cancer in AYAs. Table 33.4 shows selected cost-effectiveness ratios from these studies. Table 33.5 lists selected ratios from two other articles that addressed treatment of hematologic diseases in AYAs. It is likely that other analyses have been published since this review was conducted, as the number of cost-utility articles published each year has grown substantially over the last 10 years [28].

While cost-effectiveness tables facilitate value comparisons across interventions and diseases, they cannot answer a fundamental question – namely, which interventions are worthwhile? Or equivalently, how low must the cost-effectiveness ratio be to warrant an intervention's cost? In other words, what is an acceptable "price" for a QALY? This question is fundamentally difficult to answer because QALYs are not explicitly bought and sold in markets, the typical mechanism for establishing values for goods and services. In the United States, $50,000 per QALY has conventionally been advanced as a benchmark for good value, although more recently, some have suggested this value should be $100,000–150,000 per QALY [37]. The topic is controversial, however, with work in the UK suggesting that at least in that country, interventions should be regarded as "good value for the money" only if the cost-effectiveness ratio is more favorable than 13,000 lb (around $20,000) per QALY [38].

33.6.4 Cost-Benefit Analysis

Cost-benefit analysis assesses interventions by comparing their costs to the monetized value of their benefits. A key advantage of this approach is that it obviates the need for identifying the value of a QALY or some other health benefits.

However, the value of health outcomes must be monetized – i.e., assigned a monetary value. That step can raise objections because it can be interpreted as implying that health outcomes are no dif-

Table 33.4 Cost-effectiveness analyses for cancer of the cervix uteri

Description	2008 US$/QALY	References
Human papillomavirus (HPV) vaccination of females at age 12 versus no vaccination in Mexican population ages 12 and over	3,000	[75]
Human papillomavirus (HPV) vaccination of males and females at age 12, with a temporary 5-year catch-up program for females ages 12–24 versus human papillomavirus (HPV) vaccination of females at age 12, with a temporary 5-year catch-up program for females ages 12–24 in Mexican population ages 12 and over	19,000	[75]
HPV vaccines and screening every 5 years starting at age 30 versus no vaccination, conventional screening every 5 years starting at age 25 in adolescent girls	21,000	[76]
Universal vaccination against high-risk human papillomavirus (HPV) infection versus no vaccination in hypothetical cohort of 12-year-old girls in the United States	28,000	[77]
Penta-annual PAP smear versus current scenario in Israeli women aged 20–65	30,000	[78]
Pap test every 2 years until the age of 100 versus Pap test every 2 years until the age of 75 in Hypothetical cohort of US women – age 20	71,000	[79]
HPV vaccines at age 12, triennial screening starting at age 25 versus vaccination and screening every 5 years starting at age 21 in adolescent girls – age 12+	70,000	[76]
Three doses of human papillomavirus vaccine versus current scenario in Israeli women aged 12, in their school setting	85,000	[78]

ferent from other goods and services that can be valued in terms of money. The dominance of cost-effectiveness analysis over cost-benefit analysis as the most common health economic evaluation methodology is consistent with a sense "that the fulfillment of health needs should be exempt from direct competition with other claims on resources, and that health cannot be measured with the same currency as other goods or services" (p. 27) [39]. Monetization of health benefits introduces other ethical complications by inviting the inclusion of economic impacts that may not be appropriate. For example, including labor productivity in the calculation of therapeutic benefit value can penalize individuals whose prospect for future employment is inherently limited (e.g., the elderly or people with severe physical limitations).

On the other hand, relying on QALYs as the "common currency" introduces its own ethical dilemmas. By accounting for longevity, QALYs place a higher value on avoiding deaths among individuals with the highest additional life expectancy. This issue can have implications for individuals whose life expectancy has been compromised by therapies with side effects. On the other hand, use of QALYs can help to highlight the value of innovation that replaces life-shortening therapies with therapies that better preserve normal life expectancy.

Finally, monetization of health benefits presents methodological challenges. The absence of markets where health benefits are explicitly traded means that values for these outcomes must be indirectly inferred. Two approaches dominate the literature. The first, expressed preference elicitation, uses survey methods to ask respondents to report the value they place on various outcomes. The hypothetical nature of the questions asked is the main limitation of this approach since it contributes to the tendency of respondents to overstate what they would be willing to pay for various health benefits [40].

A second approach, often referred to as revealed preference elicitation, avoids the limitations associated with the hypothetical nature of the stated preference scenarios. Instead, revealed preference techniques estimate the implicit value individuals place on health when deciding among jobs (with different health risks) or purchases with health or safety implications (e.g., car purchases). These techniques assume that decisions are well informed and consistent with preferences. This assumption is open to question given that, in many cases, it is unlikely that many

Table 33.5 Cost-effectiveness analyses for hematologic malignancies

Description	2008 US$/QALY	References
Laparotomy and tailored treatment versus mantle and para-aortic splenic radiation therapy in 25 year-old patients with early-stage Hodgkin's disease	31,000	[80]
Combined modality therapy, no laparotomy versus laparotomy in 25 year-old patients with early-stage Hodgkin's disease	95,000	[80]
Autologous bone marrow transplantation versus five additional courses of CHOP chemotherapy in patients between 15 and 60 years old with non-Hodgkin's lymphoma of intermediate- or high-grade malignancy stages II–IV who were partial responders to initial three courses of CHOP	Increases costs and makes health worse	[81]

people are even aware of the magnitude of the risks they are trading off.

33.7 Using Preference-Based Measures and Decision Aids to Improve Shared Decision-Making

AYA patients with cancer face a series of difficult and challenging decisions about treatment modalities and treatment intensity. These choices, made in conjunction with their clinicians, can affect the chances of survival, relapse, and both major and minor sequelae. What follows is a speculative argument that preference-based (utility) measures have the potential to play an important role in such decision-making.

33.7.1 The Decision Problem

Clinicians are experts on the health status production function, the identification of treatment options, and likelihood of various outcomes. Patients (and family members) are experts in the values that they attached both to the processes of treatment and potential outcomes [41]. Of course, the epidemiologic evidence in AYA cancer is often less complete than the evidence both in adult and pediatric oncology. One remedy to this problem is the prospective routine use of HRQL assessments both during treatment and throughout survivorship care [42–44]. Over time evidence on the HRQL of the treatment process and long-term outcomes will accumulate, providing clinicians and future patients with valuable information on what to expect.

Given the prominent trade-offs in many treatments for AYA cancers between enhancing the probability of survival but with accompanying higher risks of future sequelae (heart disease, breast cancer, infertility, etc.), there is the potential to improve shared decision-making by developing and evaluating some kind of decision aids [45–48]. Decision aids have been developed in a number of clinical contexts including adjuvant therapy for breast cancer, prostate cancer, and hormone replacement therapy for menopause. Many of these aids display the advantages and disadvantages of the relevant choices.

In a systematic review of 55 randomized controlled trials used to evaluate decision aids, O'Connor et al. [48] found that, relative to standard practice, the use of decision aids increased patient participation in decision-making, improved patient knowledge, reduced decisional conflict, produced more realistic expectations, and reduced the proportion of patients who were undecided. The use of decision aids was not, however, systematically associated with improved satisfaction with the decision process, health outcomes, or the choice of treatments. Developing such an aid has the potential to improve decision-making in AYA cancer.

More ambitiously, a decision tree aid could be created. A decision tree would combine information on the advantages and disadvantages of various treatment choices and with the probabilities of the outcomes. The preference that the patient attaches to the various health states associated with treatment and long-term outcomes could then be elicited. (See Feeny [49] for several examples of decision aids and trees.) Clinicians would provide information on the probabilities; patients would provide informa-

tion on the value attached to the health states and the expected utility of various alternatives could be explored. This information could then inform patient-clinician deliberations about the best course of action for that patient, taking account of the values of the patient as well as the risks that that patient faces.

33.7.2 The Feasibility of Eliciting and Using Utility Scores

The evidence on the ability of adolescents to participate in preference-elicitation interviews and provide valid data is limited. Juniper et al. [50] in a study of children with asthma found that children 12 years of age or older (Grade 6 reading level) were readily able to provide meaningful data. The pediatric patients in the study had typically been dealing with asthma for some time and thus had become familiar with the effects of asthma and its treatment on their HRQL. These results imply that, in general, it should be possible to collect meaningful data in the context of AYA cancer.

But are preference scores stable over time? Saigal et al. [51] examined the stability of preference scores for five hypothetical health states describing the range of health outcomes experienced by children who survived very low birthweight. Saigal et al. [51] enrolled two cohorts of women: a group of high-risk pregnancy women who might have to face the challenges of giving birth to a child with low birthweight (mean age 31 years; interviewed at 24 weeks of gestation, 1 week after delivery, and at the child's 12-month corrected age) and women with very low birthweight newborns (mean age 29 years, interviewed 1 week after delivery and at the child's 12-month corrected age). Results from the multivariate repeated measures analysis of variance indicated stability in the utility scores for the five health states; these results are consistent with results from other studies. Clearly the evidence on the stability of utility scores is not extensive, but it is interesting that late 20- and early 30-year-olds, within the AYA age range, appeared to have stable preferences for health states.

Yet the stability of preferences for the health states of children seen in the Saigal et al. [51] study might not generalize fully to the decision-making context for AYAs with cancer. The women in the Saigal et al. [51] study were, for the most part, involved in a situation in which they had had the opportunity to think seriously about the possible range of health outcomes for children of low birthweight. Further, these women were, for the most part, older than many young adult AYA patients and therefore typically had more life experience upon which to draw in formulating their valuation of the various potential health outcomes.

For many, if not most, AYA cancer patients, the diagnosis of cancer represents their first serious health problem. Typically, these patients have had less life experience on which to draw in formulating their valuations. Ratcliffe et al. [52] reported that adolescents attached more importance to mental health than physical health when compared to adults who evaluated the same health states. At the risk of over-interpreting these results, it may be that many, if not most, adolescents had already had experience with mental health problems but had not yet experienced many physical health limitations, so therefore placed a greater weight on mental than physical health. Yet the challenges likely to face AYA patients will involve both mental and physical health issues as well as a host of potentially far-reaching issues such as infertility.

Of course, even though AYA patients may have generally been in good health up to the time of their diagnosis, they may have had the opportunity to observe family members dealing with health problems. It may be useful to examine the extent to which family health history (relatives who had breast cancer or heart disease) is associated with the preference scores provided by AYA patients.

An important limitation to the decision tree approach outlined here is that many decisions are typically made following the receipt of a diagnosis and before many patients have experienced the effects of treatment or have had the opportunity to learn about the likely future health states that they would be experiencing and think about

the value that they would attach to those health states. Careful iterative counseling is likely to be important.

It would also be useful to compare the preferences of AYA patients to community preferences. Community preferences are embedded in the scoring functions of major generic preference-based measures of HRQL such as the EQ-5D-3L [53] and Health Utilities Index Mark 3 [54]. If as a group AYA patients have preferences similar to the broader general population, then for group-level analyses, these generic preference-based measures would be more applicable.

In pilot studies to examine the effectiveness of preference-based shared decision-making (or, more generally, various potential types of decision aids), it will be important to examine the stability of preferences for various prominent hypothetical health outcomes. It will also be important to assess HRQL frequently so that the trajectory of the HRQL experienced can be described accurately. A better understanding of the HRQL burden of cancer treatments has often been the stimulus in the search for less toxic treatments with fewer sequelae.

The use of preference-based measures of HRQL to monitor patients as they undergo treatment as well as in long-term follow-up will provide important information that can be used to improve practice. The creation and evaluation of decision aids and decision trees, in conjunction with the elicitation of the preferences of patients for the health states that they are in or might experience, have the potential to importantly improve the quality of care in AYA cancer.

33.8 Health-Related Quality of Life (HRQL) Measures as Predictors of Utilization and Survival

Within the field of clinical research, including cancer research among AYA patients, HRQL, as discussed in Chap. 30 by Klassen et al., is considered an important clinical outcome in itself. However, HRQL can also serve as a predictor of future outcomes of interest. There is considerable literature indicating that HRQL measures, controlling for sociodemographic and major clinical factors, are predictive of clinical events and even survival. Additionally, HRQL measures have been shown to predict healthcare utilization, controlling for the same factors. Of note, most of the literature on this topic is on adults rather than AYAs.

In this section, we review studies on all age groups. Given the paucity of literature in the cancer field on HRQL predicting healthcare utilization, we also reviewed studies of the general population and other disease areas. We then discuss issues regarding collecting HRQL data, including time, rater, HRQL measures, and domains. In addition, we discuss conclusions and implications of the relationship between HRQL and clinical outcomes and healthcare utilization, including identification of at-risk groups who would benefit from proactive interaction and possible risk stratification for treatment.

33.8.1 Pediatric and AYA Literature

Among studies exploring how HRQL and outcomes are related in pediatric and AYA populations, only one specifically looked at a population of cancer patients [55]. In this study of 274 patients up to the age of 18 years who had undergone a hematopoietic stem cell transplant [55, 56], Terrin et al. evaluated the ability of HRQL to predict transplant-related mortality, using joint modeling. They found that a half standard deviation increase in emotional, physical, and role functioning and global HRQL were associated with decreased hazards ranging from 30 to 46 %, after adjustment for baseline sociodemographic and clinical characteristics.

Other literature concerning the predictive value of HRQL in clinical and health utility outcomes among AYA or pediatric populations included a general population of 317 children aged 2–18 years, enrolled in a California Medicaid managed care plan, by Seid et al. [57] and 112 children aged 7–18 years old who were diagnosed with inflammatory bowel disease (IBD), reported by Ryan et al. [58]. The Seid

study assessed healthcare cost for a general population of children enrolled in a managed care plan, on the basis of health plan utilization claims and encounters. This analysis demonstrated a significant association between HRQL and variance of healthcare costs over 6, 12, and 24 months. Additionally, the group identified a high-risk group of patients, based on low physical functioning scores, citing the staggeringly disproportionate healthcare costs that emerged from this stratification.

In the Ryan study, HRQL was a significant predictor of a range of utilization outcomes, including a number of IBD-related hospital admissions, gastroenterology clinic visits, emergency department visits, psychology clinic visits, telephone contacts, and pain management referrals.

HRQL measures and domains varied by study with the Pediatric Quality of Life Inventory (PedsQL 4.0) used in both noncancer population studies [57, 58] and the Child Health Ratings Inventories (CHRIs)-General in the pediatric transplant study [55]. Domains of HRQL that were associated with either clinical events or healthcare utilization included physical functioning, role functioning, emotional functioning, global or overall HRQL, and general health. All studies which included participants less than 18 years old relied on parent-proxy report of HRQL.

HRQL scores are an appealing predictor of clinical outcomes and healthcare utilization because they provide information that exceeds what is available from clinical or sociodemographic factors. To demonstrate the predictive quality of HRQL scores, all three studies adjusted for a combination of factors. Sociodemographic variables included age, gender, race/ethnicity, marital status, education, income, and insurance, while clinical variables included illness duration, disease type or subtype, depression severity, disease severity, chronic condition status, and treatment type. It should be noted that some studies showed attenuation of the relationship between HRQL and clinical outcomes or healthcare utilization after adjustment for sociodemographic and clinical factors. However, the relationships remained significant and the models explained more variance in the outcome.

33.8.2 Adult Literature

In general, literature concerning HRQL as a predictive factor is more robust in the adult cancer population. The body of literature which links HRQL to clinical outcomes, especially survival, in the adult cancer population [59–65] is much more well developed compared to either children or AYAs, as illustrated by the existence of both a meta-analysis [63] and review article [64]. Adult studies either addressed patient populations with single cancers, most commonly lung or breast, or a variety of different cancer types.

However, studies that link HRQL to healthcare utilization are scarce in adult cancer populations. There is some established evidence of a relationship between HRQL and healthcare utilization in the general population.

Within the adult cancer studies, common HRQL measures included different versions of the Functional Assessment of Cancer Therapy (FACT) [63, 64] and the European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) [63, 64]. Predictive domains identified in the Quinten et al. meta-analysis included physical functioning, pain, and appetite loss. In addition to these commonly predictive domains, individual studies have identified a wide variety of HRQL domains that are predictive of clinical outcomes and utilization.

Similar to the pediatric and AYA cancer studies, the most common clinical outcome in the adult cancer literature was survival. In all adult studies, at least some domain of HRQL was able to predict survival. Surprisingly, mortality could be predicted as far as 9 years after HRQL assessment in some studies [61, 66]. The Quinten et al. [63] meta-analysis found domains of HRQL provided significant prognostic information in addition to age, sex, and distant metastases and improved predictive accuracy of survival relative to sociodemographic and clinical factors alone. The Gotay et al. [64] study has similar findings that HRQL was predictive of survival even after adjustment with such clinical variables as performance status, treatment, cancer stage, weight loss, and serum markers.

Review of the literature demonstrated no studies addressing the relationship of HRQL to healthcare utilization in the adult cancer population, but a few studies examined the general population [67–69], including primary care patients [67] or representative samples of Canadians responding to a health survey [68, 69]. One study found that HRQL, severity of illness, and diagnoses were all predictive of health service charges and that combining all of these factors into the same model accounted for the most variability in charges [67]. The Health Utilities Index (HUI) was used in the two Canadian studies and was found to be associated with overall health costs and total number of visits to health practitioners during that fiscal year [68] and the use of general practitioner services, specialist services, and hospital stays during a 12-month period [69]. These findings were present even after adjustment for demographic (e.g., age, sex) and clinical (e.g., chronic conditions) factors. Interestingly, Lima et al. [68] also stratified respondents by age and determined that the effect of HUI was significantly stronger in persons younger than 45, alluding to greater predictive potential for HRQL in younger adults. The Kephart et al. [69] study also found that a single item of self-perceived health was predictive of utilization as well.

33.8.3 Considerations When Collecting HRQL

When using HRQL to predict clinical events or utilization among children or AYAs with cancer, several factors should be considered. First, the appropriate interval for HRQL assessment and prediction of clinical outcomes or utilization should reflect the clinical course of the cancer type, the treatment regimen, and the sensitivity of the tool. Future research may be needed to identify this interval, which is likely to vary with disease stage or disease course. Consider, for instance, the illustrative range of time at which HRQL has been shown to have predictive power. Studies to date have demonstrated HRQL to be predictive of events or utilization just 1 month after assessment [60] or nearly a decade after assessment [61, 66].

Another factor to consider when collecting HRQL is whether self-report and/or parent-proxy report should be used. When collecting HRQL on pediatric cancer populations, it is often recommended that both child and parent raters be included as each may offer different perspectives [70, 71]. However, many AYA patients may live and function independently of a parent proxy, prompting self-report only to be a more feasible assessment option. Conversely, in the case of adolescents transitioning into adulthood, parents may still be heavily involved in helping make healthcare decisions, and their proxy ratings of HRQL may provide meaningful information above the AYA self-report when predicting healthcare utilization. It should be noted, however, that while a number of the generic preference-based measures such as the HUI 2/3 are not suitable for very young children, these measures are suitable for assessing HRQL both in children and adults, providing for more continuity in assessments of HRQL over time.

Furthermore, there is a wide array of HRQL measures and domains available for use with AYAs. Many measures were either developed for pediatric populations (<18 years old) or adult populations (≥18 years old). Any of these HRQL measures could be used, but attention should be paid to the appropriate age range of respondents. Additionally, the development of measures, or the use of existing adult and pediatric measures, that span the age of AYAs may be warranted. Based on the studies presented here, the domain of physical health, including functioning, well-being, pain, and symptoms, was the most commonly associated with clinical events or healthcare utilization. Global or total HRQL scores, as well as single general health items, were also predictive.

33.8.4 Conclusions and Implications

The literature suggests that HRQL can predict clinical outcomes, including survival, and healthcare utilization, even after controlling for sociodemographic and clinical factors. To date,

most articles within the cancer population have focused on adults, and within the cancer population, most of the research has explored the relationship between HRQL and survival. The two studies that did evaluate healthcare utilization in the pediatric and AYA age range were not analyses of cancer patients, but instead studied a general pediatric population and a pediatric population with IBD. While we may surmise that the predictive value of HRQL in adult cancer populations and pediatric and AYA noncancer populations may translate to the AYA cancer population, additional research is necessary to affirm the predictive relationship of HRQL and diverse outcomes in the AYA cancer population specifically.

Going forward, HRQL measurement requires minimal ongoing clinician involvement, which is advantageous because measures can be completed either during a clinical encounter or remotely between visits, and they can be repeated at appropriate intervals as part of regular clinical care [72]. Seid and colleagues offered a discernible example of the usefulness of HRQL in their 2004 study. By combining information from HRQL and chronic condition status, the group identified a high-risk group of children with increased healthcare cost. This high-risk group thus comprises promising candidates for proactive care coordination [57]. By following the method of Seid et al., future identification of at-risk individuals could permit intervention that may improve health outcomes. Additionally, the adult cancer literature, including a meta-analysis and review, provides considerable evidence that HRQL can be predictive of survival, controlling for sociodemographic and clinical factors [63, 64]. Considering the simplicity of HRQL collection, the relationship between HRQL and mortality has potential application in treatment decisions and stratification of patients in clinical trials. Taken together, this literature suggests that HRQL gives nuance to the patient experience that provides differentiation beyond the clinical determinants.

In conclusion, HRQL may help predict clinical events and utilization and serve as a marker warranting interventions that may improve clinical outcomes and reduce unnecessary and costly healthcare utilization. Researchers and clinicians should be encouraged to collect HRQL measures on their AYA patients with cancer.

Conclusion

In 2013, the Institute of Medicine (IOM) released a report calling attention to the pressing need for a new method to deliver high-quality and affordable cancer care. The report reflects a need for patient-centered oncology care in which patient's needs, values, and preferences are made a priority [73]. The total cost of cancer treatment, including the portion to which the patient is responsible, has the potential to influence treatment decisions markedly. This, compounded with the sky-rocketing cost of healthcare nationally, undoubtedly motivates the first recommendation of the 2013 IOM report [73], to "provide patients and their families with understandable information about cancer prognosis, treatment benefits and harms, palliative care, psychosocial support, and estimates of the total and out-of-pocket costs." As Shih et al. [74] argue, a disregard for economic evaluation threatens quality oncology care in the United States. Therefore, it is imperative that patients and providers alike are empowered to make informed care decisions by way of valid economic cost estimation and purposeful appreciation of patient preferences.

That said, patients diagnosed with cancer as adolescents and young adults frequently find their lives interrupted at a critical period of transition or development. The needs, values, and financial status of these patients deviate noticeably, if not profoundly, from adult or pediatric cancer patient populations. It is critical to understand trends of health utilization, patient preference, and outcome in these patients. Research to date has been scant.

Economic evaluation is an involved process, which necessitates an appreciation for the components of cost, the way in which benefits can be defined (e.g., survival or quality-adjusted survival), and how components come together in formal analyses such as cost-utility or cost-effectiveness. An effective analysis

must accurately consider preferences and how the values of the beneficiary can influence decisions. The importance of this consideration is especially pronounced in economic evaluation of medical care, in which HRQL is an underlying facet of all treatment decisions. Patient-reported outcomes, including self-reported health status, offer invaluable potential for improving quality and compassionate decision-making. Patient-reported outcomes can contribute on a larger scale to analyses of healthcare resource distribution and also clinically as predictors of healthcare utilization or clinical outcomes such as survival. From the perspective of individual patient-provider benefit, patient-reported outcomes provide an avenue for patients to inform their own care and improve shared decision-making.

As illustrated by the paucity of literature regarding AYA cancer, there is a clear opportunity for research that will progress the achievement of high-quality cancer care for all patients. Shih et al. [74] call for the urgent need for reform in the US healthcare system to address the historic lack of cost consideration in health policy, decision-making, and operations. This chapter serves to create a blueprint for conducting and interpreting studies with the ultimate goal of improving efficiency, clinical outcomes, and quality of care in AYA oncology.

Note The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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DRAFT: AYA Advocacy in Action – Achievements, Lessons, and Challenges from a Global Movement for Change

34

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Abstract

The last decade has seen the emergence and transformation of Adolescent and Young Adult (AYA) Oncology into an established and globally recognized field. An international advocacy movement has contributed significantly to this achievement. What began as a small number of passionate individuals in different countries has grown into an organized, professional, and vocal network advocating for change not only in their own country, but for AYAs worldwide. Recognizing the important role advocacy has had in advancing the AYA agenda, this chapter outlines the history of the AYA advocacy movement and explores key components of its success. It details the vital role of individual and organizational champions, examines a number of successful strategies, and discusses the challenges and distractions faced by advocates. Providing examples from a number of different countries, insight is offered into common approaches and issues as well as highlighting situations where unique tactics were adopted. It concludes that, while advocacy has provided impetus, created community, established momentum, and raised the profile of the AYA field, there is still a need to seek further change and recognition that the movement will have to continue to evolve in order to meet this challenge.

34.1 Introduction

Many of the early articles written on Adolescent/Young Adult (AYA) Oncology use the analogy of an emerging field that was in its own adolescence, going through all the associated growing pains and challenges [1]. Furthering that analogy, the intervening years have seen the expansion of knowledge and experience, maturing the field into a young

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adult with the resources to match. It has been a journey of both physical growth and intellectual and emotional development. Fertilizing this expansion, pushing and easing the way for the changes have been a dedicated global campaign of advocacy. As noted by Vance, "Many people to tend to think of cancer as a purely medical or scientific issue, but it is also a political one" [2].

AYA advocacy, like the rest of the AYA oncology field, has had to evolve and become more sophisticated in order to progress the agenda, to address various challenges, and to take advantage of new opportunities and tools as they arise. A distinct change occurred within a decade, from dedicated efforts being "few and far between" to an international momentum that has "become more organized, public, and professional" ([3], p. 2314). While each country's advocacy movement to advance the cause of AYA oncology has its own distinct flavor, timeline, and channels of implementation, it is possible to identify a number of key components that seem to be essential to success. We will also explore common challenges faced by all AYA advocacy movements, regardless of geography.

34.2 The Key Components for Success

From Australia and New Zealand to the UK and across the ocean to North America, awareness of AYA oncology has been on the upswing for several decades. On each continent, advocacy movements began in different ways and have progressed in unique styles at different speeds. Although the progression of AYA oncology has varied around the world, there are common advocacy components that appear from country to country. We will highlight and discuss some of these key components, including the identification and use of "champions," the role of independent advocacy organizations, the empowerment of young people as advocates, and the building of networks.

34.2.1 Champions

The emergence of AYA oncology as a growing and significant field has undoubtedly been greatly aided by the persistence of a number of key people who have acted as "champions" for the cause [3]. While champions come in all forms—from healthcare practitioner to patient advocate to celebrity—all have been vital in progressing and promoting the AYAO agenda in the medical, political, and public arenas. Although the use of them has been at times a deliberate strategy, the origin of the most effective champions appears to have been a result of personal exposure and intimacy with the issue.

Understandably, personal involvement is how many patients (including celebrities) and their supporters begin their advocacy journey. Beyond that, a common feature linking these AYAO champions has been their willingness and desire to engage with this age group, which creates a strong foundation for their engagement and fuels their passion to achieve better outcomes and experiences for AYAs.

While the work of individuals pushing the AYA cause has often been a catalyst for local change, the more strategic use of champions in recent years has had wider-reaching benefits in gaining media attention or influencing public opinion, providing an important tactic for the movement.

34.2.2 Champions: Passionate Practitioners

In every country where AYAO advocacy has gained a foothold, there appears to be a correlation with the existence of "individual dedicated practitioners" who have spearheaded efforts in the field [4]. These champions in the medical field have come from across the spectrum of disciplines and have played a key role in promoting the needs of AYAs not only in their local institutions, but often in national and even international arenas.

Many, if not most, medical champions appear to be those who have day-to-day interactions with

adolescent or young adult patients. The exposure to the unique challenges that this age group faces and the inability of current systems to adequately meet their needs have propelled many practitioners into advocate roles through frustration and a desire to change the status quo. Often they are championing the AYA cause locally at first and then more widely [5]. Caring for adolescents and young adults is a very different experience to that of treating children or older adults, and the most passionate medical champions respond to AYA patients—who are sometimes of their same age—in the same way that many pediatricians feel "called" to treat children.

While many medical champions have emerged organically from their passion for working with young people, there are also examples of the deliberate cultivation or recruitment of new champions within the medical field. For instance, in the UK, the National Cancer Action Team set up the National Teenage and Young Adult (TYA) Cancer Guidance Implementation Group (now replaced by a Teenage and Young Adult Cancer Clinical Reference Group) which is required to develop and implement standards and measures in every cancer center designated to deliver specialist services to this age group. The UK has also set up a National TYA Cancer Research Group, a National TYA Cancer Intelligence Group, and a National TYA Cancer Survivorship Group, all of which provide professional development opportunities, taking interested parties and turning them into champions as they evolve in their understanding of and dedication to advancing the cause of AYAs.

In Canada, the development of Regional Action Partnerships (RAPs) that report into the National Task Force has allowed individual champions working on the national level to tap their local networks, introducing their colleagues to a discussion of how best to advance the AYA cause in their own regions. Such a structure serves as both an educational and recruiting tool, giving professionals the opportunity to understand the movement and subsequently develop as new champions alongside their veteran colleagues.

34.2.3 Champions: Celebrities

AYAO champions have not been restricted to just the medical field. There are a number of celebrities and high-profile individuals who have also made a significant impact by using their standing and personal platform to advocate for AYAO issues. Many (although not all) do this because of their own cancer experience. Celebrities have been strategically used in a number of countries to help raise awareness of the cause, seek funding, and push political agendas [3].

The most well-recognized example in the AYAO field is the former international cyclist, Lance Armstrong, whose LIVESTRONG Foundation dedicated significant resources explicitly to AYA issues. In addition, he was formally involved in the launch of Youth Cancer Services in Australia. More recently, Diem Brown, a US reality show personality and ovarian cancer survivor, used her personal platform and social media presence to bring the public along on her cancer journey right to the end of her life, highlighting in a very personal way many key AYA issues.

In New Zealand, the game of Rugby Union holds a special prominence, and the national team, the "All Blacks," are highly visible in public life. CanTeen NZ enlisted the support of Dan Carter, one of the most high-profile players, to be an ambassador for the organization. The public interest in Carter has ensured CanTeen has ready access to the media for the delivery of their campaigns and key messages.

But a celebrity does not have to be an athlete. In the USA, Congresswoman Debbie Wasserman Schultz, a young breast cancer survivor herself, worked with the Young Survival Coalition, a leading young women's breast cancer advocacy organization, as the champion for the Breast Cancer Education and Awareness Requires Learning Young Act, or the EARLY Act. The EARLY Act is passed in 2010, creating an education and outreach campaign for young women and healthcare providers to highlight the breast cancer risks facing young women 45 and under.

In the UK, the Teenage Cancer Trust has been strategic in its use of celebrities for both

fund-raising and awareness [3]. In particular, they have greatly benefitted from the long-term support of the rock band, The Who, in raising their public profile and launching a concert series that has raised significant funds over the last 15 years. More recently, members of the band, impressed by the progress made in the UK by the TCT, spearheaded the establishment of the Teen Cancer America organization in order to support similar change in the USA.

While Australia has not had the equivalent of a local celebrity with the cachet of Lance Armstrong or The Who, the concept of utilizing the support of high-profile people has still been embraced. As part of a strategy to raise the profile of the issue and also generate funding, CanTeen and a philanthropic corporate partner organized a "Captains Dinner" inviting the leaders—or "Captains"—of a diverse range of fields such as politics, industry, sport, and entertainment. The guests, which included the Prime Minister, were educated about the issues by AYAO patients and asked to support the cause both financially and in helping to raise awareness.

34.2.4 Champions: Families and Friends

An often less recognized but still important set of AYAO advocacy champions originates from the family and supporters of AYA patients. While their advocacy is often delivered directly on behalf of the patient [4], here are a significant number of individuals who have devoted time, skills, and resources to advocating on a bigger scale.

Examples of parents, partners, and friends becoming champions of the AYAO cause range from the establishment of organizations or foundations to lobbying politicians and driving fund-raising campaigns. In Australia and the USA, for example, several hospitals have received funding from families to help establish dedicated AYAO units in honor or memory of their loved one and to support AYA-specific services and professional education. Many smaller US foundations partner with more established nonprofits—often disease specific—and direct funds to particular initiatives within those organizations.

One example is Jill's Legacy, a volunteer subsidiary of the US-based Bonnie J. Addario Lung Cancer Foundation. Jill's Legacy is dedicated to raising funds for lung cancer research in young people. It was founded by Jill Costello's friends and teammates after the 22-year-old, nonsmoking, college student/athlete lost her battle with lung cancer. This arrangement is a good example of the mutual benefit that occurs when a friend- or family-driven initiative is brought under the aegis of an established advocacy organization that can provide back-end infrastructure and channels for effective distribution of funds. It allows the smaller organization to maintain passion and laser focus on their key function—typically fund-raising and awareness—while pushing the larger organization to explore programmatic avenues they may not otherwise have considered. In this case, the Addario Foundation has developed an innovative new study called the Genomics of Young Lung Cancer to look at lung cancer in patients under 40. This model reduces competition for limited funds, streamlines messaging, and amplifies the impact of both organizations.

34.2.4.1 The Role of Independent Advocacy Organizations

While individual advocates have been vital in promoting and advancing the AYAO field, there is recognition that the dedicated work of a number of nonprofit organizations has been crucial to many of the larger steps forward in the field [4–6]. As Perlmutter et al. argue "…the journey from cancer patient, or caregiver, to advocate may be a natural response to cancer. However, strong leadership and organization are required to leverage this common instinct into successful systemic change, which is a primary goal of organized cancer advocacy" ([7], p. 4611).

As independent entities, nonprofit organizations can openly apply political pressure and have the ability to make quick decisions or take creative approaches to issues without bureaucratic restraints. They have the capacity to work and act in ways that may not be open to individuals, particularly health professionals working

within the system [8]. The most effective organizations possess a national profile, strong professional networks, and access to media, celebrities, and publicity opportunities. They may also have the resources (including dedicated staff and volunteers and experience in awareness building) and financial means to dedicate to issues. And they combine these capabilities with the passion and firsthand insight of the patients they support. As a result, there is an acknowledgment that "… we, as a professional community, would not have gotten anywhere close to what we have achieved without advocates" ([5], p. 15).

While there are many invaluable and dedicated organizations working to support the AYA group, each country appears to have had a key organization that has taken the lead and acted as a central or coordinating point for developing and delivering the advocacy agenda. "There are no more important agents of change than the community of advocacy groups, exemplified by the Teenage Cancer Trust in the United Kingdom, CanTeen in Australia, and the Lance Armstrong Foundation (LAF) based in the United States" ([6], p. 2248). These groups are by no means the only AYAO advocates making significant achievements, but rather they are recognized for the foundational role they have played in focusing and often binding together the work of key players.

In terms of collective impact theory, these organizations are referred to as the "backbone organization" [9]. While marshaling and utilizing the support of others, they provide the structure and drive the processes. Backbone organizations are willing to build collaborations across sectors, drive the collection of shared data, and seek expertise from others, while maintaining the momentum required.

Interestingly, in the AYAO field, advocacy was not always the original mission of some key or backbone organizations. For example, the Australian organization CanTeen never intended to be, as it became known a "powerful public advocacy group" [10]. Indeed some tension was caused internally when resources and focus were intentionally diverted toward this purpose. CanTeen was originally established by a group of patients and health professionals in Australia (and later, New Zealand) as a peer support organization. However, through years of providing increasingly sophisticated services to patients, it became apparent that without broader change to the system, their needs could not be met, so an advocacy agenda was established and ferociously pursued.

Other organizations have developed specifically to create an advocacy response to the issue. The National Cancer Institute partnered with the (then) Lance Armstrong Foundation in 2006 to hold the Adolescent and Young Adult Oncology (AYAO) Progress Review Group (PRG). Subsequently, the Foundation created the LIVESTRONG Young Adult Alliance, comprised of an array of organizations and institutions with a mission interest in young adult oncology, to act as an implementation body for the PRG recommendations. "The Alliance is composed of advocates from small and large NGOs, healthcare providers from academic and community centers, cancer researchers, and government representatives. Considerable progress has been facilitated by having all stakeholders base their advocacy efforts on a common resource, which promotes the dissemination of a clear message shaped by contributions from the scientific, medical and advocacy communities" [3]. In 2012 the LIVESTRONG Foundation spun off the Alliance into an independent nonprofit renamed Critical Mass, which has since assumed the backbone role by continuing to convene stakeholder organizations on an annual basis, aggregating resources and data, and providing a forum for knowledge sharing and collaboration building.

In parallel with the development of Critical Mass, which works primarily with AYA professionals, the young adult organization Stupid Cancer has grown into the largest non-disease-specific advocacy organization on the young adult patient side. Through skillful use of social media, brand building, and emerging technology, Stupid Cancer offers a broad community for young adults seeking to connect with their peers and acts as a megaphone for the presentation of young adult cancer issues in the public domain.

The Teenage Cancer Trust launched in the UK in 1989 in response to the identified needs of the AYA group. It started out advocating for specialist care within the health system and raising funds to develop specialist facilities that, over time, became an international benchmark. Since its inception, the TCT has "acted as a patient advocate and political pressure group, and that has brought to public attention the need for changes while providing support for specialist staff and hospitals" [8]. Over time, their focus broadened to program development, staff training, research, and international collaboration. Through the efforts of the charity, national groups were set up across the spectrum of service delivery to ensure standards and measures. The result has been to bring specialist services for AYA into the mainstream in the UK health system with universal acceptance of their necessity.

Alternatively, the advocacy movement in Canada is more of a hybrid; organized and driven by a group of medical champions who had been involved in the international AYA movement and sought to bring that experience to their own country by pulling together a National Task Force to examine how to address the needs and issues of AYAs in a way that was appropriate for the Canadian cancer care system. The National AYA Task Force was established as a joint initiative of the C^{17} Council of Pediatric Centres and the Canadian Partnership Against Cancer, an independent organization funded by the federal government "to accelerate action on cancer control for all Canadians."

34.2.4.2 Importance of the AYA Advocate

While these organizations were all created for a variety of reasons amid unique circumstances in their own countries, they share a key tenet. It is a principle that appears to have united the movement globally and is at the heart of all AYAO advocacy work: that the young people they represent should be at the center of everything [8]. All initiatives should be grounded in putting the young person first, their cancer second. It is this common principle that has driven and united the AYA advocacy agenda around the world.

One of the components that has ensured that the AYA patient remains at the center of advocacy initiatives is the consistent representation and meaningful involvement of patient or consumer advocates at all levels, not only as the public face of the issue, but often with significant roles in strategy and day-to-day operations. There are few AYA committees that exist without consumer representation, and, in some cases, such as the Youth Cancer Services in Australia, there are entire advisory bodies that have been made up of young people. In the USA, Critical Mass brings AYA patient advocates—many of whom are survivors themselves—together with their healthcare professional counterparts on equal footing. The TCT in the UK succeeded in reaching a formal agreement that every national cancer group or panel established that was related to AYA matters (including research and standards and measures) had to have a young person included.

Sharing the stories and views of AYA patients publicly has also been recognized as "a powerful tool to pull in media and political support and create a swell of influence for positive change" ([4], p. 1111). It has also been argued to be a cost-effective strategy and, with limited budgets, the passion and energy young adult advocates can leverage for the cause are important assets in changing policy and priorities at institutional and government levels [1].

Given the relatively small number of young people diagnosed with cancer (as compared to the over-40 population), there appears to be strong representation and high efficacy in the AYAO population. A theory has been proposed that the reason young people are such effective advocates is related to the timing of the cancer within the general context of their lives. Not only do they possess that passion and energy previously referred to, but it is thought they may simply have more time available, with fewer family and work commitments than older age groups [1]. Additionally, advocacy itself is not an unknown concept to this age group, especially in the current digital and social media context that surrounds every aspect of their lives.

In some places, formal advocacy training programs have been developed; designed specifically

to ensure that young people have the necessary knowledge, skills, and confidence to advocate successfully, they also promote consistency and professionalism of messaging. In Australia, CanTeen has run a number of advocacy training workshops dedicated to increasing the ability of their membership, with content modules specific to AYAO issues, key messages, and strategies. External professionals with expertise in media training, political lobbying, and presentation skills have been involved. Some young people volunteer, while others have been sought out because of their experiences. And while the majority of the programs have been tailored to specific AYAO issues, CanTeen has also partnered with other nonprofit cancer organizations to deliver broader advocacy skills training to young cancer patients and their families.

Jimmy Teens TV was an inspiring UK initiative that has since become international. The organization, largely run by young survivors of cancer with professional support, taught young people how to make their own films about their experiences. There are now thousands of films on a central website on every single topic imaginable, categorized, and accessible to any newly diagnosed patient. The wealth of testimony provides not only an incredible resource for patients but is now commonly used by professionals to train new staff and to learn about the impact of cancer on young people. Renamed JTV, the organization currently has both radio and TV shows on digital channels accessible to young people.

34.2.4.3 AYA "Style"

Requiring the involvement of young people and supporting them as frontline advocates have contributed to ensuring that the AYA approach and communication styles reflect the population it represents. A common thread linking much of the international advocacy efforts appears to be a strong sense of humor underpinning key messages. This is not an agreed-upon strategy or tactic, but rather an organic representation of the cohort. The tone and communication style of the major advocacy groups generally favors plain language and maintains a sense of fun, despite the serious topics.

Dark humor (and sometimes, ahem, bad language) abounds across many of the media and messages, particularly those targeting the young people themselves. While this is not necessarily unique to the AYA population, there is certainly a heavily weighted representation of it in the advocacy work of this age range. A longtime fixture in the online store for US-based organization Stupid Cancer is a black rubber wristband displaying an unmistakable middle finger salute which you can use to show your true feelings about cancer. The "TCT Find Your Sense of Tumour" conference combines serious presentations with fun and ridicule in the UK, and campaigns such as Check 'em Lads (UK), Mr. Ballsy (USA), Fuck Cancer (USA and Canada), and Save the Hooch (USA) have all served to deliver vitally important messages to AYAs with cancer-utilizing humor as their primary vehicle.

34.3 Building Networks

Many of the advocacy groups and individuals discussed in this chapter (and the hundreds more across the world that are doing invaluable work) act on their own, but also within informal and formal networks. Local peer groups, professional interest meetings, online chats, and raucous discussions at conferences that turned into joint research are all branches of the AYAO network. Uniting those individuals and groups, utilizing existing networks, and building new ones where necessary have been the cornerstones of the success of AYAO advocacy. It is a key tenet of advocacy that one can strengthen and amplify the message by uniting voices [4]. In bringing people together both locally and globally to support the issues, there has been the creation of an international AYAO community—a community that has provided the opportunity to promote sharing and learning, with downstream effects including greater cooperation in areas such as research and increased access to expertise [11]. There are also the benefits of combining resources and avoiding duplication [12].

For those who have worked in the AYA oncology field over the last decades, familiar faces and

names dominate. And while it is difficult to quantify, having a small but dedicated fraternity seems to have produced the benefits of quicker collaborations, fewer competitive barriers, and greater sense of collegial relationships. Networks offer opportunities for these informal friendly relationships to develop into more formal collaborations. Barr provides a number of examples of important and successful examples including the Canadian National Task Force and the AYA initiative of the International Society of Pediatric Oncology, which he argues "can heighten awareness considerably and lead to cooperative endeavours that will forge meaningful advances in the field of AYA oncology" ([6], p. 2248).

Some networks were built specifically to help enhance and advance the AYAO field. One example from the UK is the Teenage and Young Adults with Cancer (TYAC), a multidisciplinary health professional organization that was founded in 2004. "Its genius is to bring all together to share experience and learn from each other in what is still a very new specialty" [8]. Similar ventures include the US-based Society for Adolescent and Young Adult Oncology (SAYAO), which primarily serves health professionals, and Critical Mass, which brings together both patient advocates and health professionals to learn from and share with one another.

In Canada, the National AYA Task Force has expanded their structure and reached through several national strategic meetings and the establishment of Regional Action Partnerships, or RAPs, a network that extends into every region across the country. The RAPs provide a way to channel national insights to the regional and local levels and vice versa, as well as grow the base of support in the healthcare professional community.

A broader advocacy initiative in Europe supported by the European Parliament is the European Network for Cancer Research in Children and Adolescents (ENCCA), a collaboration of every European Community country funded by the EU to explore a common ground in the AYA field and to come up with common standards and methods of collaboration on a range of issues. The group includes professionals, professional organizations, advocacy organizations, and young advocates addressing topics such as research, service models and delivery, ethics, cultural differences, and professional education.

Existing networks—those that may be considered slightly tangential or at the periphery of the AYA oncology world—have also been sought out and embraced for the support they could offer. In both the UK and Australia, related AYA organizations and charity networks were approached to address how they could work together to benefit the age group [4]. As part of its lobbying of the government, CanTeen worked with other major Australian charities in the sector to provide their support in writing for dedicated AYAO services, demonstrating a unified stance in a sometimes disparate sector. Redkite, an Australian nonprofit organization supporting young cancer patients and their families, embraced the momentum created by the network and has continued to contribute strategic support as well as provide consistent representation on AYAO decision-making bodies.

Other international advocacy collaborations, while formed easily based on existing relationships, and with the best of intentions, have not achieved the hoped-for success. In the early 2000s, SeventyK, a California-based organization, had begun to look at a charter of rights for young people with cancer in the USA. This led to an International Task Force with representation from CanTeen Australia, CanTeen New Zealand, LIVESTRONG, SeventyK, and Teenage Cancer Trust to write an International Charter of Rights for Young People. Once complete, the aim was to petition for grassroots support from around the world and then lobby for government endorsement from every country. While this outcome was never achieved, it is perhaps an important lesson in advocacy. Despite the best of intentions, success for such a worthy cause could not be achieved without significant financial, political, and professional support and, perhaps, one organization designated as the "backbone" for such an effort. Each of the national advocacy organizations was already hard-pressed to deliver on their own national initiatives and had neither the time nor resources to give the initiative the focus

and drive it needed to succeed. That said, the International Charter of Rights still stands as a very important advocacy statement that remains a relevant reference point.

34.4 Funding: Raising and Spending

One of the greatest challenges in extending and strengthening the AYAO field is finding funding to finance change. Lack of funding can sink even the most worthy initiatives, and there are several reasons that may explain the challenges to raising funds for AYA advocacy: First, it is a new field that is still building awareness and credibility (in some countries more than others) as a valid field worthy of dedicated funds that will necessarily be reallocated from elsewhere. There can be difficulty for funders to determine what advocacy initiatives to finance and what changes will have the most impact, when there is no agreed-upon or proven model of care. Additionally, just as AYA patients are carving a new space out of the cancer continuum between children and older adults, AYAO advocacy is also a newcomer in a crowded space, where most fundraising traditionally supports research and patient programs in a specific disease or addressing a specific issue.

Of the "backbone" nonprofit organizations mentioned, none has dedicated itself to raising funds to cure the cancers which affect this age range, although there are many disease-specific AYA organizations operating in that sphere. However, all of the backbone organizations have strategically sought and invested funds into furthering the broader advocacy agenda, which includes promoting AYA research funding as a priority. They have made investments in everything from bricks and mortar to funding training and professional development for health practitioners.

In a number of countries, nonprofits have funded key AYAO staff roles, with the end result that the relevant health authority assumed responsibility for the positions once they realize the impact. In New Zealand, CanTeen recognized the impact that a specialist AYA nurse role could have in improving the experience of an AYA patient going through treatment and provided the funding for four dedicated positions. After careful scrutiny, the NZ health system acknowledged the effectiveness of the role and took over the funding, expanding the number of positions.

In Australia, recognizing that providing financial support was one of the quickest ways to ensure change in a complicated health system, CanTeen sought and secured funding from the federal government for dedicated AYA services. Their "opportunistic advocacy to government and clinicians had been a vital factor in driving this process. It had resulted in the unique funding model, whereby a non-government organization with a vested interest [CanTeen] was charged with administering a federal government initiative" ([13], p. 119).

The use of the term "opportunistic" perhaps fails to adequately convey the depth and degree of planning and deliberate strategy that was involved and required. CanTeen put extensive resourcing into a detailed plan that included research, meetings, conferences, presentations to government, building of relationships and partnerships, training of advocates, bringing in international experts, liaising with professional associations and individual medical practitioners, and producing public relation and media campaigns. Using the "opportunity" of a federal election to leverage a funding commitment was the final piece in a lengthy and well-orchestrated campaign.

In the UK, rather than targeting government funding, the TCT undertook a deliberate strategy of involving corporations and individuals in raising the necessary resources to fund facilities, program staff, staff training, and conferences for young people and professionals alongside a number of other initiatives.

Although AYA advocate charities may at one time or another fund infrastructure, staff, and research; real and lasting change requires institutional and health system investment that contributes to institutionalizing AYA initiatives within existing structures. The power of advocacy and advocate organizations could be seen as a jump start, either through public pressure or

start-up funds that support a particular approach or initiative until need, efficacy, and/or utility is demonstrated and the approach or initiative is adopted.

34.5 Strategies and Tactics

While the elements outlined above have all been vital components in advancing the AYA oncology agenda to date, there are also a number of specific strategies or tactics utilized that are worth noting. While by no means a comprehensive list, the examples canvassed in the next section showcase common strategies employed by the international AYA advocacy community in order to push forward change. They range from traditional tactics such as lobbying government to promoting the setting of standards and the evolving use of social media.

34.5.1 Political Lobbying

Advocacy has a traditional base in political lobbying and the AYAO field is no exception. In order to achieve the kind of change that has occurred to date (and is hoped for in the future), it has been important to find ways to influence and work with a range of government and bureaucratic entities. Making contacts, utilizing networks, building relationships, partnering on projects, providing mutually beneficial media opportunities, understanding budget cycles, and applying public pressure if required are just some of the more common tactics employed by the AYAO community in order to promote awareness, raise funds, and garner support for improving outcomes.

As previously mentioned, in Australia CanTeen recognized that federal government funding would be a significant change agent in the AYA field. Asking for budgetary allocation (in this case timed with an election) was the final step in a lengthy courtship with both the elected representatives and the bureaucracy. It built on a carefully constructed foundation that involved actions such as presenting at government inquiries and meeting with Ministers, as well as taking advantage of more informal opportunities (including inviting Members of Parliament to attend programs and bringing young patients to share their stories at pertinent events), all aimed at building awareness of the organization and promoting rapport.

Both CanTeen and the TCT in the UK are organizations that have deliberately cultivated strong relationships with key individuals both in the elected government and within the bureaucracy that supports it. The TCT has invited (and had attend) the leader of the National Cancer Action Team to every FYSOT conference held, ensuring their active role in proceedings was memorable, thanks to the young people attending. They regularly launch publications at the Houses of Parliament, inviting Members of Parliament, VIPs, and the press.

While traditional approaches to lobbying government have been employed by the advocacy community, there have also been other avenues explored. One example is the establishment of partnerships. The National Cancer Institute and LIVESTRONG partnership bringing together professionals and advocates in the guise of the AYAO PRG have been termed both “landmark” ([4], p. 1110) and “…an innovative, public-private sponsorship” ([14], p. 43). The partnership continued in subsequent years, with the LIVESTRONG Foundation funding follow-up meetings by the Institute of Medicine and the National Cancer Institute, allowing a demonstration of federal support even in a time of budget cuts and limited federal resources.

34.5.2 Conferences

An advocacy approach that has been utilized in a number of different countries is the organization of conferences targeting AYA patients and the professional AYA community. Notably, funding for these meetings has often come from or been sourced by the advocacy organizations. Conferences have been used not only as a vehicle for sharing the latest research and knowledge in the field but also have the added benefits of

awareness raising and bringing together some of the previously mentioned champions. Sometimes they even inspire new ones to emerge.

Two regular conferences hosted by the Teenage Cancer Trust have different audiences and aims: The International Conference on Teenage and Young Adult Cancer Medicine endeavors "to further encourage professional interest in the challenges of treating young people." On the patient side is the annual conference of 500 teenagers and young adults with cancer—dubbed "Find Your Sense of Tumour" (FYSOT) by the young people themselves—which provides young people with an "opportunity to challenge medical and political establishments and have their voice heard" ([4], p. 1110) through interactions with health professionals and key invited guests such as politicians and the National Cancer Director. The gathering presents an opportunity to survey those present; their views and opinions are then utilized to influence health planners and decision-makers in the design and implementation of services.

CanTeen also utilized this strategy in Australia in some of its early advocacy work, hosting a conference in 2006 that brought together a number of international experts with key local players [4]. One of the aims was to provide credibility to both the issue and the organization as an advocate for it. The conference was also designed to increase awareness of the topic in Australia, canvass solutions, and begin to create momentum for the issue. The organization hosted a similar event in late 2015, and while celebrating some significant achievements from the last decade, it used the opportunity to refocus and find ways to further progress the agenda.

In the USA, the annual Critical Mass Annual Conference is in its tenth year. Originally established to develop a road map for organizations wanting to help advance the national agenda, it has evolved into a forum for knowledge sharing and collaboration development. It is also no longer the only meeting of its kind by any stretch: the Society of Adolescent and Young Adult Oncology hosts an annual national meeting. And a growing number of regional and local meetings and symposia for professionals—Cleveland, Ohio; Texas; and Los Angeles, California, are three examples—have important roles to play because they enable attendance of health professionals and advocates who might not ordinarily manage to attend national conferences. Geography provides a significant challenge in larger countries like the USA, and the regional meetings serve to promote multidisciplinary education, dialogue, and collaboration between many more professionals and advocates.

On the patient and caregiver side, Stupid Cancer brings nearly 500 attendees together in the USA under the banner of "CancerCon," with the aim "to connect, get educated, build community and unite to drive the change we wish to see" [15]. In Canada, the patient organization Young Adult Cancer Canada hosts an annual Survivor Conference as well as smaller gatherings called "Retreat Yourself" to build community among young Canadian cancer survivors.

34.5.3 Professional Development and Qualifications

The development and delivery of a range of professional development programs and qualifications is a great benefit to the field by creating more knowledgeable and expert practitioners. It is also a powerful advocacy tool, providing profile and establishing credibility for the AYA oncology sector, as well as developing new, knowledgeable champions who can share their knowledge and passion as they move through their careers. Advocacy groups have been at the forefront of pushing for and promoting these qualifications and, in many instances, assisting with their funding and even content.

One of the leading examples of these initiatives is a postgraduate course at the University of Coventry, UK, supported by the TCT, which has had international reach. This online course has enabled students from many countries to attain experience and a qualification invaluable to both their careers and the AYA movement. The TCT was also seen as instrumental in advocating for the establishment of a University Chair in Teenage and Young Adult Cancer

Medicine [3], providing further credibility for the field. The Teenage and Young Adult professional body, TYAC, has also delivered twice yearly education meetings for the UK health professionals in the field.

More recently in Australia, as part of federally funded Youth Cancer Service, one of the earliest dedicated AYA services, ONTrac at PeterMac, produced an educational framework designed to build awareness and expertise among health professionals [13]. While in the USA, LIVESTRONG and the American Society of Clinical Oncology collaborated on the program "Focus Under Forty," a "continuing medical education curriculum for healthcare providers including oncologist, primary care physicians, and midlevel providers" ([14], p. 46). LIVESTRONG/the Alliance also helped to create a tool kit that acts a guideline document regarding AYAs and clinical trials and collaborated with Nurse Oncology Education Program to produce a free continuing education video.

The AYA@USC program in Los Angeles, California, has implemented a Summer Oncology Research Fellowship Program for first-year medical school students pursuing interests in oncology research. Students participate in clinical or laboratory research studies, mentored by a faculty member at either Children's Hospital of Los Angeles or the USC Keck School of Medicine. A novel new experiential learning component to the Summer Oncology Fellowship is called the AYA Patient-Student Partnership Experience, which extends into the first semester of the second year of medical school. This program matches med students with AYA physician mentors and an AYA patient(s) undergoing treatment. In addition to monthly meetings and coursework, the student will attend the patient's clinical consultations, treatments, inpatient visits, surgeries, and other visits/procedures wherever feasible. Through experiential learning using a model of peer-to-peer support, the student will gain direct experience with AYA oncology care, challenges, and opportunities.

In Canada, the Task Force supported the development of a postgraduate training program leading to the award of a diploma in AYA oncology from the Royal College of Physicians and Surgeons of Canada. While the program has yet to be implemented, it is hoped that physicians opting for the program would increase the number of AYA champions and help support the goal of the creation of multidisciplinary, AYA-focused healthcare teams.

Change in clinical practice and shifts in research priorities do not happen quickly or easily; developing a generation of new AYA oncology champions can, over the years, gradually tip the scales toward a cultural shift, normalizing AYA as an accepted point of difference along of the cancer continuum.

34.5.4 Supporting Standards of Care

In a similar manner to this support for professional development, the advocacy community has also sought to promote the development and implementation of standards for the AYAO field. While providing numerous benefits for patients in terms of better care is a tremendous and desired outcome of standards, this support has also had a different strategic purpose attached. As a tactic it has been employed in two specific ways.

Firstly, by ensuring there is AYA inclusion in any broader oncology standards of care. This not only raises the profile of the area, it can also be used as leverage for change in lobbying in a range of entities. The second manner in which supporting standards has been employed as a tactic relates to the perception that standards provide an important level of credibility and authority to the field. In short, setting universal standards helps to ensure that AYA oncology as a discipline becomes "part of the establishment" ([8], p. 260).

In the first use, AYA inclusion in a range of national oncology standards has been used to push the agenda both locally and internationally. For example, in the Australian context, reference was consistently made in early lobbying efforts to the UK's NICE Guidance on Improving Outcomes in Children and Young People with Cancer [16] as well as New Zealand's initial attempts at a Adolescent/Young Adult Cancer Service Nationwide Service Framework (they are

currently in the process of drafting new AYA Standards of Care). And there was almost a domino effect as following the dissemination of the Senate Community Affairs Reference Group 2005 report into cancer care, which included two specific recommendations for AYA oncology standards of care. CanTeen used these standards to publicly call attention to the need for change in the field. When the government body Cancer Australia formally responded to the recommendations by forming an AYA Cancer Reference Group, it in turn called for the development of a National Service Delivery Framework for AYA patients. In order to ensure this measure was progressed quickly, CanTeen "offered to collaborate with Cancer Australia to facilitate this recommendation" ([13], p. 119).

In the UK the aforementioned National Guidance has now been transformed into detailed National Standards and Measures to which every designated cancer center must comply.

In the USA, the LIVESTRONG Alliance employed the second use of the tactic, recognizing the role standards can play in providing greater credibility. The Alliance's Standards Task Force, which was "focused on guidelines for the care of AYAs with cancer and on training guidelines for healthcare providers who care for them" ([14], p. 45), produced a white paper on standards, and a position statement on professional training that was published in the Journal of Clinical Oncology [17]. In 2012, the National Comprehensive Cancer Network—a not-for-profit alliance of 26 of the world's leading cancer centers and "the arbiter of high-quality cancer care"—published both patient and provider guidelines for AYA. While none of these documents set requirements or mandates, they lay the foundation for future advocacy initiatives that may do so.

34.5.5 The Internet, Social Media, and Public Perception

It is difficult to overestimate the impact that the rise of the Internet has had on the AYA oncology movement. Prior to the late 1990s, in countries without any formal mechanisms to support peer connections (CanTeen in Australia had a more developed in-person peer network than other countries at this point), individual AYA patients were isolated and disconnected, lost among the crowd of older or younger patients surrounding them. As a group, AYAs had no identity, no voice, and no sense of community. A growing number of AYA-focused websites drew the members of this fragmented and geographically dispersed population together, both online and face to face. The forerunner was Planet Cancer, whose irreverent combination of making light of the impact of cancer while offering serious support became a template for many online communities. As AYAs formed meaningful personal relationships on and offline, they validated their experiences as young people with cancer, leading to a sense of group identity through connection to a broader peer community and reducing isolation and disenfranchisement.

The relationships and community forged in the early 2000s were the foundation of today's AYA oncology movement. What started with websites and message boards has evolved into offerings in the online app universe: Stupid Cancer's Instapeer is a new mobile app offering support on demand, instantly connecting AYA patients with a peer through their smartphone. Although new tools and platforms continually change the mechanism of content and service delivery, the pillars of peer connection and knowledge sharing have remained constant. The rise of social and digital media channels—from Facebook and Twitter to Instagram, Pinterest, YouTube, digital radio, blogs, and other social platforms—has also exponentially increased the capacity for message amplification and targeted message delivery, powerful tools of AYA advocacy that raise the profile of AYA oncology in the broader social conversation.

This increased exposure through social media channels has also helped AYA oncology bubble up into mass media. Several recent major motion pictures have addressed the topic, including Oscar-nominated *50/50*. Another box-office success was *The Fault in Our Stars*, based on the young adult novel of the same name (the success

of which was largely precipitated by the huge social media following of author John Green, whose book was based on his personal friendship with a young woman with cancer). Several network TV series have also built concepts around AYA cancer, including *Side Order of Life*, *the Red Band Society*, and *Chasing Life*. The US-based advocacy organization Stupid Cancer has adeptly built relationships with such shows, providing input on scripts and connections with patients and survivors to play extras and give a ring of authenticity while also offering the shows and their stars access to a ready-made base of fans through their robust social media audience and digital radio show.

An interesting development on social media in recent years has been the growing presence of AYA oncology healthcare providers, most notably on Twitter. Just as AYA patients and survivors have been isolated, the professional AYA champions often find themselves swimming upstream in their own institution as they try to advance an AYA agenda internally. The ability to connect with like-minded peers as well as AYA advocates and patients online facilitates easy sharing of knowledge and best practices and helps build the sense of community that can keep someone's passion for advocacy burning bright.

In the UK, TCT established an online community of advocates called TCTeeNation whose membership was any young person with cancer who wanted to be active in consultation on relevant topics. Facilitated discussion, surveys, and voting were used to garner collective opinion on a range of critical topics. The outcomes were used both internally and externally by the charity to bring about change that was important to young people.

Social media is also having a revolutionary impact in terms of fund-raising and raising profile. Traditional methods are being complemented by online donations, targeted advertising, creative campaigns, and crowdsourcing initiatives. Local advocates can greatly enhance their reach through online donation mechanisms and dedicated fund-raising tools and websites. An extraordinary example of this occurred in the UK in 2014, when a young patient named Stephen Sutton was fund-raising for the TCT. After learning that his cancer was incurable, Stephen started a Facebook page and Twitter campaign, as well as his own website and blog, telling his story and asking people to share photos of themselves to promote it [18]. The campaign went viral, ultimately raising more than 5 million pounds for the TCT and generating an extraordinary amount of international media coverage, both online and in traditional formats. Stephen also utilized his profile to meet with the British Prime Minister to highlight the needs of AYAs.

34.6 Challenges and Distractions

While much has been achieved and advocacy has had significant impacts on the AYA field, it has not been without a number of challenges. These have been, at best, a distraction and, at worst, threatened to derail or halt the momentum of the progress. While some are common to advocacy in general (such as the challenge of volunteers, fund-raising, and uniting disparate partners around a common purpose and agenda), others are more specific to the field. There are ongoing debates in the AYA oncology field that, when present, have the ability to sidetrack the conversation, splinter collaborations, and slow momentum.

34.6.1 Leadership Continuity

It is clear that strong leaders in the field have a significant role to play in driving forward the agenda. However the most successful have been those that instill a collaborative approach: The LIVESTRONG Foundation using its influence to develop the AYA Alliance in the USA; Teenage Cancer Trust joining forces with Cancer 52, an alliance of over 80 rare cancer charities, to engage health decision-makers in the UK; and CanTeen Australia ensuring other nonprofit organizations and health professionals are represented on the Youth Cancer Services National Advisory Groups; the "community" of the US, UK, Australia, and New Zealand AYA organizations

is combining forces to deliver the International Charter of Rights.

With limited resources being applied to a new field like AYA in health systems around the world, it is often the independent advocacy organizations that have the ability and drive to push through new ideas and innovations. It is often their creativity and ingenuity that find ways to turn philosophies into actions, creating change and galvanizing support.

So when there is a void in leadership or a change that has not been planned, the impact can be extremely challenging to a movement. The impact of the adverse publicity surrounding Lance Armstrong could have been devastating for the LIVESTRONG Foundation, and it is a testament to their staying power that they were able to ride that storm and stay strong. An overdependence on personality can be a dangerous thing, and advocacy organizations need to be sure to have contingency plans to manage catastrophe.

34.6.2 Competition

While competition within collaborative communities is usually limited and well managed, there are many examples within the history of advocacy where harm has been done. In the 1980s and 1990s, there were some challenging times within the HIV/AIDS movement where radical organizations clashed with others trying to deliver services. Furthermore, there is likely to be a finite amount of money that can be raised for a particular cause. Public goodwill and generosity can be fickle and show trends of interest. So when the "fashion" for giving to a certain issue switches to something new, a movement can find organizations within it competing for dwindling resources. Like any industry, mergers and acquisitions take place and charities can fail to thrive like any other business. In such circumstances, the "fight for the limelight" and the public dollar can become intense.

The AYA movement has been fortunate that it has never been through such an era but it would be wise to be prepared for such a possibility. Furthermore, it will be helped by an approach that allows for the different constituents to coexist and find their own style of operating. Some will work best in collaboration and partnership with professional institutions; others may want to sit outside of "the system" and take a more independent stance about the changes they seek. Successful movements find ways to enable a dialogue to take place between all parties and build on common ground.

34.6.3 Age Range

The definition of the AYA age range is an ongoing debate that continues to linger [19], raised anew primarily by newcomers to the movement who require education and explanation to gain an understanding of the historical context. As a population, AYA is considered difficult to define, with some arguing the understanding is "evolving with time" ([10], p. 302) and complicated by a field that "crosses traditional boundaries and disciplines" ([1], p. 478). The definition has been argued in many forums internationally, and some consider that "It is questionable if another decade will close the debate" ([1], p. 481).

As an issue it is complicated by the different models of care and health systems that exist worldwide. What may make sense in one country may not work in another. For example, in the UK, AYA services were initially aimed at 13–24-year-olds, while, in the USA, the NCI Progress Review Group used the much larger 15–39-year range, relating the decision to a number of clinical factors including poor improvement in survival [1]. In Australia the federally funded Youth Cancer Services are open to 15–25-year-olds, while the ONTrac at PeterMac program, "Australia's first dedicated outreach service for young people with cancer" originally provided support for those 16–30 years ([10] p.303).

While this could create confusion, groups representing subsets of larger populations have generally shown willingness to speak of themselves as a part of a larger whole. In general, the tenor of the AYA oncology movement worldwide has been open and accepting enough to encompass all approaches, allowing the

differences to contribute to rather than disrupt the direction of travel.

34.6.4 Other Issues

In a similar manner to the age-range debate, there are other matters of concern to the general AYA oncology area which also cause varying degrees of disturbance and angst for the advocacy field. These include issues such as siloed healthcare delivery systems (which make it difficult to know who to target with advocacy approaches and complicated to achieve change) and the limited amount of dedicated research and common outcome or impact measures. Without comparable data, there is increased difficulty in demonstrating success, identifying issues, and providing support for arguments for greater attention, resources, and funding.

Additionally, there is the lack of a "one-size fits all" style model of care for AYAs. Differences in health systems, bureaucracy, training, and funding are all well-recognized barriers to a single model, but even geography can prove potentially problematic, such as in a country like Australia where the sheer size of the country versus the spread of population is a very practical consideration in terms of models of care [10]. Unfortunately, not having an agreed model creates a number of complications for the advocacy agenda. Similar to the issue of lack of impact measures, the absence of a common model means that it is difficult to make arguments for the efficacy of a standard approach or have a common understanding for consistent key messaging. It can also create confusion or a sense of disunity as individual, particular groups, or even countries argue for different approaches.

It should be acknowledged that division or public difference within the AYA advocacy community itself is also a challenge. Like the population it represents, the advocacy community is a diverse group with wide-ranging ideas and differing methods of advocating. While there has been a tremendous amount of goodwill, synergy, and collaboration, there is also the risk of opinions, personalities, and approaches clashing.

The common denominator in all these issues is the ability to draw focus and resources away from progressing the greater AYA agenda. The most passionate of the people involved can be distracted, collaborations can falter, and messages become confused. With such a large agenda still to move forward, the need to dodge such obstacles and maintain momentum is paramount.

Throughout the global progression of the AYA oncology movement, however, these differences have not stood in the way of collaborations and respect for each other's strengths. In other movements, such differences have become battlegrounds, and it is both encouraging and reassuring that this has not been allowed to happen in AYA oncology. The movements in each country have recognized the imperative to find their own ways, responding to the unique circumstances of each country, but within an overall philosophy of benefit for the entire population.

For example, in the USA the age range was originally developed in response to research about the lack of improvement in survival rates; as in, this whole group is failing in outcomes and survival; therefore, it must be addressed as a group. In the UK, however, the focus was much more on the transition ages and addressing the institutional failures in clinical treatment and professional support at this crucial time. In Australia, the focus was much more around the social and emotional needs of young people in their transition years outside of the hospitals and the health system. What is unique about our movement as a whole is that we have celebrated the strengths of each approach, as well as our differences, and are willing to learn from one another as each country begins to tackle aspects of the problem that may already be addressed in other countries.

Conclusion

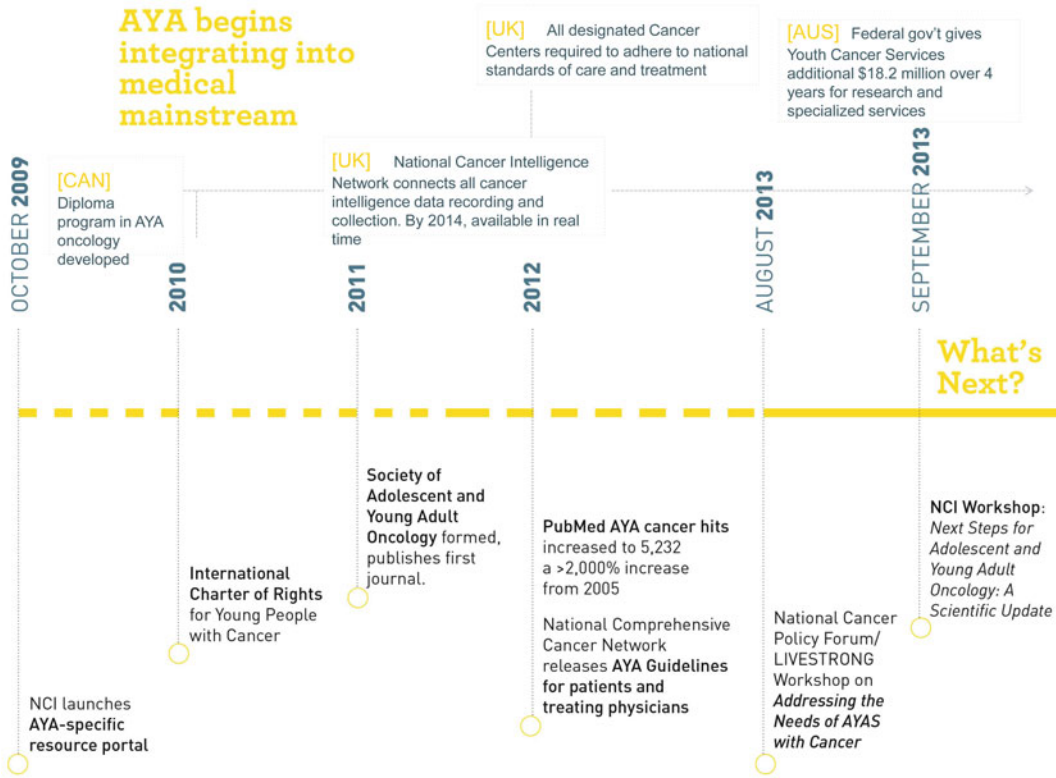
Advocacy, and the broad community that has supported and enacted it, has undeniably had an important impact on the progression of Adolescent and Young Adult Oncology around the world [3, 5]. It has provided impetus and breakthroughs, created community,

raised the profile of the field, and established momentum. From the trailblazers in the field to the local champions and from the numerous small organizations and supporters to the key backbone organizations who have taken a lead in coordinating and focusing the agenda, it has been a collaborative effort.

Much has been achieved and should be celebrated, but the work is not done. There is recognition that the "support and utilization of the peer advocacy community" is one of the most important issues or themes facing AYA Oncology in the next ten years" [1]. Advocacy will continue to be needed in order to overcome the challenges mentioned above, to ensure more change occurs and that outcomes improve and services for AYAs continue to evolve.

As the pace of social media and the technology that supports it increases, there will be new approaches and strategies adopted. This will not mean the replacement of traditional advocacy, but rather an increase in the arsenal of tactics the advocacy community has at its disposal. And a sense of humor will *always* be an important asset.

There is a risk of losing momentum due to the loss of good people, either to cancer or the fact that people move on with their lives and leaders may choose to leave the cause or step down their engagement. However, the strength of the movement depends on its ability to cultivate new leaders. The objective is to make these changes the mainstream, and, as such, they need to become woven into the fabric of future services. For that, the next generation of leaders and contributors and the generation after are even more important than those trailblazers and champions who have helped the movement through its adolescence.



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Conclusions, Perspectives, and Future Considerations

35

Ronald D. Barr, Lynn Ries, Andrea Ferrari, Jeremy Whelan, and Archie Bleyer

As a result of the AYA age range adopted by the US National Cancer Institute Progress Review Group, the authors of this second edition have risen to the challenge of extending the upper age limit from 29 to 39 years. This has uncovered some unanticipated revelations, especially in the realms of epidemiology and biology. For example, in the former, a remarkable and hitherto unknown incidence of prostate cancer in young adults has come to light, while in the latter, the age-related trajectory of characteristics that typify cancers in the AYA population has been expanded to bridge the gap between adolescents and older adults, as in acute lymphoblastic leukemia (ALL) and colorectal cancers. Another important finding is the overdiagnosis of some cancers in AYAs, as best evidenced by renal and thyroid carcinomas. These data have been amplified in the chapters on individual diseases.

The chapter on *Access and Models of Care* derives experiences from several parts of the world, offering examples for others to emulate while emphasizing the modified nostrum that "one size does not fit all." Elements of special importance to AYAs with cancer – psychological support, sexuality, and oncofertility – receive separate detailed attention. High survival rates, at least in high-income countries, prompt a focus on survivorship. The chapters on rehabilitation and exercise, financial issues, late effects, health-related quality of life, and future health discuss critical elements of the cancer journey. For those who are destined to have that journey cut short, the contributions on ethical issues and palliative/end of life care are particularly relevant.

In 2009 several of the editors of the first edition of this book proposed a list of themes [1] to be addressed in the forthcoming decade. These have been expanded in Table 35.1 and are discussed briefly in the following:

1. Elucidation of parameters other than age that define the AYA patient. In a broad sense, these

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Table 35.1 Priorities in AYA oncology

1. Elucidation of parameters other than age that define the AYA patient
2. Development of and participation in clinical trials benefiting AYA patients
3. Specialization of health services delivery
4. Focus on oncofertility
5. Professional training in AYA oncology
6. Addressing the economic costs of cancer care
7. Expanding access to health-care and health insurance coverage
8. Application of developmental behavior therapy to understanding the experience of cancer in young adulthood
9. Improving adherence of AYAs to cancer treatment and diagnostic studies
10. Support and utilization of the peer advocacy community

require greater understanding of the biology of cancers and their AYA hosts. The former will yield to powerful technologies such as next-generation sequencing studies, as described by Pui and colleagues with respect to ALL [2]. The focus on host biology must surely be the physiological trajectory from childhood to adult life and how the inherent changes impact cancer and its treatment. Specimens of tumor and normal tissue from AYAs are more underrepresented in biorepositories than for any other age group.

2. Development of and participation in clinical trials benefiting AYA patients. Collaborative initiatives involving pediatric and medical oncologists are beginning to bear fruit with respect to trial design, including changing limits on age eligibility, that are facilitating the availability of trials to AYAs with cancer. A nut that is proving at least as hard to crack is increasing the accrual of AYAs to these opportunities. There are many pitfalls on the pathway to enrollment [3] requiring multiple tactics to effect improvement, as exemplified by successes in the United Kingdom [4] and the United States [5].
3. Specialization of health services delivery. It has become a mantra in the AYA cancer community that programs, including physical facilities, designed to meet the specific needs of AYA patients (Fig. 35.1) will result in better outcomes. The jury has been sequestered but the verdict not yet given, for the evidence has not been subject to the requisite rigorous analyses. These must range from patient-reported outcomes to formal economic evaluation. Moreover, assessments must encompass a spectrum of elements including locus of care, transitions [6], long-term follow up, and future health and well-being. In view of the considerable commitments, not least pecuniary, to mushrooming AYA programs, in-depth assessment of their value must be a high priority.
4. Focus on oncofertility. If there is one issue that is peculiarly apposite for AYA oncology, this is surely it. Emblematic of the reproductive age span, the AYA population has a dominant interest in the preservation of their fertility. Responding to that need, Teresa Woodruff (who coined the term oncofertility [7]) and her colleagues formed the Oncofertility Consortium in 2006. As stated on their website https://oncofertility.northwestern.edu, "The Oncofertility Consortium is a national interdisciplinary initiative designed to explore the reproductive future of cancer survivors." This has provided a stimulus for others. In Canada the Cancer Knowledge Network launched the Oncofertility Referral Network in 2014 and is working in collaboration with the Canadian Fertility and Andrology Society to develop a national database that will provide performance metrics in this important area.
5. Professional training in AYA oncology. A stated priority of the standards committee of LIVESTRONG is to foster the development of educational programs, leading to formal certification, in AYA oncology for a wide spectrum of health-care professionals. Independently, initiatives in the United

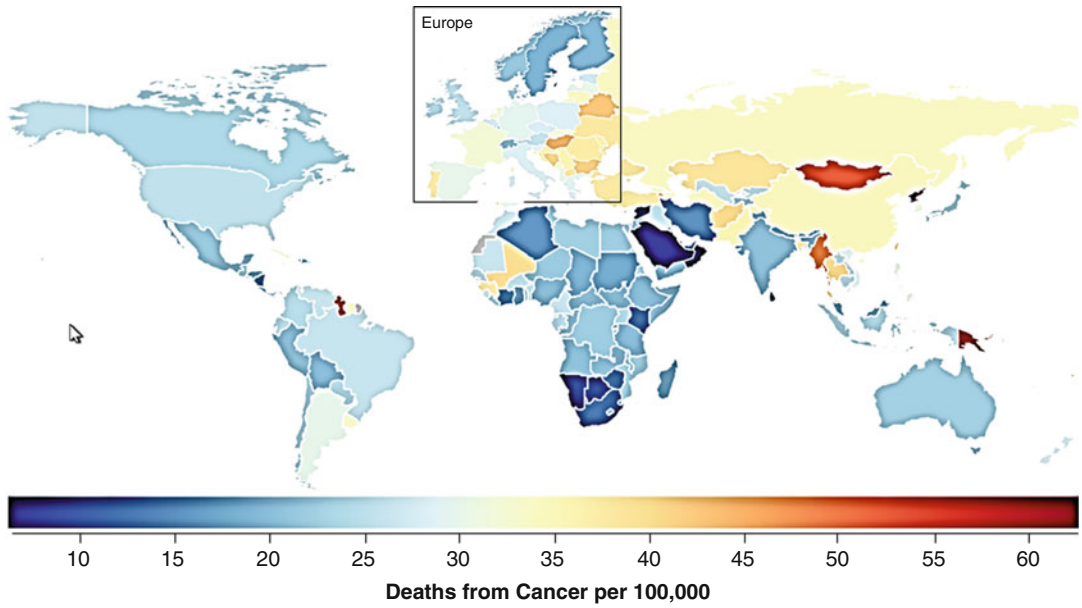

Fig. 35.1 Average cancer death rate during 2013 in 15- to 49-year-olds in 188 countries (Modified from Institute for Health Metrics and Evaluation (IHME) [36])

Kingdom, Australia, and Canada have risen to the challenge. In the United Kingdom, the University of Coventry offers three modules of e-learning, available to all health-care professionals, leading to a postgraduate certificate in teenage and young adult cancer care (http://www.coventry.ac.uk). A similar two semester course is offered by the Royal Children's Hospital in Melbourne, Australia, that provides a graduate certificate of adolescent health and well-being oncology stream (http://www.rch.org.au). As indicated in the Introduction, the Royal College of Physicians and Surgeons of Canada has acknowledged adolescent and young adult oncology as an area of focused competence with a full-time 1-year program for physicians that leads to a diploma in this subject. Additionally, the American Society of Clinical Oncology has 11 current online modules on AYA oncology available at http://university.asco.org/focus-under-forty.

6. The economic cost of medical care is a greater burden on AYAs than on any other age group. In general, they have the least economic resources and, among cancer survivors, the greatest financial hardship [8]. This issue has become all the more acute with the dramatic increase in the cost of cancer drugs that has affected both parenteral and oral medications [9, 10]. In the United States, the most common cause of personal bankruptcy is medical expenditure [11], and a large group of prominent oncologists worldwide has published a request for government regulation on cancer drug costs [12].
7. The role of health insurance for AYAs has also become all the more acute, especially since delays in and suboptimal medical care lead to more advanced stages of cancer in AYAs [13–15]. Since the first edition of this book, the United States made health insurance available to most 18- to 25-year-olds via their parents' health insurance policies. An estimated 4,000 AYAs were diagnosed with cancer during the first 15 months after insurance companies in the United States were required to cover, up to the age of 26, patients who would otherwise not have been insured [16]. The lack of health insurance for AYAs is more problematic in the United

States than elsewhere but underlies the socioeconomic differences in cancer survival outcomes and prevention described in this book.

8. Application of developmental behavior therapy to understanding the experience of cancer in young adulthood. The high prevalence and likely underestimation of psychological distress in AYA survivors of cancer is well described [17]. Regrettably this is related in part to unsatisfied needs for psychological support. This is particularly problematic in the age group 20–29 years [18], defining a population for whom services are especially necessary. The contributions of peer support programs have been important in reducing this deficit, as have the numerous social media targeting the AYA cancer survivor community. Nevertheless, high proportions of these young people report distress, compounded by unmet needs for information, counseling, and practical support. Developing a valid tool for the detection of psychological distress in this population remains in itself an unmet need [19].
9. A specific need is to improve adherence to treatment and diagnostic evaluation. AYAs are the age group that has the least compliance with oral medication and, in the United States at least, the least health insurance to cover the costs of clinical, hospital, and drug costs. In AYAs with leukemia, decreased adherence to oral medications has been associated with lower disease-free survival rates [20, 21]. In adolescents with ALL, only one-third of blood samples showed concentrations of the 6-mercaptopurine active metabolite within the therapeutic reference range [22]. Nonadherence to oral 6-mercaptopurine has been found to increase at an odds ratio of 1.07 per year of age [23]. Young adults with chronic myeloid leukemia, for whom oral therapy with BCR-ABL tyrosine kinase inhibitors is critical, have been shown to have a lower adherence than older adults [24].
10. Support and utilization of the peer advocacy community. The field of AYA oncology has been advanced considerably as a result of the highly effective national initiatives undertaken by communities of advocates and support groups. These have been especially well developed in Australia [25], the United Kingdom [26], and the United States [27]. Particularly notable contributions have been made by LIVESTRONG in the United States that include position statements on quality of care [28] and the training of health professionals [29]. It is anticipated that more initiatives of this sort will be forthcoming. Moreover, as these entities work increasingly and synergistically with organizations of health-care professionals, the pace of progress in AYA oncology will only accelerate, to the benefit of young people with cancer at large.

A review of the unmet needs of AYA with cancer was undertaken by the Institute of Medicine in the United States at a workshop in July 2013 [30]. Particular attention was paid to the psychosocial aspects, integrating data from the AYA HOPE Study [31], an online survey conducted by LIVESTRONG, information provided by the Behavioral Risk Factors and Surveillance System [32] that focused on employment, and the Medical Expenditure Panel Survey [33] that identified the health and economic burden experienced by AYA survivors of cancer. Clearly many needs remain unmet.

This second edition of *Cancer in Adolescents and Young Adults* highlights the need to revise the classification system for cancer in AYAs [34], an anticipated outcome of the effort of preparing this edition. As noted by Heidi Adams in her Foreword, interest in AYA oncology has gathered a considerable "head of steam." The metric of the number of publications is useful and will continue as a yardstick. The editors, for example, continue to stimulate interest [35] and, will draw attention to the need for good performance indicators, such as clinical trial accruals, increased availability of cancer and host tissue in biospecimen banks, accelerated translational research, and utilization of oncofertility services, as well as rigorous economic evaluation. The need for bio-

specimens of AYA tumor and normal tissue merits emphasis since AYA tumor and normal tissue samples are more underrepresented in biorepositories than for any other patient age. Without adequate specimens, theme #1 above and in the table cannot be addressed effectively.

As enunciated by others [35], "it should be clear to all that real results can only be achieved if there is genuine cooperation between, and leadership by, both pediatric oncologists and medical oncologists. While, historically, adult and pediatric healthcare professionals may be unaccustomed to working with each other, their respective experiences and resources should be pooled for the benefit of the AYA patient. It is encouraging to know that willing hands are reaching out to cross the divide."

There is no room for complacency. The great majority of AYAs with cancer, residing in low- and middle-income countries, cannot avail themselves of the advances described in this volume. Figures 35.1 and 35.2 are derived from a resource developed recently by the Institute for Health Metrics and Evaluation in conjunction with the University of Washington for global comparison of disabilities [36]. Their geographical-visualization world map for cancer illustrates that, for the year 2013, the death rate in 188 countries varies more than tenfold, from 6 to 63 deaths per 100,000 populations per year. The

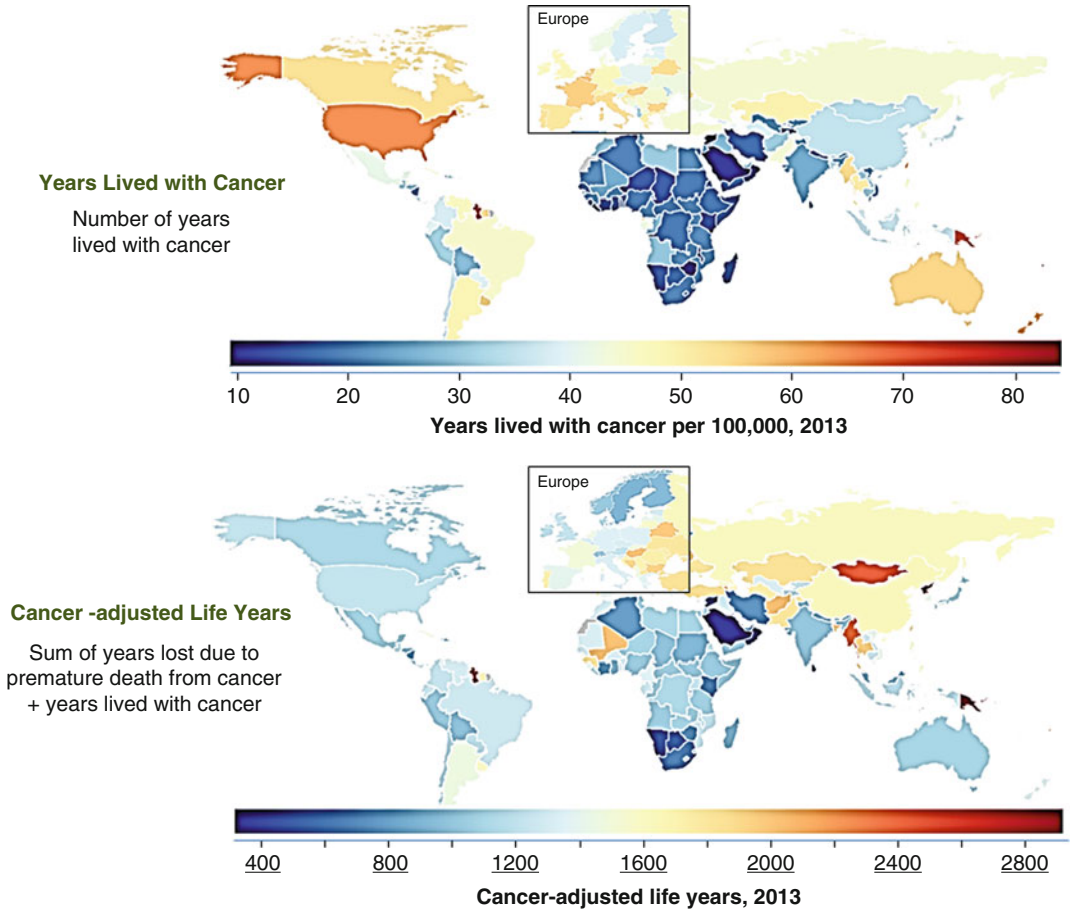

Fig. 35.2 Average number of years lived with cancer (*upper* panel) and average number of disability-adjusted (*lower* panel) during 2013 in 15- to 49-year-olds in 188 countries (Modified from Institute for Health Metrics and Evaluation (IHME) [36])

highest cancer death rates among 15- to 49-year-olds worldwide were in Southeast Asia and Eastern Europe, and the lowest rates were in the Middle East, Africa, and the Americas (Fig. 35.1). The 15- to 39-year age data were not available from this resource.

In considering the burden of disease while alive, countries with the most number of years lived with cancer, between the ages 15 and 49, included the United States, Canada, Australia, France, Italy, Belarus, Hungary, Papua New Guinea, and Guyana (Fig. 35.2, upper panel) [36]. Those with the least number of years lived with cancer in this age group were in Africa, the Middle East, India, China, and Southeast Asia (Fig. 35.2, upper panel). The total impact of cancer, as measured by the sum of years lived with cancer plus the years lost due to premature death from cancer ("disability-adjusted life years"), was greatest in Asia and eastern Europe and least in the Middle East, most countries of Africa, North and Central America, most countries of South America, and the Nordic Countries (Fig. 35.2, lower panel).

A comparison of the death rates (Fig. 35.1) with the years lived with cancer (Fig. 35.2, upper panel) provides some explanations for the wide variation in the death rate. The lower mortality rate throughout most of Africa is likely due primarily to a lower incidence. The high death rate and few years of life lived with cancer in Mongolia and Myanmar implicate very poor survival. With both a high rate of deaths and years lived with cancer, the age group in Papua New Guinea and Guyana may also face poor survival. The lower death rates in North America, Western Europe, and Australia can be attributed to better therapy, prolonged survival, and higher cure rates. These regions may also have a higher incidence of cancers that are potentially preventable, such a melanoma and cancer of the lung, oral cavity/oropharynx, anorectum, and uterine cervix [38].

It behooves us, as an international community of stakeholders, to advocate for inclusion of these young people in the evolving success of AYA oncology to which this book is dedicated. As stated by others [37], "though rules and recommendations might be defined to improve our chances of success, the human element remains essential; no progress will be made without the fundamental influence of forward-thinking, charismatic heads willing to dedicate their professional lives to AYA patients."

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