Hematologic Malignancies

Andreas Engert
Anas Younes *Editors*

Hodgkin Lymphoma

A Comprehensive Overview

Second Edition

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ISBN 978-3-319-12504-6 ISBN 978-3-319-12505-3 (eBook)
DOI 10.1007/978-3-319-12505-3
Springer Cham Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014959423

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

Hodgkin lymphoma has become one of the most curable malignancies, both in adult and pediatric patients. More than 80 % of all patients can be cured with risk-adapted treatment including chemo- and radiotherapy. This progress is largely due to the development of multi-agent chemotherapy more than 40 years ago and the improvements in radiotherapy. Since then, this fascinating disease has been in the focus of scientific and clinical research. Major recent achievements were the definite proof that Hodgkin lymphoma is a true malignancy derived from "crippled" B-lymphocytes. Establishing immortal cell lines from patients with end-stage disease initiated a variety of different research activities that advanced our understanding of Hodgkin lymphoma pathophysiology, biology, and immunology, in addition to providing an in vitro model for testing new therapies. The discovery of the CD30 antigen that is expressed in high density on H-RS cells substantially improved the prognostic precision. Monoclonal antibodies against this antigen were successfully used for diagnostic immunophenotyping and were exploited therapeutically. After a number of unsuccessful clinical trials with unconjugated antibody constructs or fully human monoclonal antibodies targeting CD30, this strategy has come full circle with the advent of an anti-CD30 antibody drug conjugate that has given remarkable responses in relapsed and refractory Hodgkin lymphoma.

Due to the very good prognosis and the young age of most patients affected, Hodgkin lymphoma has also become a model to study long-term effects of radio- and chemotherapy. Unfortunately, a substantial number of patients die from treatment-related long-term toxicity. We must thus very carefully balance our attempts to further improve disease control with the need to keep the risk of long-term consequences as low as possible. In addition, there are a number of relevant physical and psychosocial issues that need to be further exploited including the risk of infertility and fatigue. Fortunately, after more than 20 years of standstill, we now experience the development of new targeted treatment also for patients with Hodgkin lymphoma. This hopefully might result in more individualized and less toxic treatments for our patients. The next decade will witness additional progress relevant to exploiting the interaction between the malignant H-RS cells and the immune cells in the microenvironment, which will likely result in further refinement of our treatment strategies.

This book should give you a comprehensive overview on the most relevant biology, diagnostic and clinical aspects of Hodgkin lymphoma. We would like to express our sincere gratitude to all those who have contributed to this project.

Cologne, Germany — Andreas Engert
New York, NY, USA — Anas Younes

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Part I

Epidemiology and Pathogenesis

Epidemiology

1

Sally L. Glaser, Ellen T. Chang, Christina A. Clarke, and Theresa H. Keegan

Contents

Abbreviations

aHR	Adjusted hazard ratio
CI	Confidence interval
COX	Cyclooxygenase
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
GWAS	Genome-wide association study
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
HRS	Hodgkin Reed-Sternberg
IL	Interleukin
IM	Infectious mononucleosis
OR	Odds ratio
RR	Relative risk
SEER	Surveillance, Epidemiology, and End Results

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_1,

SES	Socioeconomic status
SIR	Standardized incidence ratio
SLE	Systemic lupus erythematosus
UK	United Kingdom
USA	United States of America
UVR	Ultraviolet radiation
VCA	Viral capsid antigen

Hodgkin lymphoma (HL) is a relatively rare malignancy, occurring in the United States (USA) at approximately 1/20th the rate of lung cancer and 1/8th the rate of non-Hodgkin lymphoma in 2010 [132]. Yet, it has inspired considerable scientific interest because of its clinical heterogeneity, with some aspects characteristic of malignancy but others recalling an infectious process; the complexity of its histology, including the infrequent malignant (Hodgkin Reed-Sternberg (HRS)) cell in an otherwise normal reactive infiltrate, and the variability of cell surface markers [173]; and its occurrence not only in older adults but also in children and young adults, in whom it is a common cancer [132]. Following MacMahon's seminal papers on HL epidemiology [171, 172], epidemiologists have worked to disentangle the complexity of HL so as to arrive at a clear understanding of its pathogenesis and etiology. However, even as study findings have helped elucidate some aspects of HL etiology, they have continued to reveal significant epidemiologic heterogeneity, which in turn complicates the interpretation of epidemiologic research conducted for HL as a single entity and perhaps challenges how it is currently categorized. Indeed, in 1999, HL was split into two main groups—classical HL, which comprises the majority of the histological subtypes, and nodular lymphocyte predominant HL, an uncommon disease considered a B-cell lymphoma despite HRS cell presence [110]. Even so, for classical HL, the central feature of its epidemiology is the consistent observation of heterogeneity in its occurrence and risk factors.

Therefore, this chapter will provide an overview of the epidemiology of HL with particular attention to its etiologic heterogeneity. It will do so for several areas of established relevance: incidence patterns, timing of exposure to common infections, the role of Epstein-Barr virus (EBV), altered immune function, genetic susceptibility, and selected lifestyle exposures. Where possible, it focuses on classical HL.

1.1 Incidence Patterns

HL has a low and relatively stable incidence with a slight male excess. Worldwide, estimated age-adjusted incidence rates for 2012 were 1.1 and 0.7 per 100,000 males and females, respectively [75]. Over time in the USA, HL incidence rates overall changed minimally since 1973 [132].

1.1.1 Heterogeneity

HL incidence varies internationally: estimated 2012 incidence rates ranged from 2.3 and 1.9 per 100,000 males and females in more developed regions to 0.8 and 0.5 per 100,000 males and females in less developed regions [75]. Additional rate variation occurs by race/ethnicity. In England, age-standardized rates of HL per 100,000 person-years for 2001–2007 were higher in South Asians than whites [218]. Within the USA, the average annual age-adjusted incidence rates per 100,000 (2006–2010) were 3.2 in non-Hispanic whites (hereafter referred to as "whites"), 2.5 in blacks, 2.3 in Hispanics, and 1.3 in Asians [225]. However, while HL rates showed little secular change for US whites, in US Asians they increased significantly, at 2.2 % annually (3.1 % in females) between 1992 and 2010 [132]; a similar, albeit larger, annual rate increase (6.5 %) occurred in Japan in that period [51]. This rate variation across relatively homogeneous populations suggests additional group-specific influences on disease occurrence.

Arguably, the hallmark of HL epidemiology is its unique variation in incidence by age at diagnosis. In 1902, Dorothy Reed (for whom the HRS cell was named in part) wrote, "The disease occurs in more than half the instances in early life; probably the majority of cases are in children" [209]. In 1957, Brian MacMahon described

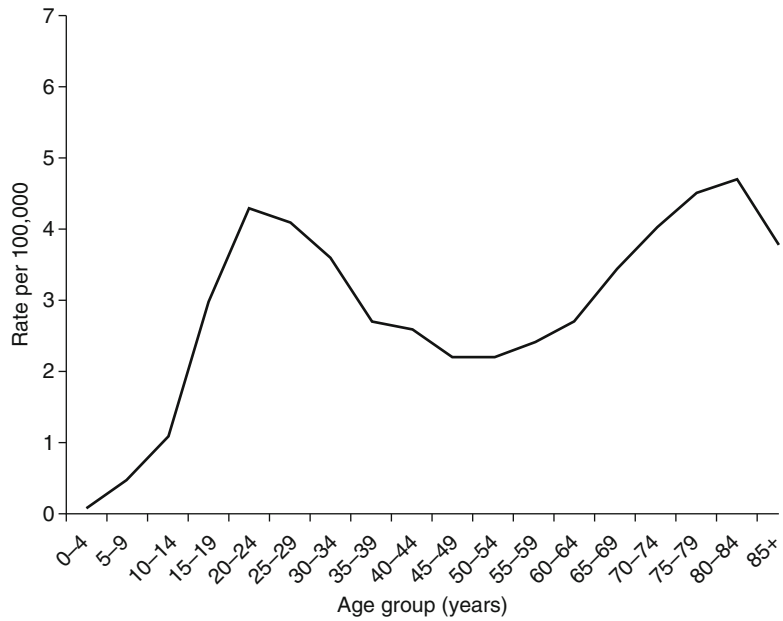

Fig. 1.1 Average annual incidence rates of Hodgkin lymphoma per 100,000 persons by age group, 2006–2010, US Surveillance, Epidemiology, and End Results program [225]

the age-incidence curve as bimodal [171] and, in 1966, the young-adult incidence peak as "…a distinct bump, almost as though a separate group of cases with a symmetrical age distribution around age 25–29 had been superimposed on the basic lymphoma pattern" [172]. While this bimodal curve remains apparent in recent US data (Fig. 1.1 [225]), its shape varies substantially by patient and tumor characteristics, including race: Fig. 1.2 shows that the young-adult peak was most pronounced in whites, intermediate in blacks, and lowest in Hispanics and Asians [225]. In 1971, Correa and O'Conor showed in international data that the magnitudes of childhood and young-adult rates for males were indirectly and directly correlated, respectively, with regional economic status [57]. Updating this analysis, Macfarlane et al. found that this correlation had weakened as international economic differentials narrowed over time [169]. However, HL rates in young adults are higher in populations experiencing improved standards of living, as noted in Singapore over time [125], and in comparisons of Asians in Asia to those who migrated to the USA [87] and Canada [8] and of US-born to foreign-born Asians in California [53]. Nevertheless, an age-specific social-class gradient persists both internationally [34] and within the USA: HL rates in California (1988–1992) varied with neighborhood socioeconomic status (SES) for young but not older adults (Fig. 1.3) [52] and the SES gradient further differed by racial/ethnic group, being strongest for Hispanic and Asian females (Table 1.1).

The age-specific variation in HL incidence rates also differs by sex. HL is slightly less common in men than women—an uncommon pattern in cancers [69]—at ages 15–29 but consistently more common in older men than women (Fig. 1.4) [225]. Furthermore, temporal rate increases seen for young adults have been more pronounced in women than men [50, 125]. HL rates also differ markedly by histological subtype (Fig. 1.5) [225]. Nodular sclerosis HL, the most common subtype (average annual age-adjusted incidence rate of 1.6 per 100,000 in the USA in the period 2006–2010 [225]), primarily affects adults under age 45. Mixed cellularity, the next most common subtype (average annual age-adjusted incidence rate of 0.3 per 100,000 in the USA in the period 2006–2010 [225]), has a slight young-adult peak and rising rates with age. The positive associations of neighborhood SES with HL incidence in California young adults (Fig. 1.3) occurred primarily for nodular sclerosis HL [52].

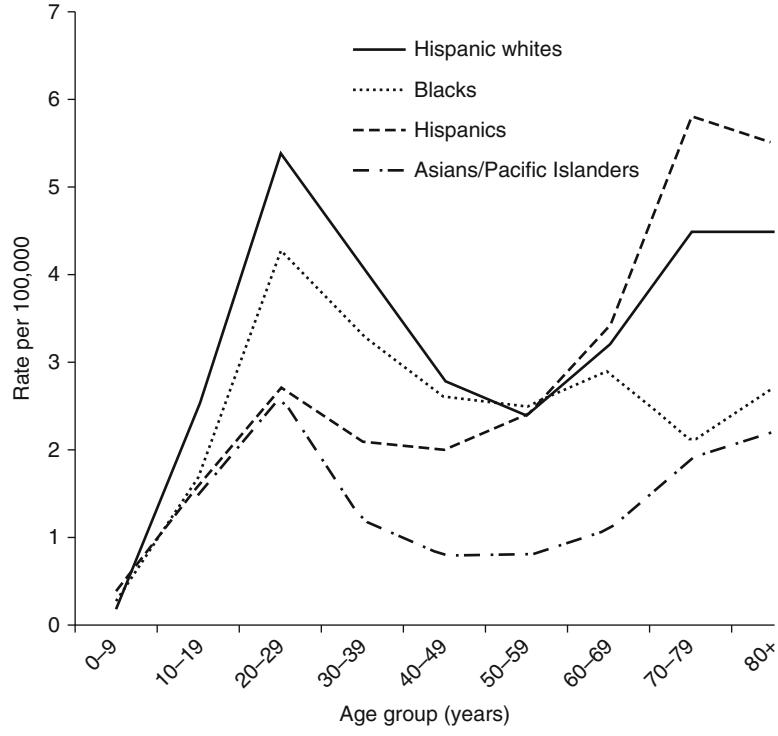

Fig. 1.2 Average annual incidence rates of Hodgkin lymphoma per 100,000 persons by age group and race/ethnicity, 2006–2010, US Surveillance, Epidemiology, and End Results program [225]

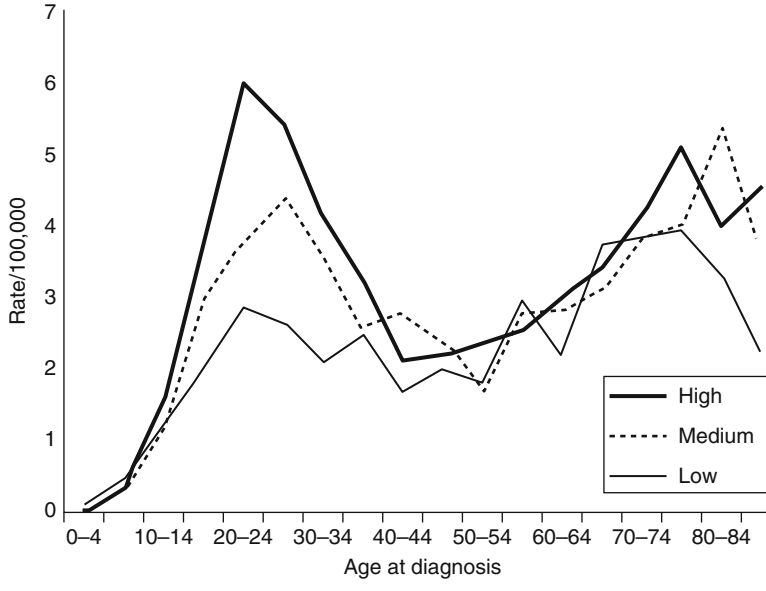

Fig. 1.3 Average annual incidence rates of Hodgkin lymphoma per 100,000 persons by age group and tertile of neighborhood socioeconomic status, 1988–1992, California [52]

Table 1.1 Average annual age-adjusted[a] incidence rates of Hodgkin lymphoma per 100,000 person-years, by race/ethnicity, age group, tertiles of neighborhood socioeconomic status (SES), and sex, 1988–1992, California [52]

	Ages 15–44 years at diagnosis												Ages ≥45 at diagnosis											
	High SES				Medium SES				Low SES				High SES				Medium SES				Low SES			
	Male		Female		Male		Female		Male		Female		Male		Female		Male		Female		Male		Female	
Race/ethnicity	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate	*N*	Rate
Whites	437	4.88	400	4.61	352	4.44	319	4.28	160	4.00	136	3.50	256	4.24	169	2.37	169	3.61	142	2.32	106	4.07	80	2.25
Blacks	18	3.92	14	3.30	29	2.93	24	2.62	42	3.44	35	2.45	<5	–	10	4.53	13	4.23	9	2.61	17	3.06	13	1.54
Hispanics	31	2.16	39	2.95	75	2.32	46	1.67	116	1.69	62	1.03	24	5.71	9	1.58	31	4.37	25	3.19	42	3.16	34	2.25
Asians	17	1.19	20	1.34	14	0.95	8	0.57	12	1.28	5	0.44	11	2.38	5	0.84	13	3.12	<5	–	11	2.60	<5	–

[a]Standardized to the 2000 US age standard

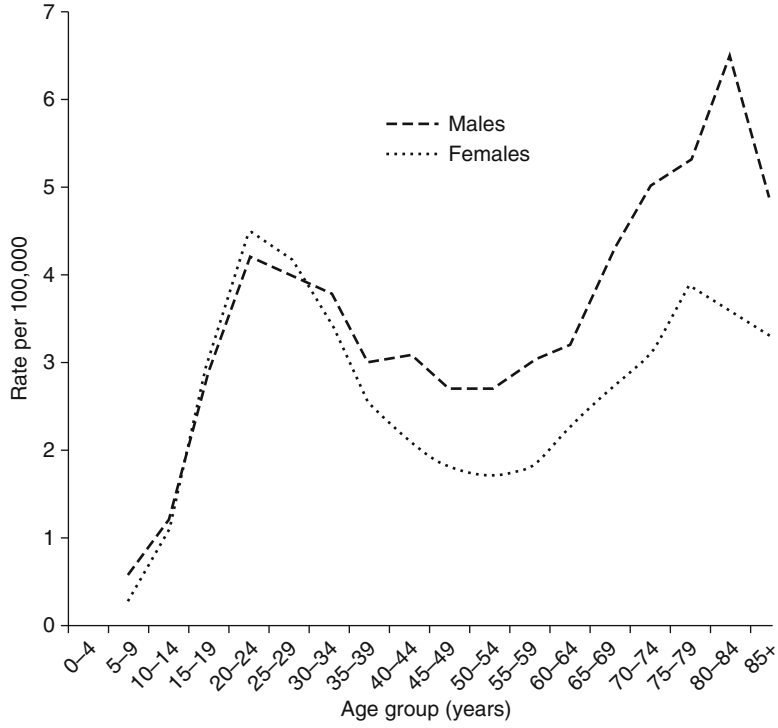

Fig. 1.4 Average annual incidence rates of Hodgkin lymphoma per 100,000 persons by age group and sex, 2006–2010, US Surveillance, Epidemiology, and End Results program [225]

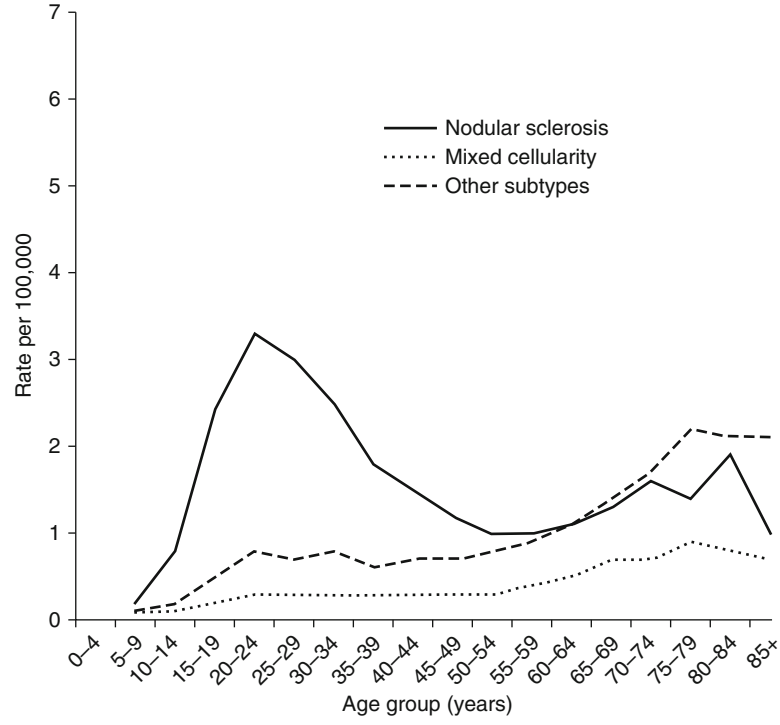

Fig. 1.5 Average annual incidence rates of Hodgkin lymphoma per 100,000 persons by age group and histological subtype, 2006–2010, US Surveillance, Epidemiology, and End Results program [225]

A challenge in sorting out these incidence patterns involves the comingling of HIV-associated and HIV-unassociated cases in many reports. In the USA, 3.8 % of all HL was estimated to be HIV-associated, but this prevalence was higher among males than females (6.0 % vs. 1.2 %) and, among males, substantial among 40- to 59-year-olds (14.2 %), non-Hispanic blacks (16.9 %), Hispanics (9.9 %), lymphocyte-depleted HL (15.1 %), and mixed cellularity HL (10.5 %) [217]. The concentration of HIV-associated cases in these subgroups may skew some of the incidence patterns and trends observed in population data.

Thus, the descriptive epidemiology of HL clearly illustrates variation in incidence across patient and characteristics. While some clustering of characteristics (e.g., young-adult HL primarily comprising the nodular sclerosis subtype) suggests etiologically distinct subgroups of HL, the inconsistency of many such associations (e.g., the occurrence of mixed cellularity HL in some young adults) prevents the clean assignment of subcategories of HL based on these characteristics.

1.2 Timing of Exposure to Common Infections

Based on epidemiologic heterogeneity in HL by age, MacMahon proposed an infectious etiology for the disease in young adults [172]. Noting similar incidence increases with age in young adults for HL and paralytic polio prior to the availability of polio vaccine, Gutensohn and Cole proposed that HL at these ages resulted from late infection with a common agent [103]. This "delayed-infection" hypothesis was supported by three lines of evidence: (1) the association between HL rates and social-class rates [52, 59, 82, 100, 103] and a twofold or greater increased risk of HL in young adults with a higher personal SES and educational level [1, 18, 55, 86, 103, 104, 216], which suggested that environmental conditions regulating exposure to infections impacted disease risk; (2) the increased HL risk in young adults associated with having an early birth order, a small family, a more highly educated mother, and, more recently, not attending nursery school [3, 18, 27, 39, 41, 104, 237], which suggested a role of protected childhood environments and thus reduced or delayed exposure to infectious agents; and (3) the finding of a threefold elevated risk of HL in young adults reporting a history of infectious mononucleosis (IM) [35, 56, 119, 120, 123, 156, 178, 210] (a manifestation of primary infection with EBV (a ubiquitous B-lymphotropic oncogenic virus that establishes latent infection and causes IM [138])) occurring in adolescence or young adulthood rather than childhood (the more usual age at infection).

1.2.1 Heterogeneity

While the timing of infection relates to HL development in general, the patterns of association vary with age. In the 1970s, HL risk in young adults (ages 15–39 years) was associated with having fewer siblings, living in a single- vs. multiple-family house, and having better educated parents, whereas in children (ages 0–14 years) and older adults (ages 55 years and older), risk increased with measures of more rather than fewer social exposures in childhood [104–106]. These age differences in risk patterns, supported by later studies [3, 18, 27, 39, 237], were interpreted to suggest three etiologic forms of HL—childhood, young adult, and older adult—an important initial paradigm of HL epidemiology. In more recent studies, many of these childhood social-class risk factors have not been associated with HL risk [41, 64, 85, 86, 123], suggesting that temporal demographic changes, such as decreasing family size, may have altered some of the childhood exposures previously relevant to HL development [41, 86].

1.3 Role of Epstein-Barr Virus (EBV)

The inference from the IM-HL association that EBV might have a direct role in HL etiology has been supported by serologic and tumor findings. After HL patients were noted to have elevated

anti-EBV titers compared to controls (e.g., [74]), Mueller et al. demonstrated that IgA and IgG antibody titers against EBV lytic and latent antigens were significantly elevated before HL diagnosis, with patterns that suggest viral reactivation and enhanced replication [184]. These findings suggest defective immunological surveillance and control of infection with EBV leading to viral reactivation and, potentially, a higher risk of B-cell transformation and HL development. In the late 1980s, this possibility was supported by detection in some HL tumors of EBV gene products that were monoclonal and expressed by all HRS cells, indicating infection prior to malignant expansion [236]. More recently, increased HL risk was associated with detectable circulating plasma or serum EBV DNA [202, 234]. HL and IM patients were distinguished by modified lytic antigens [174], and patterns of latent antigens [188], supporting the concept of immune dysregulation in HL independent of IM history.

1.3.1 Heterogeneity

The proportion of tumors with evidence of EBV in the malignant cells (hereafter called EBV-positive) varies substantially by patient demographic and tumor characteristics, providing strong evidence of the virus' varying role across subsets of HL [84, 142]. In 1,546 patients from 14 studies, the percentages of tumors that were EBV-positive were 34 and 64 % in developed and less developed countries, 23 and 70 % for nodular sclerosis and mixed cellularity histologies, 48 and 22 % in males and females, 36 % and 60–65 % in whites and most non-whites, and higher in children (57 %) and older adults (52 %) than in young adults (32 %) [84]. Similar differences in associations of EBV and HL by age, sex, and race/ethnicity emerged in more uniformly collected population-based data from 1,032 US cases (Table 1.2) [91], 537 UK cases [143], 515 Dutch cases, and 157 northern Chinese cases [135]. Estimated incidence rate curves for EBV-positive and EBV-negative HL in the UK (Fig. 1.6) show the close resemblance between age-incidence curves for EBV-positive HL and mixed cellularity (Fig. 1.5), and for EBV-negative HL and nodular sclerosis (Fig. 1.5).

Like descriptive findings, analytic findings also support EBV-positive and EBV-negative HL as separate pathogenic entities. Studies to relate risk of EBV-positive HL to IM history produced mixed findings due, in part, to possibly inaccurate self-reported history of IM [5, 41, 62, 90, 183, 190, 222]. However, in prospective data linking serologically confirmed IM with HL diagnoses from a population-based registry, Hjalgrim et al. observed that IM was associated only with risk of EBV-positive HL (estimated RR = 4.0, 95 % CI 3.4–4.5), with an estimated median time from IM to HL of 4.1 years (95 % CI 1.8–8.3) [119]. Chang et al. showed that EBV-positive HL patients were more likely than EBV-negative patients to be EBV carriers and to have more prevalent and elevated EBV antibody titers against both lytic

Table 1.2 Numbers of Hodgkin lymphoma cases and percentages with Epstein-Barr virus (EBV)-positive tumors by patient age group, race/ethnicity, and sex, California regions, 1988–1997 [91]

	White				Hispanic			
	Males		Females		Males		Females	
Age group (years)	*N*	% EBV-positive	*N*	% EBV-positive	*N*	% EBV-positive	*N*	% EBV-positive
0–14	10	50.0	11	9.1	20	70.0	9	88.9
15–34	137	25.6	189	13.2	55	38.2	47	12.8
35–54	88	19.3	84	9.5	23	47.8	28	39.3
55+	34	49.3	26	38.2	20	85.0	17	76.5
Total	304	29.9	352	17.1	118	53.4	101	37.6

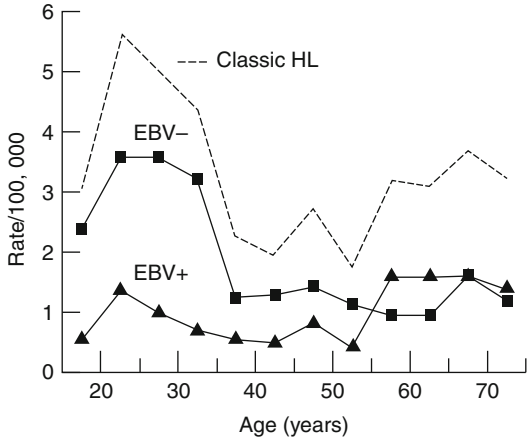

Fig. 1.6 Age-specific incidence rates of Hodgkin lymphoma per 100,000 person-years and Epstein-Barr virus (EBV) tumor status, 1993 to mid-1997, ages 16–74 years, Scotland and Northern England [143]

and latent virus antigens [40]. In pre-diagnosis sera, anti-EBV antibody patterns were altered in EBV-positive but not EBV-negative HL [161], and detectable pretreatment circulating EBV DNA appeared to be a feature of EBV-positive but not EBV-negative disease [79, 80]. These findings support an aberrant immune response to EBV and thus abnormal immunity in patients with EBV-positive HL compared to those with EBV-negative HL, with risk likely exacerbated by differences in other factors (Table 1.3). Jarrett suggested that HL represents four entities—one in children (EBV-positive), one in young adults experiencing late EBV infection (EBV-positive), one in older (and any immunosuppressed) persons (EBV-positive), and one (EBV-negative) primarily in young adults [141, 144].

1.4 Immune Function

A role for immune function in HL pathogenesis is anticipated, as HL is a B-cell malignancy characterized by immune dysregulation and, within the tumor, by a reactive inflammatory infiltrate and abnormal cytokine expression [173]. Indeed, the etiologic importance of immune function has been demonstrated directly by associations of HL risk with HIV infection (which depletes T-helper cell populations) and iatrogenic immunosuppression after organ transplantation, with diseases involving immune dysregulation, and with evidence of inflammation.

1.4.1 Immunodeficiency

Risk of HL is strongly increased in persons with primary immune deficiencies [187] and with immunosuppression subsequent to HIV infection or organ transplantation. From large linkages of US population-based AIDS and cancer registries, HL risk in HIV-infected populations was estimated at 11.5-fold (95 % CI 10.6–12.5) higher than in the general population, with greater risks for the mixed cellularity (RR = 18.3, 95 % CI 15.9–20.9) and lymphocytic depletion (RR = 35.3, 95 % CI 24.7–48.8) histological subtypes [78]. Compared to HIV-unrelated HL, HIV-HL is clinically more aggressive, portends poorer survival, and is almost uniformly EBV-positive [16]. Among HIV-infected persons, HL risk is higher for those with CD4 cell counts of 150–199 cells/μL than for those with fewer than 50 cells/μL [21], implying greater risk with moderate than with severe immunodeficiency. Accordingly, HIV-HL rates have increased since the introduction of highly active antiretroviral therapies in 1996 [73], presumably because of related improvements in average CD4 counts. With iatrogenic immunosuppression following solid organ transplant, HL incidence is at least three times higher than in the general population (standardized incidence ratio (SIR) = 3.6, 95 % CI 2.9–4.4), with risk significantly elevated and increasing with time 1 year after transplant [54]. This observation also supports a role in HL pathogenesis for prolonged, moderate immunosuppression, as opposed to the acute, severe immunosuppression typical of induction therapy. In patients who had undergone bone marrow transplantation, the incidence of HL was estimated at sixfold (SIR = 6.2, 95 % CI 2.7–12.0 [211]) and nearly 15-fold higher (SIR = 14.8, 95 % CI 3.9–32.9) than expected [11]. HL occurring post transplant is also thought to be largely EBV-positive [211].

Table 1.3 Risk factor patterns for Hodgkin lymphoma (HL) subclassified by tumor Epstein-Barr virus (EBV) status, selected studies

Risk factor	Study	Patient group	Adjusted odds ratios (95 % confidence intervals)		
			EBV-positive HL vs. controls	EBV-negative HL vs. controls	EBV-positive vs. EBV-negative HL
Social-class measures					
Lower vs. higher education	[40][a]	All adults			0.8 (0.6–1.0)
Single vs. shared bedroom, age 11	[90][b]	Young-adult women	**4.0 (1.1–14.4)**	1.0 (0.7–1.6)	
N of older siblings (trend per sibling)	[123][c]	Young adults	0.77 (0.56–1.05)	1.01 (0.83–1.22)	**0.65 (0.45–0.95)**
N of older siblings (trend per sibling)		Older adults	**1.35 (1.06–1.70)**	0.84 (0.68–1.03)	**1.60 (1.12–2.29)**
EBV infection					
Elevated antibody to VCA	[161][d]	All adults	3.1 (1.1–8.7)	1.7 (0.9–3.5)	1.4 (0.5–3.8)
Anti-EBNA-1: anti-EBNA-2 ≤ 1.0			4.7 (1.6–13.8)	0.4 (0.1–1.3)	14.0 (2.7–72.5)
IM	[123][e]	Young adults	**3.96 (2.19–7.18)**	1.36 (0.81–2.26)	**2.68 (1.40–5.12)**
Years since IM: 1–4			**11.86 (3.10–45.3)**	0.41 (0.04–3.75)	
Smoking					
Current vs. never	[37][f]	All adults	**2.26 (1.69–3.02)**	**1.40 (1.08–1.81)**	
Current vs. never	[145][g]	All adults	**1.81 (1.27–2.56)**	1.02 (0.95–1.52)	**1.45 (1.02–2.05)**
Former vs. never			1.28 (0.93–1.78)	1.02 (0.79–1.33)	1.11 (0.79–1.57)
Ultraviolet radiation					
High (quartile 4) vs. low lifetime	[180][h]	All adults	**0.56 (0.35–0.91)**	0.86 (0.63–1.19)	

[a] $N = 95$ EBV-positive HL cases, 303 EBV-negative HL cases (OR adjusted for age, sex, education level)
[b] Ages 19–44: $N = 24$ EBV-positive HL cases, 187 EBV-negative HL cases; ages 45–79: $N = 13$ EBV-positive HL cases, 44 EBV-negative HL cases (OR for EBV-positive HL vs. controls adjusted for age, race/ethnicity, Catholic religion, ever smoking, childhood household size, birth order, bedroom sharing at age 11, and number of playmates at age 8; OR for EBV-negative HL vs. controls adjusted for age, race/ethnicity, Catholic religion, lactation, birthplace, living in a rented family home at age 8, childhood household size, birth order, bedroom sharing at age 11, and number of playmates at age 8)
[c] Ages 18–44: $N = 85$ EBV-positive HL cases, 253 EBV-negative HL cases; ages 45–74: $N = 57$ EBV-positive HL cases, 104 EBV-negative HL cases (OR adjusted for age, gender, country, history of IM, maternal education)
[d] $N = 40$ EBV-positive HL cases, 88 EBV-negative HL cases (OR adjusted for age, sex, race, year of serum collection, and histology)
[e] $N = 95$ EBV-positive HL cases, 303 EBV-negative HL cases (OR adjusted for age, sex, education level, smoking status, elevated VCA IgG and IgA, and EA IgA and EBNA-1: EBNA-2 ≤ 1.0)
[f] Subset analysis within a meta-analysis of 14 case-control and 3 cohort studies
[g] Pooled analysis of seven case-control studies. Case series analyses, EBV-positive vs. EBV-negative, took into account the correlation between EBV status and histology
[h] $N = 208$ EBV-positive HL cases, 526 EBV-negative HL cases (OR adjusted for age, sex, study center, education/socioeconomic status, and skin pigmentation)

1.4.2 Autoimmune Conditions

HL risk is increased in persons with certain autoimmune diseases, although such evidence is impacted by the often-small sample sizes given the rarity of these conditions and by the possibility of reverse causality [223]. A large Scandinavian database linking disease registries showed HL risk ($n = 9{,}314$ cases compared with 37,069 controls) increased twofold for systemic autoimmune disease overall, with significantly elevated ORs ranging from two to

five for rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome, and sarcoidosis [154]. In 1,155 HL cases over age 67 years at diagnosis from the Surveillance, Epidemiology, and End Results (SEER)-Medicare data and controls from the Medicare files, HL risk was similarly elevated among those with a history of SLE, scleroderma, or rheumatoid arthritis [7]. The association between autoimmune disease and HL risk appears to occur irrespective of age possibly due to autoantigen-mediated chronic B-cell stimulation leading to emergence of a malignant clone (perhaps further enabled by acquired resistance to apoptosis in autoimmune disorders) [70], to immunosuppressive treatment for autoimmune disorders, and/or to shared environmental and/or genetic risk factors for both autoimmunity and HL [223].

1.4.3 Inflammation

Cytokines, produced in HL tumors by HRS cells and believed to act as autocrine growth factors and maintainers of the inflammatory infiltrate [173], have been linked to HL risk through findings of elevated serum/plasma levels of interleukin (IL)-2 [61]; IL-6 [22, 60, 81], including before treatment [22, 81]; IL-10 [112, 117, 127]; IL-12 [61]; CC chemokine ligand (CCL)117 and CCL22 [193]; and inflammatory marker YKL-40 [22]. Genetic evidence for cytokine associations with HL risk is described below.

Further, a role for chronic and, perhaps, subclinical inflammation in HL etiology has been suggested by reduced risks of HL with regular aspirin use (OR = 0.60, 95 % CI 0.42–0.85) in a large US case-control study [42], with >2 vs. ≤2 prescriptions of low-dose aspirin (OR = 0.7, 95 % CI 0.5–1.2) in a prospective nested case-control study in linked northern Danish cancer registry and prescription databases [46] and, in a larger version of that study, with long-term (≥7 years) vs. never/rare use (OR = 0.65, 95 % CI 0.39–1.09) [48]. In contrast, risks of HL tended to be elevated for use of other NSAIDS, although confounding by indication was not ruled out. Aspirin may exert a protective effect by triggering HL cell death through inhibition of NF-κB [10, 242], which is constitutively activated in and required for survival by HRS cells [12, 13, 118, 140], or through its irreversible binding to the active site of cyclooxygenase (COX)-1 and COX-2 [232], potent mediators of inflammation and tumor growth overexpressed in HL [96, 133].

1.4.4 Heterogeneity

The lack of variation in associations of aspirin use and the *NFKB1* polymorphism with HL risk by age group, sex, and tumor EBV status (described below) suggests that inflammation is an essential underlying component of HL pathogenesis [45, 46]. However, relative risks of HL after organ transplant are higher in males than females [207], inferring gender-related variation in the importance of immunosuppression. For autoimmune conditions, stratified analyses to inform heterogeneity of risk have been limited by low statistical power. However, HL risk with systemic autoimmune disease was stronger for mixed cellularity HL in a subset of Swedish patients with histological subtype information [154], while Baecklund et al. found that risk of HL with rheumatoid arthritis did not vary by histological subtype or EBV presence [9].

1.5 Genetic Susceptibility

1.5.1 Familial Aggregation

Case studies showed that families of HL probands can have affected 1st-, 2nd-, and 3rd-degree members with HL [128, 165] and with hematologic [23, 68, 93, 167, 200, 208] and other malignancies [32, 101, 168, 177]; can share human leukocyte antigen (HLA) haplotypes [38, 111]; and can be consanguineous [32, 108]—consistent with an inherited predisposition. HL risk was found to be nearly 100 times higher in identical than fraternal twins [170], indicating a substantially stronger effect of shared genes than shared environment. Case-control and cohort

studies have reported a three- to sevenfold increased risk of HL in first-degree relatives of patients [31, 44, 77, 92, 99, 101, 108, 113, 149, 176, 205, 208, 213] and familial associations with hematopoietic malignancies [36, 44, 49, 235]. Linkages of population-based cancer and family record registries yielded similar findings [6, 64, 93, 95, 115] as well as showed higher HL risks for siblings than parents of cases [93], a younger age at diagnosis for familial than nonfamilial cases [6, 203, 220], and an elevated family occurrence of some autoimmune diseases [121, 159]. In affected families, analyses have implicated the HLA region of chromosome 6 and polymorphisms of various cytokine genes, as reviewed below. In 44 high-risk families, a genome-wide linkage screen found strong linkage consistent with recessive inheritance on chromosome 4p, as well as on chromosomes 2, 4q, 7, 11, and 17 [94]. A study of 97 HL patients from high-risk UK families identified a risk-elevating deletion in the *NPAT* gene on chromosome 11q22.3 [214].

1.5.2 Immune Gene Polymorphisms

The highly polymorphic HLA system, which plays an essential role in immune function and recognition of self vs. foreign antigens, has long been associated with HL risk [15, 111, 128, 129, 166], including class II polymorphisms (*DRB5-0101*, the haplotype of *DRB*1501-DQA1*0102-DQB1*0602*, and a *TAP1* allele) in family studies [111], and various HLA genotypes in population studies, with considerable patient subgroup specificity as described below. While this evidence suggests recessive inheritance and additional genetic and environmental factors [15, 38, 204, 219], it is unclear whether the identified associations involve true susceptibility alleles or reflect the strong linkage disequilibrium in the HLA region [2], although findings from recent genome-wide association studies (GWAS) (described below) have introduced greater precision into genetic findings.

HL risk has been linked with several single nucleotide polymorphisms (SNPs) in *IL6* [163], including a promoter region polymorphism (−174G>C) in young adults [60]; in *IL1R1* (involved in activation of NF-κB) and *IL4R* (expressed on HRS cells) [163]; with *IL12* + 1188A>C in 90 case twins vs. 90 convenience controls [61]; and with *IL10* −1082A>G (possibly restricted to EBV-positive cases [65]) and *IL10* −3575 T > A (in predominantly late-stage patients over age 40 [243]). Patients homozygous for *IL10* −592C>A and −1082A>G had elevated IL-10 plasma levels [127]. An intronic SNP in *NFKB1* was linked to increased HL risk (rs1585215 GG vs. AA: OR = 3.5, 95 % CI 2.2–5.7, $P_{trend} = 1.7 \times 10^{-8}$), as were *NFKB1* haplotypes ($P_{global} = 6.0 \times 10^{-21}$) [45]. In 200 hospital-based cases and 220 population controls, HL risk was associated with combinations of variants of several anti-inflammatory (*ILR4*, *TLR7*, *IL10*) and proinflammatory (*IL18*, COX-2) genes (ORs rising with increasing numbers of adverse alleles compared to none: for heterozygotes = 1.10, 95 % CI 1.02–1.83; for two risk alleles = 1.35, 95 % CI 1.06–3.75; for three to four risk alleles = 3.26, 95 % CI 1.27–7.34, ($P_{trend} = 0.01$)) [182]. In a large European study, HL risk was associated with several SNPs in genes in the JAK-STAT pathway (*STAT3*, *STAT6*, and *TP63*), particularly *STAT6*, which appeared to reduce risk 40–45 %, and for *IFNG*, also associated with risk of SLE [33].

1.5.3 Other Candidate Genes

A recent analysis identified an elevated HL risk with several DNA repair genes (allelic variants in *XPC*, *NBN*, *XRCC3*, and *XRCC1*) and documented significant gene-gene interactions (for *BEV* and *DSB* SNPs involved in oxidative damage repair) [181].

1.5.4 Genome-wide Association Studies

By early 2014, four GWAS in persons of European origin had been conducted to identify common genetic variants that confer

susceptibility to HL [63, 72, 76, 231]. The first identified putative susceptibility loci at 2p16.1 (the transcription factor *REL*), 8q24.21 (the RNA oncogene *PVT1*), and 10p14 (the transcription factor *GATA3*), while also confirming a strong association with *HLA-DRA* [72]. The second identified new loci at 6p21.32, which contains *HLA-DRB1* and *HLA-DQB1*, and confirmed a previously detected SNP in the HLA region [63]. The third GWAS identified two new loci for overall HL in the HLA region, one adjacent to the class-I-related ligand *MICB* and the other at *HLA-DRA* [231]. A genome-wide meta-analysis combining two large European sets, including one previously published [72], identified new loci at 3p24.1 (the eomesodermin transcription factor *EOMES*) and 6p23.3 (intergenic to the G-protein/elongation factor *HBS1L* and the transcription factor *MYB*) [76]. Together, these findings strongly implicate HLA class I and class II components in HL susceptibility and offer additional insight into the genetic and mechanistic origins of HL. Of note, the HLA locus (specifically, *HLA-DRB1* and *HLA-DQB1*) was also implicated by a GWAS and linkage analysis combined with a gene expression profile analysis conducted to identify genetic factors influencing the antibody response to EBV protein EBNA-1 in Mexican American families [212]. Four putative HL susceptibility SNPs previously identified in the HLA region were also associated with the antibody response to EBNA-1, highlighting immune-related mechanisms by which EBV may contribute to HL pathogenesis.

1.5.5 Heterogeneity

The association of HL risk with familial lymphoma has been reported to vary by age, sex, and familial relationship. In linked Swedish registry data, Goldin et al. found HL risk higher for families of probands than controls under 40 years (RR = 4.25, 95 % CI 1.85–9.77) and older than 40 years (RR = 2.56, 95 % CI 0.90–7.25) [93]. In similar data, Crump et al. noted HL risk to be increased 8- to 11-fold in persons under age 37 with an affected sibling and sevenfold for those with an affected parent [64]. Other studies found higher risks of familial lymphoma for HL patients younger than 60 years at diagnosis [36] and for offspring diagnosed under age 50 years [116]. Some studies, but not all [64], noted higher HL risk for male relatives of patients (particularly brothers), for same-sex siblings, and for siblings compared with parents of cases [6, 93, 99, 114, 226]. Same-sex concordance has been hypothesized to reflect a susceptibility gene in the pseudoautosomal regions of the sex chromosomes [130, 131] or shared environmental exposures. Multiplex families with EBV-positive HL have been reported [146], but tumors in familial cases do not appear consistently to be concordant for EBV [165].

Associations of HL risk with HLA genotype appeared heterogeneous by patient and disease characteristics. Risk was increased for HLA class II *DPB1*0301* in whites [25, 199, 229, 230] but decreased for *DPB1*0201* [25] and for *DPB1*0401* in Asians using population-stratified controls [199]. In northern Chinese, *HLA* class I but not class II expression was associated with EBV-positive vs. EBV-negative HL [134], and *HLA-A*02* positivity did not differ significantly between HL cases and controls or between EBV-positive and EBV-negative HL [136]. The *HLA-A*02:07* subtype (rare in Caucasians) was associated with higher risk of EBV-positive HL and lower risk of EBV-negative HL [136]. *DPB1*0301* associations were restricted to nodular sclerosis HL in one study [151] and to EBV-positive tumors in young adults in another [4]; the risk association with a *TAP1* allele was limited to nodular sclerosis [111]. For EBV-positive HL, risk was elevated with specific class I A microsatellite markers (D6S265, D6S510) (ORs of 6.0, 95 % CI 1.7–22.1, to 9.8, 95 % CI 2.7–34.9, for seven SNPs) [67], whereas for EBV-negative HL, it was associated with a class III marker (D6S273) [194]. Subsequent studies detected associations of *HLA-A*01* with increased risk and *HLA-A*02* with decreased risk of EBV-positive HL and significantly lower prevalence of *HLA-A*02* patients among 152 EBV-positive patients (35.5 %) than 322 EBV-negative patients (50.9 %) [192]. Further analysis revealed several

HLA alleles significantly associated with HL overall (*HLA-B5* and *HLA-DR7* [the latter inversely associated]), with EBV-negative HL (*HLA-DR2*, *HLA-DR5*, and the haplotype *HLA-A2-B7-DR2*), and with EBV-positive HL (*HLA-B37* and *HLA-DR10*, as well as *HLA-A*01* and *HLA-A*02* [the latter inversely associated]) [137]. A pooled study confirmed independent dose-response relationships of *HLA-A*01* and *HLA-A*02* with EBV-positive HL risk and showed that the *HLA-A*02* allele appeared to protect against the association between history of IM and risk of EBV-positive HL [126]. In GWAS, previously reported associations with class I variants in *HLA-A* and *HCG9* were restricted to EBV-positive HL, and a previously reported class II variant in *HLA-DRA* was restricted to EBV-negative nodular sclerosis HL [231]. As HLA-A molecules present EBV peptides to T cells, it is feasible that SNPs with low affinity for EBV and thus an inefficient immune response could affect risk of EBV-positive HL [29, 67, 191]. Observations linking risk of IM in young adults with HLA class I polymorphisms (including markers D6S510 and D6S265) [175], and results showing overlap in putative susceptibility genes between the EBV antibody response and HL risk [212], strengthen support for a role for management of EBV infection in the etiology of EBV-positive HL.

1.6 Selected Lifestyle and Environmental Risk Factors

1.6.1 Smoking

Early case-control and cohort studies found that self-reported cigarette smoking was associated with an increased risk for HL [19, 30, 40, 62, 89, 122, 150, 164, 194, 195, 239]; recently, this risk was further explored in two meta-analyses [37, 215], a pooled analysis [145], and a large cohort of UK women [155]. The meta-analyses found an increased risk of HL in current cigarette smokers (OR = 1.4, 95 % CI 1.2–1.6 [37]; pooled effect estimate = 1.3, 95 % CI 1.1–1.6 [215]) with significant dose response effects for the number of cigarettes smoked per day, years of smoking, and pack-years [37, 215]. Current (but not former [37, 145, 215]) smoking was associated with an increased risk of HL (as above), with associations in both nodular sclerosis (pooled effect estimate = 1.35, 95 % CI 1.12–1.63) and mixed cellularity subtypes (pooled effect estimate = 2.53, 95 % CI: 1.72–3.72) [215]. In a subset analysis, Castillo et al. found that currently smoking men and persons over 30 years of age increased HL risks of 78 and 76 %, respectively [37]. However, a subsequent metaregression analysis found no differences by age and conflicting results for gender [215]. Current cigarette smokers were found to have a higher risk of EBV-positive HL [37, 145] and mixed cellularity HL (OR = 1.6, 95 % CI 1.3–2.0) (Table 1.3) [145], while smoking generally was not associated with increased risk of nodular sclerosis or EBV-negative HL [89, 122, 145, 239]. Tobacco smoke may impact HL pathogenesis through its associated immunosuppression [224], especially that permitting reactivation of latent EBV infection.

1.6.2 Alcohol Consumption

Moderate alcohol consumption has been associated with reduced risk of HL. Five case-control studies reported a significant halving of HL risk for drinkers at most levels of total alcohol intake [18, 19, 97, 147, 194], while four others reported nonsignificant protective effects or null associations [150, 179, 228, 239]. Few of these studies had sufficient numbers of cases to assess level of drinking by relevant HL subtypes, although one study reported null associations for both EBV-positive and EBV-negative diseases [239]. However, as most of these studies used nondrinkers as reference groups, their findings may be biased by pre-diagnostic "alcohol-related pain" [24], which could have led to voluntary cessation of alcohol consumption before development of full-blown HL. One prospective cohort study reported nonsignificant protective effects of alcohol similar to those reported by case-control studies [164], but used nondrinkers as opposed to

lifetime abstainers as a reference group. A prospective cohort study of women found occasional drinkers to have a lower HL risk than nondrinkers, but without evidence for a lower HL risk with increasing alcohol intake [155]. Alcohol could influence lymphomagenesis through its moderate immunosuppressive effects [66].

1.6.3 Ultraviolet Radiation Exposure

A large, population-based case-control study in Sweden and Denmark detected a consistent inverse association, with significant inverse dose response trends, between risk of HL and exposure to ultraviolet radiation (UVR), as estimated by sunbathing habits, sunburn history, sun vacations abroad, and solarium visits [71]. Subsequent studies mostly reported no significant association, although small sample sizes constrained statistical power [26, 47, 98, 206, 241]. In a recent, large, pooled analysis of four case-control studies including 1,320 HL cases and 6,381 controls, inverse associations with HL risk were detected for history of sunburn (OR = 0.77, 95 % CI 0.63–0.95) and sunlamp use (OR = 0.81, 95 % CI 0.69–0.96), with a significant inverse exposure-response trend detected in association with estimated lifetime UVR exposure [180]. Inverse associations were especially pronounced for EBV-positive HL (Table 1.3). The putative inverse association between UVR exposure and HL risk may be a consequence of activation of antiproliferative vitamin D production by UVR [107], immunomodulation by regulatory T cells induced by UVR [197], or triggering of the DNA damage response by UVR [17, 196].

1.6.4 Body Size and Physical Activity

HL patients have been found to be significantly heavier at birth and heavier and taller as children than controls matched on age, sex, and social class [139]; intrauterine characteristics have been noted as possible contributors to birth weight associations in recent cohort studies (fetal growth, adjusted hazard ratio (aHR) of childhood/young adult HL = 1.09, 95 % CI 1.03–1.16 per standard deviation increment, $P_{trend} = 0.005$ [64]; placental length, aHR = 0.7, 95 % CI 0.53–0.92 [14]). Adult height also has been implicated as a risk factor in some studies [104, 109, 148, 189] but not all [157, 164, 201, 238]. Adult height could be associated with HL risk because of better nutrition [102, 221], which, like HL risk, is likely related to higher childhood socioeconomic status [185, 186]; common genetic determinants [67, 94, 102, 151]; or promotion of nascent HL tumors in taller persons by higher circulating levels of insulin-like growth factors and other growth hormones [102, 198]. Obesity has been associated with a nearly two- [201] to threefold [238, 240] increased risk in men but not in women [28, 43, 238, 240], although one study found a nonsignificant association in both sexes [164]. The stronger relationship between obesity and HL risk in men may be due to their greater tendency to visceral adiposity [238]. A meta-analysis of five prospective studies found an increased risk of HL for obese, but not overweight, men and women [160], while a prospective cohort of women found increased risks of HL for both overweight and obese women [189]. Higher body mass index was associated with increased HL risk in young-adult women but reduced risks in older women [148, 162]. Higher body size could influence risk of HL by triggering higher levels of IL-6 [60], insulin resistance, compensatory hyperinsulinemia, or increased production of growth factors, including estrogens [20]. A meta-analysis of seven case-control and five cohort studies did not find evidence for an association of HL risk with physical activity [233].

1.6.5 Reproductive Factors

The marked, unusual, age-varying gender patterns of HL incidence rates, particularly the change from female-dominated in young adulthood to male-dominated at later ages, provoked some interest in the effect of reproductive factors on HL risk [83, 100]. Studies have described a slight to moderate decrease in HL risk with

higher parity, with some finding a more protective apparent effect in women of reproductive age [1, 58, 152, 153, 158, 227, 244] and one confirming no effect in men or due to social-class confounding [58]. These data, and findings of lower HL risk with nursing, exogenous hormone use, and a history of endometriosis [88], suggest an effect of steroid or other hormones on HL pathogenesis, possibly through influences on regulation of immune system development or function.

1.7 Summary

The epidemiology of HL reveals a disease with complex pathogenesis, with the distinctive patterns of its incidence rates and risk profiles by age, race/ethnicity, sex, economic level, and tumor characteristics. Efforts to interpret and summarize these heterogeneous findings have resulted in models of multiple-disease etiologies [141, 172]. However, epidemiologic efforts to further understand etiologic pathways have been hampered by two challenges. One is the recent observation that some markers of childhood social class initially predictive of risk no longer are associated with HL [41, 86]. This change leaves few established risk factors for HL, especially for the largest subgroup of patients, i.e., young adults with EBV-negative HL [124]. Moreover, the factors shown to strongly impact risk (e.g., HIV infection) have low population prevalence, and few novel ones have been identified. Thus, epidemiologic research into the etiology of HL currently lacks strong leads, especially for EBV-negative young-adult disease. The other challenge to advancing the epidemiology of HL, given its heterogeneity, is the problem of conducting adequately powered studies in meaningful patient subgroups of such an uncommon disease. The apparent importance for HL etiology of age, sex, tumor EBV status, histological subtype, genetic predisposition, and environmental exposures indicates that, to be informative, studies must be large enough to examine and disentangle the joint contributions of these factors to HL development.

The accumulated epidemiologic evidence points to HL as an uncommon outcome in at least two circumstances: (1) under conditions of sustained, moderate immunosuppression (as with HIV infection or organ transplant) and (2) in otherwise healthy persons with subclinical immune dysfunction provoked by early and concurrent environmental exposures, including EBV infection. Beyond this, however, our understanding of HL etiology remains poor. To meet the ultimate public health goal of disease prevention, epidemiologic research into HL must be focused in novel directions and involve study populations of substantial size in order to address its etiologic heterogeneity.

Acknowledgements The authors thank Juan Yang for help with this chapter. The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement U58DP003862-01 awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the author(s), and endorsement by the State of California, Department of Public Health the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

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The Role of Viruses in the Genesis of Hodgkin Lymphoma

2

Ruth F. Jarrett

Contents

Abbreviations

BART	BamHI-A rightward transcripts
cHL	Classical Hodgkin lymphoma
DDR1	Discoidin domain receptor 1
EBER	EBV-encoded small RNAs
EBNA	EBV nuclear antigen
EBV	Epstein–Barr virus
HHV	Human herpesvirus
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
HPyV	Human polyomavirus
HRS	Hodgkin and Reed–Sternberg
IHC	Immunohistochemistry
LMP	Latent membrane protein
MCHL	Mixed cellularity Hodgkin lymphoma
MCV	Merkel cell polyomavirus
MV	Measles virus
NSHL	Nodular sclerosis Hodgkin lymphoma
ORF	Open reading frame
PyV	Polyomavirus
SNP	Single-nucleotide polymorphism
TTV	Torque teno virus

2.1 Introduction

Hodgkin lymphoma (HL) is a heterogeneous condition. Seminal papers published in 1957 and 1966 suggested that HL in younger and older adults had different etiologies and further suggested an infectious etiology for young adult HL [1, 2]. Subsequent epidemiological studies

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_2,

provide broad support for these hypotheses [3, 4]. Data linking young adult HL with a high standard of living in early childhood and lack of child–child contact suggest that delayed exposure to common childhood infections may be involved in the etiology of these cases [5, 6]. There is now compelling evidence that a proportion of cases of HL are associated with the Epstein–Barr virus (EBV). Paradoxically, older adult and childhood cases of HL are more likely to be EBV associated than young adult cases [7–9]. In this article, I will review studies on viral involvement in HL with a focus on classical HL (cHL), since nodular lymphocyte-predominant HL is considered a separate disease entity. The association with EBV will be discussed with an emphasis on findings which support a causal role for EBV in this malignancy. Studies investigating direct involvement of other exogenous viruses will be summarized.

2.2 Hodgkin Lymphoma and Epstein–Barr Virus

EBV is a gamma-herpesvirus with a worldwide distribution [10, 11]. Over 90 % of healthy adults are infected by EBV and, following primary infection, the virus establishes a persistent infection with a reservoir in memory B cells [12]. Although EBV is an extremely efficient transforming agent, the virus is kept under tight control by cell-mediated immune responses, and both primary and persistent infections are usually asymptomatic [10].

EBV infection can be lytic or latent. Lytic infection is associated with expression of a large number of viral genes, production of progeny virus, and death of the infected cell; in contrast, latent infection is associated with expression of a small number of EBV genes, persistent infection, and growth transformation [10]. In B cells transformed by EBV in vitro, six EBV nuclear antigens (EBNA1, 2, 3a, 3b, 3c, and LP, also called EBNA1–6) and three latent membrane proteins (LMP1, LMP2A, and LMP2B) are expressed [11]. In addition, noncoding viral RNAs are transcribed in latently infected cells [11]. These include two small nonpolyadenylated transcripts, the EBERs, and over 40 viral microRNAs located within an intron of the BARTs (*B*amHI-*A* *r*ightward *t*ranscripts) or around the coding region of the BHRF1 gene [11, 13–17]. Expression of the full set of latent genes is known as latency type III and is associated with transformation of B cells [11]. EBV gene expression in EBV-positive lymphomas occurring in the context of immunosuppression frequently follows this pattern, but more restricted patterns of EBV gene expression are observed in other malignancies, including cHL [10]. The EBNA3 family proteins are immunodominant, and the other latent antigens elicit only subdominant or weak cell-mediated immune responses [18, 19]. The pattern of gene expression in EBV-associated malignancies most probably depends on both the lineage and stage of differentiation of the infected tumor cells and the host EBV-specific immune response.

In EBV-associated cHL (also referred to here as EBV-positive cHL), the Hodgkin and Reed–Sternberg (HRS) cells are infected by EBV, and the infection is clonal, i.e., all the tumor cells are derived from a single infected cell [20–23]. The virus is present in all of the HRS cells, and EBNA1, LMP1, LMP2A, and 2B as well as the EBER RNAs and BART microRNAs are expressed; the remaining EBNAs are downregulated [22–27]. This pattern of gene expression is referred to as latency type II [10]. EBV infection of HRS cells can be readily demonstrated in sections of routinely fixed, paraffin-embedded material using either EBER in situ hybridization or LMP1 immunohistochemistry (IHC) (Fig. 2.1). Reagents for both assays are commercially available.

2.2.1 EBV and the Pathogenesis of Hodgkin Lymphoma

The molecular pathogenesis of cHL and the origin of the HRS cell are described in detail in the following chapter. Briefly, HRS cells have clonally rearranged immunoglobulin genes with evidence of somatic hypermutation, indicating a derivation from B cells that have participated in a

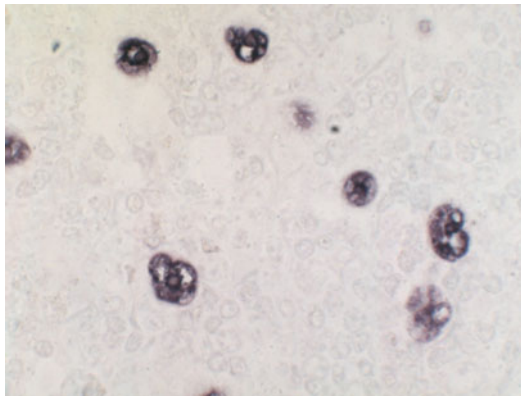

Fig. 2.1 EBV EBER in situ hybridization staining of EBV-positive Hodgkin and Reed–Sternberg cells. The characteristic staining pattern is observed in the nuclei of Hodgkin and Reed–Sternberg cells

germinal center reaction [28, 29]. A pathognomonic feature of these cells is the global suppression of B-cell signature genes and inappropriate expression of genes associated with other hemopoietic lineages [30, 31]. Importantly, HRS cells do not express B-cell receptors (BCRs). Survival of germinal center B cells normally requires signaling through both BCRs and CD40; HRS cells must therefore have acquired a nonphysiological survival mechanism(s). Functional studies of EBV, and LMP1 and LMP2A in particular, support a role for the virus in HRS cell survival, transcriptional reprogramming, and immune evasion, as summarized below.

In 2005, three independent groups published data showing that germinal center B cells lacking BCRs could survive and be immortalized by EBV [32–34]. In elegant experiments, Mancao and Hammerschmidt (2007) later showed that this survival function was dependent on LMP2A expression [35]. A series of in vivo and in vitro studies from the Longnecker laboratory further defined LMP2A function [36–38] and showed that this viral protein can mimic an activated BCR and provide a survival signal to BCR-negative B cells [36]. LMP2A expression in B cells also results in downregulation of B-cell-specific genes and induction of genes associated with proliferation and inhibition of apoptosis, a gene expression profile similar to that seen in cHL-derived cell lines [39]. Constitutive activation of Notch1 by LMP2A, and subsequent inhibition of E2A and downregulation of EBF, two transcription factors that regulate B-cell development, appears to be involved in both survival signaling and transcriptional regulation [38]. Although these data suggest a role for LMP2A in the survival and reprogramming of HRS cells, many of the intracellular molecules involved in BCR signaling are downregulated in established HRS cells, and therefore, the precise contribution of LMP2A in cHL is not clear.

CD40 signaling plays a critical role in the positive selection of germinal center B cells expressing high-affinity immunoglobulin and their subsequent exit from the germinal center [40]. EBV LMP1 is an integral membrane protein which interacts with several signal transduction pathways to activate NF-κB, Jun N-terminal kinase (JNK), and p38 mitogen–activated protein kinase [41–45]. In this way, LMP1 mimics a constitutively active CD40 molecule, although provides a more potent and sustained signal [10, 11]. Many of the genes that are transcriptionally regulated by LMP1 in germinal center B cells are also CD40 and NF-κB targets [46]. Activation of the NF-κB pathway, which is a feature of both EBV-positive and EBV-negative HRS cells, leads to upregulation of antiapoptotic genes and is thought to play a key role in HRS cell survival [47–49]. LMP1 expression in germinal center B cells also leads to increased expression of Id2, an inhibitor of the E2A transcription factor mentioned above, and repression of B-cell signature genes [46]; therefore, LMP1 may also contribute to transcriptional reprogramming. Cader et al. (2013) also reported that LMP1, but not CD40, upregulates the discoidin domain receptor 1 (DDR1), a receptor tyrosine kinase expressed by HRS cells in the majority of cHL cases irrespective of EBV status [50]. Engagement of DDR1 by collagen leads to activation of downstream signaling pathways including NF-κB and phosphatidylinositol 3-kinase/Akt, thus providing a link between expression of LMP1 and pro-survival signaling from the tumor microenvironment.

The EBV genome is normally maintained as an episome in infected cells, i.e., it does not integrate. The EBNA1 protein is responsible for

maintenance of the genome in episomal form, genome replication, and genome partitioning during mitosis [11, 51]. EBNA1 can also influence both viral and cellular gene expression and appears to confer a B-cell survival advantage, although the impact of EBNA1 on oncogenesis in vivo is controversial [11, 52–55]. Interestingly, in the context of cHL, overexpression of EBNA1 in vitro leads to the appearance of multinucleated cells [52]. The precise function of the EBER transcripts is also unclear, but expression of these small RNAs appears important for efficient EBV-induced B-cell growth and transformation [11, 56].

The function of the EBV BHRF1 and BART microRNAs and their role in oncogenesis are being actively studied at present, and there are excellent recent reviews of this subject [17, 57]. Studies of mutant viruses lacking some or all of the microRNAs suggest that they play an important role in initial stages of B-cell transformation by EBV [17]. Only a relatively small number of EBV-encoded microRNA targets have been verified to date, but the collective data point to roles in immune evasion (targeting of MICB) and regulation of apoptosis (targeting of Bim, PUMA, Caspase 3, and IPO7) [17, 57, 58]. Ross et al. (2013) also reported downregulation of the B-cell transcription factor EBF1 by microRNA BART11-5p [59]. EBV-associated malignancies, including cHL, Burkitt's lymphoma, and nasopharyngeal carcinoma, show deregulated expression of BART microRNAs with subtle differences between tumor types [27]. It is therefore likely that these virally encoded microRNAs play a role in cHL pathogenesis. EBV also regulates the expression of host microRNAs; infection of primary B cells leads to a conspicuous downregulation of many microRNAs with the notable exception of mIR-155, which is highly expressed by both EBV-positive and EBV-negative HRS cells [60, 61]. Analysis of host microRNAs in cHL is described in more detail elsewhere in this volume, but it has been reported that EBV status of tumors is associated with differences in expression pattern [62].

2.2.2 Risk Factors for EBV-Associated Hodgkin Lymphoma

It is clear that EBV is associated with only a proportion of cHL cases, around one third in industrialized countries [8, 9, 63]. EBV-associated cHL cases are not randomly distributed among all cHL cases, and the demographic features and risk factors for development of EBV-positive and EBV-negative cHL show distinctive features [8, 9]. Childhood (<10 years) and older adult (50+ years) cases are more likely to be EBV associated than young adult cases (15–34 years) [7, 8, 63]. Among EBV-associated cases, males predominate with a ratio of approximately 2:1, whereas males and females are more evenly represented among EBV-negative cases [9, 63]. In developing countries, where childhood cHL is more common, a higher proportion of cases are EBV associated [8, 9]. Material deprivation is associated with an increased proportion of EBV-positive childhood cHL cases in industrialized countries, and there is some evidence that this also holds true for older adult cases [63, 64].

EBV infection usually occurs in childhood and, in many parts of the world, there is almost universal infection by the age of 5 years. If infection is delayed until adolescence, as is increasingly occurring in industrialized countries, primary EBV infection manifests as infectious mononucleosis in around 25 % of individuals [65]. Infectious mononucleosis is associated with an increased risk of EBV-associated cHL [66–69]. The increased risk appears short-lived with a median time interval between infectious mononucleosis and cHL of approximately 3–4 years [68, 69]. Thus, in both developing and developed countries, there appears to be a period following primary EBV infection, probably lasting several years, in which risk of EBV-associated cHL is increased. cHL occurring in the context of immunosuppression is almost always EBV associated (see Chap. 1) [70, 71], and it is likely that the increased incidence of EBV-associated cHL that occurs in older adults is related to immune senescence. On the basis of

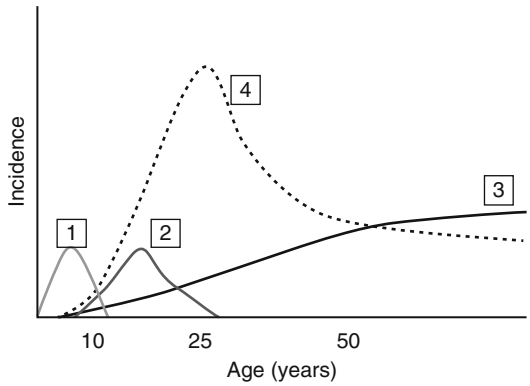

Fig. 2.2 The four-disease model of classical Hodgkin lymphoma. This model divides classical Hodgkin lymphoma into four subgroups on the basis of EBV association, age at diagnosis, and age at EBV infection. Three groups of EBV-associated disease are recognized: (*1*) a childhood disease, usually occurring below the age of 10 years, which is more common in developing countries; (*2*) a disease, most commonly seen in young adults, which occurs following infectious mononucleosis; (*3*) a disease associated with poor control of EBV infection, which is typified by the older adult cases but can occur at other ages, particularly in the context of immunosuppression. (*4*) Superimposed on these is a single group of EBV-negative classical Hodgkin lymphoma cases, which account for the young adult age-specific incidence peak seen in industrialized countries. The incidence of each of these four disease subgroups will determine the overall shape of the age-specific incidence curve in any particular geographical locale

the above data, we have proposed an extension of MacMahon's model of HL that divides cHL into four subgroups on the basis of EBV association, age at diagnosis, and age at infection by EBV (Fig. 2.2) [2, 72].

Recent data also suggest that humoral and cell-mediated responses to EBV modulate risk of EBV-associated cHL. Levin and colleagues (2012) [73] examined anti-EBV antibody profiles in serum samples from military personnel (mainly young men) that had been collected several years before the diagnosis of cHL [73]. Individuals who subsequently developed EBV-positive, but not EBV-negative, cHL were more likely to have elevated antibody titers to EBV viral capsid and early antigens and an anti-EBNA1/anti-EBNA2 antibody ratio $\leq$1.0 when compared to controls. Decreased anti-EBNA1/anti-EBNA2 antibody ratios have been previously associated with EBV-associated cHL [74], and it has been suggested that a ratio $\leq$1.0, which persists for more than 2 years after infectious mononucleosis, indicates defective control of persistent EBV infection [75]. Variations in EBNA1 titer have been shown to be significantly associated with polymorphisms in the human leukocyte antigen (HLA) region [76], suggesting that titers may, in part, be genetically determined and relate to the findings described below.

Data from HLA association studies and genomewide association studies (GWAS) show clear associations between cHL risk and both HLA alleles and single-nucleotide polymorphisms (SNPs) in this region. Although some SNPs appear to be associated with all cHL, independent of EBV status, most HLA associations differ between EBV-positive and EBV-negative subgroups [77–81]. Both HLA class I and II alleles are associated with EBV-positive cHL, whereas EBV-negative cHL is largely associated with class II alleles [79–81]. Since class I and II alleles present peptides from pathogens to CD8- and CD4-positive T cells, respectively, this suggests that genetically determined differences in the cell-mediated response to EBV influence disease risk. HLA-A*01 is associated with an increased risk of EBV-associated cHL, whereas HLA-A*02, specifically A*02:01, is associated with decreased risk [79–82]. Associations with these alleles are independent, i.e., the increased risk associated with A*01 is not simply due to lack of A*02, and effects are dependent on the copy number of each of the alleles (Fig. 2.3) [80]. As a result, there is an almost tenfold variation in odds of EBV-associated cHL between HLA-A*01 homozygotes and HLA-A*02 homozygotes [80]. More recent data suggest that B*37:01 is also associated with an increased risk of EBV-positive cHL [81, 83]. Class II alleles have been less extensively studied, but Huang et al. (2012) reported an increased frequency of DR10 alleles in patients with EBV-positive cHL compared to controls, and we have detected protective effects of DRB1*15:01 and DPB1*01:01 [81, 83].

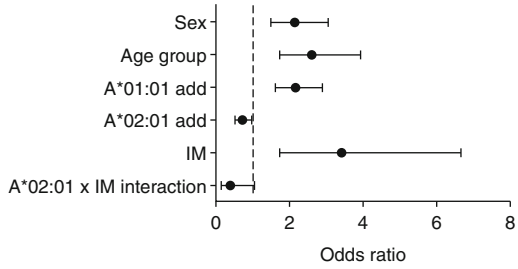

Fig. 2.3 Odds ratios and 95 % confidence intervals for development of EBV-associated classical Hodgkin lymphoma from a case series analysis of HLA and non-HLA risk factors. Data derived from a comparison of EBV-positive and EBV-negative classical Hodgkin lymphoma (cHL) cases described by Hjalgrim et al. [80]. Add, additive; IM, infectious mononucleosis. Odds of EBV-associated classical Hodgkin lymphoma is increased in males compared to females, cases aged 50 years and over compared to those aged 15–34 years, cases who have HLA-A*01:01 alleles, and cases with a past history of infectious mononucleosis. Odds ratio of EBV-associated classical Hodgkin lymphoma is decreased in cases who have HLA-A*02:01 alleles; there is an interaction between A*02:01 and infectious mononucleosis such that risk associated with prior infectious mononucleosis is abrogated in A*02:01-positive individuals

Cytotoxic T-cell responses, restricted through HLA class I, are critical for the control of EBV infection, and A*02 is known to present a wide range of peptides derived from EBV lytic and latent antigens, including those expressed by HRS cells [18, 19]. In contrast, there are no well-characterized A*01-restricted EBV epitopes [19], and EBV-specific T-cell responses restricted through A*01:01 have not been described [84]. The observed associations with HLA-A therefore seem biologically plausible. However, HLA-A*01 is in strong linkage disequilibrium with HLA-B*08, which is associated with immunodominant EBV-specific cytotoxic T-cell responses, and yet there is no protective effect associated with this allele [83]. The biological basis of associations between HLA alleles and EBV-associated cHL is therefore not straightforward and requires further investigation. Further work is also necessary to determine whether the critical HLA-A-restricted cell-mediated immune responses are directed toward EBV-infected HRS cells or whether it is the control of persistent EBV infection and the host: virus equilibrium, which is all important. The increased risk associated with individual class I alleles favors the idea that failure to respond to a particular protein, or very restricted group of proteins, determines risk; this focuses attention on EBV proteins expressed by HRS cells. Consistent with this, no EBNA1, LMP1, or LMP2 epitopes restricted by B*37:01 have been identified although a B*37:01-restricted EBNA3C epitope has been described [19].

As mentioned above, prior infectious mononucleosis is associated with an increased risk of EBV-positive cHL [66–69]. Propensity to develop infectious mononucleosis has been associated with the same genotypic markers (microsatellites and SNPs) as EBV-positive cHL, albeit with lesser statistical significance [85]. It therefore appeared possible that the association between infectious mononucleosis and EBV-associated cHL could result from shared genetic susceptibility rather than a temporal association. HLA-A typing of over 700 cHL cases with available self-reported history of infectious mononucleosis revealed that prior infectious mononucleosis was independently associated with EBV-associated cHL after adjusting for the effects of HLA-A alleles (Fig. 2.3) [80]. In addition, a statistically significant interaction between prior infectious mononucleosis and HLA-A*02 was detected; the effect of this was to abrogate the increased risk of EBV-associated cHL following infectious mononucleosis in HLA-A*02-positive individuals [80]. These results suggest that infectious mononucleosis is associated with an increased risk of EBV-associated cHL and that this risk is modified by the EBV-specific cytotoxic T-cell response restricted through HLA-A*02. Thus, it is possible that different HLA alleles exert their effects at different stages in the natural history of EBV-associated cHL.

Associations with childhood cHL and infectious mononucleosis suggest that there is a window of time following primary EBV infection when there is an increased risk of EBV-associated cHL and that genetic factors, specifically HLA-A genotype, modify this risk. EBV-associated cHL patients have higher numbers of EBV-infected cells than patients with EBV-negative disease [86], and infectious mononucleosis patients have very high numbers of circulating EBV-infected B cells, which decrease over time [87]. The number

of EBV-infected cells carried by an individual may therefore influence risk of EBV-associated cHL. If this is indeed the case, then it would be theoretically possible to decrease the risk of EBV-positive cHL by EBV vaccination or by treatment of infectious mononucleosis.

2.2.3 EBV and Hodgkin Lymphoma: A Causative Association?

In the absence of good animal models and the ability to prevent EBV infection, it is difficult to prove that the association between EBV and cHL is causal; however, consideration of the viral, molecular, and epidemiological data provides support for this idea. (1) The EBV infection in EBV-positive cHL tumors is clonal indicating that all the tumor cells are derived from a single EBV-infected cell. (2) In EBV-associated cases, all HRS cells are infected by the virus. Although EBNA1 facilitates both synchronous replication of the viral episome with cellular DNA and genome partitioning, this process is not 100 % efficient [51]. If the virus is not required for maintenance of the transformed phenotype, a gradual loss of viral genomes from the tumor cells would be anticipated. (3) EBV is consistently associated with a significant proportion of cHL cases. Although most adults are infected by EBV, only 1–50 per million B cells are infected in healthy individuals [88]. If EBV were simply a passenger virus, i.e., present in a B cell that was subsequently transformed by other mechanisms, EBV-associated cHL would be a rare occurrence. (4) LMP1 and LMP2A have plausible biological functions in the pathogenesis of cHL, as described above. (5) Crippling mutations of immunoglobulin genes have been described in a quarter of cHL cases, and almost all of these cases were EBV associated [89]. This suggests that EBV is required to rescue HRS cells (or precursors) that have destructive mutations of their immunoglobulin genes. (6) Deleterious mutations of the TNFAIP3 gene, a negative regulator of NF-κB, are much more frequent in HRS cells from EBV-negative compared to EBV-positive cases (see Chap. 4) [90]. Likewise, mutations of the gene encoding the NF-κB inhibitor IκBα have been described only in EBV-negative cases [91–94]. This suggests that HRS cells in EBV-negative cHL have developed alternative strategies to constitutively activate NF-κB. (7) EBV-associated cHL cases share genetic risk factors for disease development, which are generally distinct from those associated with EBV-negative cHL [77–81, 95]. (8) In some cases, development of EBV-associated cHL is temporally related to primary EBV infection [68, 69, 71]. (9) Individuals who subsequently develop EBV-associated cHL have abnormal EBV antibody profiles prior to diagnosis [73].

2.2.4 EBV and the Clinicopathological Features of Hodgkin Lymphoma

Although the above data indicate that EBV-positive and EBV-negative cHL have distinct natural histories, the phenotypic expression of both processes appears remarkably similar (Fig. 2.4). Gene expression profiling of HRS

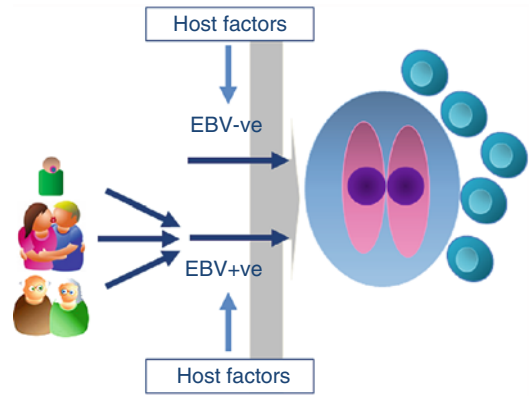

Fig. 2.4 The natural history of classical Hodgkin lymphoma. At present classical Hodgkin lymphoma (cHL) is divided into two etiological subgroups: EBV positive and EBV negative. EBV-positive cHL arises either following primary infection, which usually occurs in early childhood or adolescence, or in association with some degree of immune dysregulation, such as immune senescence. Host factors also influence disease risk; some genetic risk factors are common to all cases, whereas many are specific to either EBV-positive or EBV-negative cHL. Despite these differences in the natural history of cHL, the resultant disease is remarkably similar in all cases. Cases of mixed cellularity cHL are more likely to be EBV-positive than nodular sclerosis cases, but gene expression profiling of isolated Hodgkin and Reed–Sternberg cells suggests that EBV has little impact on the overall gene expression profile

cells suggests that EBV has only a small influence on the transcription profile of established HRS cells [96]. However, EBV status does show clear associations with histological subtype. In most series around 60–70 % of MCHL cases are EBV associated, compared to ~25 % of NSHL cases [8, 9]. Despite this difference, it is clear that "barn door" NSHL cases can be EBV positive, and so the lack of a complete correlation between histological subtype and EBV status is not simply due to the criteria used in, and subjective nature of, histological subtyping. In industrialized countries, NSHL is more common than MCHL and, in our experience, the majority (just) of EBV-positive cases are in fact NSHL and not MCHL.

Early studies investigating clinical outcome in relation to EBV status in cHL appeared conflicting, but a more consistent picture is now emerging [97–100]. In young adult patients, there appears to be no significant difference in overall survival by EBV status. In contrast, EBV positivity is associated with inferior outcome among patients aged 50 years and over. It is not clear whether this difference is related to the disease process itself or whether it is a reflection of the underlying comorbidity or immune dysregulation that potentially predisposes to EBV-associated cHL. EBV status is not routinely used in therapeutic decisions, but it is possible that this group of patients would benefit from alternative treatments, such as third-party cytotoxic lymphocyte infusions. Further studies investigating this issue and other targeted treatment options in EBV-positive patients are required.

2.3 Non-EBV-Associated Hodgkin Lymphoma Cases

As mentioned above, young adult cHL cases are the group least likely to be associated with EBV, and yet it is for these cases that there is most epidemiological evidence pointing to viral involvement. Early studies reported consistent associations between young adult HL and correlates of a high standard of living in early childhood [101]. Recent studies have generally not detected associations with the same social class variables, and this probably reflects temporal changes in living standards; however, one study observed an increased risk of young adult HL in individuals with ≤1 year of preschool attendance [6, 69]. Together, the data suggest that diminished social contact in early childhood is associated with an increased risk of this disease. From this it is inferred that young adult HL is associated with delayed exposure to a common childhood infection. Interview and questionnaire data generally support the idea that young adult HL patients have experienced fewer common infections in childhood [66, 102].

It has frequently been suggested that EBV is involved in all cases of cHL but uses a hit-and-run mechanism in "EBV-negative" cases. This possibility is very difficult to exclude, but the available data indicate that this mechanism cannot account for all "EBV-negative" cases. Importantly, not all cases are EBV infected [74, 103]; in fact, we found that EBV-negative cHL cases in the 15–24-year age group were more likely to be EBV seronegative than age-matched controls [103]. In addition, there is no evidence for retention of fragments of integrated EBV genomes in "EBV-negative" cHL biopsies [103, 104].

We believe that another viral agent may be involved in the pathogenesis of EBV-negative cHL. This agent is likely to be a virus which infects many people early in life; therefore, candidates include herpesviruses and polyomaviruses. These are discussed in further detail below. The *Anelloviridae*, the virus family that includes Torque teno virus (TTV) and related viruses, also fits these criteria. zur Hausen and de Villiers [105] have suggested that TTVs and TTV-like viruses could play a role in the development of leukemias and lymphomas that are associated with a "protected childhood environment" [105]. In their model, it is postulated that TTVs and related anelloviruses increase the risk of chromosomal abnormalities and that anellovirus load is increased in individuals who have experienced fewer infections. TTVs have been detected in HL [106–108]; however, further knowledge of these extremely common and genomically diverse viruses is required before their potential involvement in cHL can be evaluated.

2.3.1 Hodgkin Lymphoma and Herpesviruses Other than EBV

At present, there are nine known human herpesviruses (HHVs), including EBV (officially HHV-4). With the exception of herpes simplex virus 2 (HHV-2) and HHV-8, all are widespread in distribution. Like EBV, HHV-8 belongs to the gammaherpesvirus subfamily and is associated with lymphomagenesis, but there is no evidence that this virus is involved in cHL [109–112]. The alpha-herpesviruses, herpes simplex virus 1 and varicella zoster virus, have also not been detected in HL biopsies [111]. In contrast, genomes of the beta-herpesviruses, human cytomegalovirus, HHV-6A, HHV-6B, and HHV-7 have been detected in cHL tumors using sensitive molecular assays. Schmidt et al. (2000) detected human cytomegalovirus genomes by PCR in 8/86 HL biopsies [110], although smaller case series failed to identify this virus in tumor samples [111, 113–115]. HHV-7 has been detected in 20–53 % of HL biopsies by PCR [110, 111, 115]; however, negative results have been obtained using Southern blot analysis, which is much less sensitive than PCR but would still be expected to detect a virus present in all HRS cells [116]. There is therefore no evidence that HHV-7 is directly involved in cHL pathogenesis.

HHV-6 deserves special mention because this virus has been consistently linked with cHL. HHV-6 is now classified as two distinct viruses, HHV-6A and HHV-6B [117], rather than two variants but until recently many studies did not distinguish between the two viruses. Serological studies have shown that HHV-6 antibody titers and, in some studies, seroprevalence are higher in HL cases than controls [118–120]. We also found that young adults with non-EBV-associated HL had higher titers of HHV-6 antibodies than age-matched cases with EBV-associated disease (unpublished results). HHV-7 antibody titers were similar in the two groups of cases suggesting a specific association between HHV-6 and cHL.

HHV-6 genomes have also been consistently detected in HL biopsies using PCR although detection rates vary from 8 to 79 % [110, 111, 115, 120–125], and some studies have reported similar detection rates in reactive lymph nodes [115, 122]. Variations in detection rate most probably reflect differences in PCR assay sensitivity and the amount of DNA assayed, since viral genome copy numbers are often low. Detection rates of 83.6 and 87 % have been reported in NSHL [125, 126], but it is clear that PCR-positive cases include both EBV-associated and nonassociated cases [111, 122, 125, 126]. Both HHV-6A and HHV-6B have been detected within biopsies with four studies showing a clear bias toward HHV-6B [111, 121, 122, 125], one detecting a higher proportion of HHV-6A-positive tumors [110] and one detecting HHV-6A and HHV-6B as well as dual infections [126]. The low viral genome copy in many tumors suggests that the virus cannot be present in every HRS cell and raises the suspicion that the virus is simply present in T cells in the tumor microenvironment. Very high viral copy numbers must also be interpreted with caution since chromosomally integrated HHV-6 is transmitted in the germline in 0.21–5 % of individuals and results in the presence of the virus in every nucleated cell in the body [127]. Following exclusion of cases with chromosomally integrated HHV-6, studies using the less sensitive technique of Southern blot analysis have largely been negative [109, 120, 122, 123, 128]. This contrasts with the situation in EBV-associated cHL where EBV genomes are almost always detectable using this technique [7, 20, 129]. The critical question is whether HHV-6 infects HRS cells and, if so, is the virus present in every HRS cell and is the infection latent.

Early studies using in situ hybridization and IHC reported that the virus was present in cells in the tumor microenvironment, either exclusively [122, 130] or with occasional positive HRS cells [131, 132]. However, two recent studies have described HHV-6-positive HRS cells [126, 133], renewing interest in the association between cHL and HHV-6. Lacroix et al. (2010) made a polyclonal antiserum to the DR7 open reading frame (ORF) of HHV-6B (designated DR7B) to examine the cellular localization of the virus in PCR-positive cases [125, 133]. They selected this particular ORF because the equivalent HHV-6A ORF has transforming properties, and the

translated protein binds p53 and inhibits p53-activated transcription [123, 134]. It is likely that the DR7 ORF is in fact expressed as the second exon of DR6, a larger nuclear protein [135, 136]. Using this antiserum in IHC, Lacroix et al. (2010) demonstrated cytoplasmic staining of HRS cells in 28/38 PCR-positive biopsies [133]. In 17 cases, positive staining was exclusive to HRS cells, and in a further 17 cases, positive staining of cells in the microenvironment was noted. In 15 of the 38 biopsies, HRS cells also stained using an antibody to the HHV-6 gp116/64/54 glycoprotein. They further showed that DR7B bound p53, upregulated NF-κB p105 and p65 promoters, significantly increased NF-κB activation, and induced upregulation of Id2. In the second study, Siddon et al. (2012) investigated biopsies from 21 NSHL cases, including 18 that were HHV-6-positive by PCR, using multiple approaches [126]. In ten cases, staining of HRS cells was demonstrated using a commercially available monoclonal antibody raised against virus lysate (Santa Cruz Biotechnology); scattered positive HRS cells were also demonstrated using antibodies to the late viral proteins p41 and p98. Laser capture microdissection coupled with PCR confirmed the presence of HHV-6 DNA in pooled HRS cells from eight of the ten IHC-positive biopsies. This study provides the most convincing evidence to date that HHV-6 can infect HRS cells but does not show that the virus is present in every HRS cell. Furthermore, the IHC staining pattern suggests lytic replication (or abortive replication) rather than latent infection, and so the outcome of viral infection in these cells is not clear. The association between cHL and HHV-6 clearly requires further investigation, and the HHV-6 Foundation is helping to make and share HHV-6 monoclonal antibodies that work on formalin-fixed, paraffin-embedded tissue to assist with this endeavor. Although HHV-6 may play a role at some stage in cHL pathogenesis in some cases, it is the author's opinion that HHV-6 is unlikely to be the causative agent of EBV-negative cHL.

In order to search for novel members of the herpesvirus family, we and others have designed degenerate PCR assays which amplify herpesvirus polymerase and glycoprotein B gene sequences [111, 137]. The primer sequences in degenerate assays are derived from well-conserved peptide motifs in amino acid sequences of proteins; therefore, these assays should have the ability to detect genomes from known and currently unknown viruses [138]. Using herpesvirus polymerase assays, we have not detected novel herpesviruses in cHL biopsies although the assays had sufficient sensitivity to detect EBV in EBV-associated cases, as well as low-level HHV-6 and HHV-7 infection [111] (and unpublished results).

2.3.2 Polyomaviruses and Hodgkin Lymphoma

There are now (at least) 12 human polyomaviruses (HPyVs): JC polyomavirus (PyV), BKPyV, KIPyV, WUPyV, Merkel cell PyV (MCPyV), HPyV6, HPyV7, trichodysplasia spinulosa PyV (TSPyV), HPyV9, HPyV10, Saint Louis PyV (STLPyV), and HPyV12 [139–142]. JCV and BKV were discovered over 40 years ago, but the latter viruses have all been discovered since 2007 with the advent of modern molecular techniques for virus discovery. Seroprevalence studies suggest that the majority of adults are infected by BKPyV, KIPyV, WUPyV, MCPyV, HPyV6 and HPyV7, and TSPyV and a significant minority with JCPyV, HPyV9, and HPyV12 [142–145]. Among this expanding list of HPyVs, only JCPyV, BKPyV, TSPyV (associated with trichodysplasia spinulosa in immunosuppressed person), and MCPyV show clear disease associations. MCPyV, which is associated with Merkel cell carcinoma, is the only human polyomavirus to be unambiguously linked with a specific malignancy [141, 146]; however, other polyomaviruses clearly have oncogenic potential.

Using sensitive quantitative PCR assays, we found no evidence of JCV or BKV genomes in 35 cHL biopsies [147]. Hernandez-Losa et al. (2005) detected JCV in 1/20 and BKV in 2/20 cHL samples using a multiplex, nested PCR [115]. Robles

et al. (2012) reported that MCPyV seroprevalence was slightly higher in HL cases than controls, 84.4 % compared to 81.2 %, but differences were not statistically significant [148]. Two quantitative PCR studies detected MCPyV genomes in a small proportion (1/30 and 3/41) of cHL tumors [149, 150]; viral copy numbers were low making it extremely unlikely that this virus is playing any role in disease pathogenesis. To date, there have been no reports on the prevalence of the more recently identified viruses in cHL.

Degenerate PCR assays have also been applied to the study of PyVs and HL [147, 151]. Volter et al. (1997) examined five cases of HL using a degenerate PCR assay based on the viral VP1 protein but did not detect any evidence of polyomavirus infection [151]. We examined 35 cases of cHL, including 23 EBV-negative cases, using three degenerate PyV assays based on the large T antigen, and also obtained negative results [147]. The latter assays were designed before 2006 and therefore before most HPyVs were discovered. Alignment of large T antigen amino acid sequences from the recently identified viruses suggests that our assays would be able to detect KIPyV, WUPyV, TSPyV, and HPyV9 and HPyV10 but not MCPyV, HPyV6, and HPyV7; however, given the tropism of the latter viruses for skin, it is less likely that they are involved in cHL [142]. Overall, these results provide no evidence for PyV involvement in the pathogenesis of cHL, but it remains possible that an unknown PyV has escaped detection.

2.3.3 Measles Virus and Hodgkin Lymphoma

In 2003, Benharroch and colleagues reported an association between measles virus (MV) and cHL [152]. They subsequently reported that MV proteins were detectable by IHC in HRS cells from the majority of HL cases [153]. MV RNA was also detected by RT-PCR and in situ hybridization in a significant minority of the cases examined [153]. Subsequent studies have failed to confirm these associations [154, 155]. Our group found no evidence of MV in 97 cHL cases examined by IHC and 20 cHL cases investigated using RT-PCR [155]. Similarly, Maggio et al. (2007) found no evidence of MV genomes or transcripts in HRS cells microdissected from biopsies from 18 German and 17 Israeli HL cases [154]; the latter cases had previously scored positive for MV antigens [153]. Epidemiological studies have also failed to show that MV infection is a risk factor for development of cHL; on the contrary, the data suggest a mild protective effect of prior MV infection [66, 102, 156].

Conclusions

While the evidence suggesting a causal relationship between EBV and a proportion of cHL cases appears strong, current data do not show a consistent and specific association between any virus and EBV-negative cHL. This does not exclude viral involvement. cHL is a notoriously difficult disease to investigate, and virus discovery studies present particular challenges. The difficulty of obtaining large numbers of highly enriched HRS cells has precluded the use of certain techniques, such as representational difference analysis, in the analysis of cHL [138]. Next-generation sequencing methods have opened new avenues for virus discovery and have led to the identification of several novel viruses in the last few years [140, 141, 157]. Digital transcriptome subtraction [141], the technique used in the discovery of MCV, is now being applied to the study of cHL. It is likely that genomic sequence data from HRS cells will also be available in the near future. These techniques provide our best hope of discovering a new virus in EBV-negative HRS cells. It is possible that cellular mutations substitute for the functions of EBV genes in EBV-negative HRS cells. Deleterious mutations of inhibitors of the NF-κB pathway, including genes encoding A20 and IκBα, appear to be present in the HRS cells of many cases of EBV-negative cHL (see Chap. 4) [90–94], and it is possible that these mutations substitute for LMP1. However, there is no obvious link

between these mutations and the epidemiological features of cHL and involvement of another virus still appears attractive. Identification of a virus in EBV-negative cHL would open up possibilities for disease prevention as well as novel therapeutic targets, and so it is important to resolve whether, or not, such an agent exists. Exciting times are ahead.

Acknowledgments Work in our laboratory is supported by Leukaemia Lymphoma Research and the Kay Kendall Leukaemia Fund.

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Pathology and Molecular Pathology of Hodgkin Lymphoma

3

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3.1 Subclassification and Pathology

The history of Hodgkin lymphoma (HL) dates back to the first half of the nineteenth century (see Chap. 1), and it has also been an established view for quite some time that HL comprises two different disease entities, namely, classical Hodgkin lymphoma (cHL) and nodular lymphocyte-predominant Hodgkin lymphoma (LPHL) [1]. Both entities have in common that the neoplastic cell population, which can be mononucleated or multinucleated, makes up only a small percentage of all cells present in an affected lymph node. However, morphological, clinical, epidemiologic, and molecular evidence strongly support the belief that the pathogenesis of these lymphomas is distinct enough to be considered separate entities. From a diagnostic point of view, morphological details and immunohistochemistry for a selected set of markers almost always allow for a proper classification of a given lymphoma into the group of LPHL or cHL, the latter of which can be further subdivided into nodular sclerosis cHL (NSCHL), mixed cellularity cHL (MCCHL), lymphocyte-depleted cHL (LDCHL), and lymphocyte-rich cHL (LRCHL) [1].

The following sections summarize the key morphological aspects and important immunohistochemical features of HL. For clinical and epidemiologic parameters, please refer to the respective other chapters of this book.

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_3,

3.1.1 Nodular Lymphocyte-Predominant Hodgkin Lymphoma

Although the morphology of the tumor cell population of LPHL can occasionally mimic Hodgkin and Reed–Sternberg (HRS) cells of cHL, in most instances the tumor cells in LPHL, which are termed lymphocyte-predominant (LP) cells according to the current WHO classification (previously called L&H cells, for lymphocytic and/or histiocytic Reed–Sternberg (RS) cell variants), carry one large nucleus that is often multilobulated ("popcorn cell") (Fig. 3.1a). In contrast to classic HRS cells, the number of nucleoli is increased, but they are usually less prominent and less eosinophilic. LP cells are found in a nodular or follicular background that is dominated by small B lymphocytes that usually express IgD, but a more diffuse growth pattern can also be encountered, especially during progression. The follicular infiltration pattern is highlighted by the presence of CD21-positive follicular dendritic cells that tend to form a well-developed meshwork in the nodules. Immunohistochemically, LP cells demonstrate a complete B cell phenotype with expression of CD20, CD75, and, frequently, CD79a (Fig. 3.1b; Table 3.1). Moreover, the essential B cell transcription factors BOB.1 and OCT-2 are usually positive, and the expression of BCL6 and activation-induced cytidine deaminase (AID) is well in line with a germinal center (GC) derivation of the tumor cells, although CD10 is generally negative [1–3]. The negativity of the tumor cells for CD30, CD15, and Epstein–Barr virus (EBV) helps to distinguish LP cells from HRS cells in cHL, although occasionally a weak positivity for CD30 can be present in LP cells (Table 3.1). Whereas in initial lesions small B cells dominate the background, histiocytes and T cells may become more prominent during the evolution of LPHL, to an extent that LPHL may be hardly distinguishable from T cell/histiocyte-rich large B cell lymphoma (THRLBCL). "Variant histology" (e.g., depletion of small B cells in the background or unusual localization of the LP cells) appears to be associated with an inferior prognosis [4]. A prominent feature of LPHL is the often impressive rosetting of LP cells by T cells that belong to the subset of follicular T-helper cells and therefore express CD57 and PD-1 [5–7].

3.1.2 Classical Hodgkin Lymphoma: The HRS Cells

The characteristic tumor cell of cHL, the RS cell, is large and contains at least two nuclear lobes or nuclei, usually with a prominent nuclear

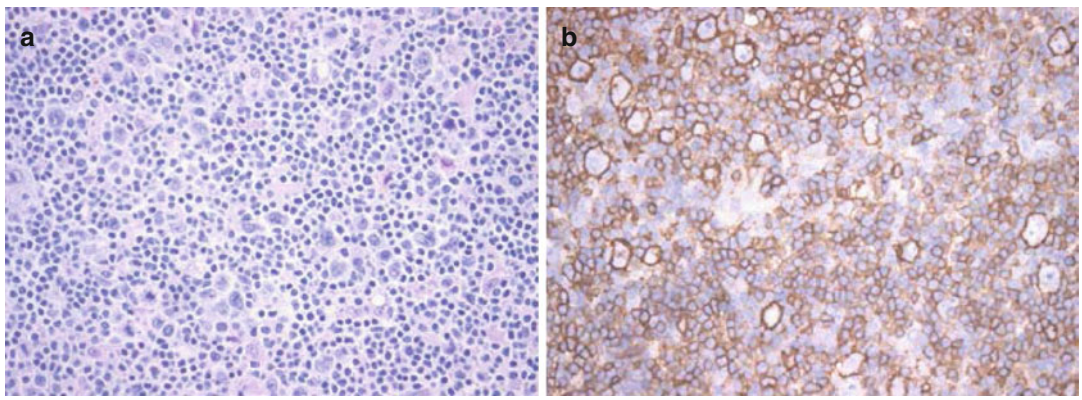

Fig. 3.1 Nodular lymphocyte-predominant Hodgkin lymphoma (LPHL). (**a**) HE-stained lymph node infiltrate showing multiple characteristic, multilobated tumor cells – termed lymphocyte-predominant (LP) cells – in a background of small lymphocytes and histiocytes (×400). (**b**) Strong CD20 expression in LP cells but also in reactive, small B cells in the background (×400). Note that some of the tumor cells show rosetting by a CD20-negative lymphocyte population. These cells are T cells that often express the follicular T-helper cell marker PD-1

membrane (Fig. 3.2a). In contrast to LP cells in LPHL, the nucleoli of RS cells are often eosinophilic. The mononuclear variant of RS cells is termed the Hodgkin cell. However, the morphological spectrum of the tumor cell population in cHL can be broad and includes variants such as lacunar cells and mummified cells. In general, the tumor cells in cHL are called Hodgkin and Reed–Sternberg cells. Immunohistochemically, the HRS cells stain positive for CD30 (Fig. 3.2c), and CD15 is coexpressed in the majority of cases, occasionally with prominent staining of the Golgi area of the tumor cell. However, CD15 is negative in a significant proportion of cHL (20–25 %) and therefore not required to establish the diagnosis of cHL [1]. CD45 is usually negative, as are the B cell transcription factors BOB.1 and OCT-2. In the vast majority of cases, the derivation of the tumor cells from the B cell lineage is indicated by a nuclear positivity for the B cell-specific activator protein PAX5/BSAP, but the staining is usually weaker compared to the staining intensity in the small reactive B cell population in the background of the infiltrate [8]. CD20 expression can be observed in HRS cells in 30–40 % of cases, but the expression is frequently restricted to a subset of the tumor cell population, and even within one HRS cell, it is of varying intensity in different parts of the cell membrane. In comparison to CD20 expression, CD79a expression is observed less frequently [9, 10]. An EBV association, either demonstrated by immunohistochemical staining for LMP1 (latent membrane protein 1; Fig. 3.2d) or by

Table 3.1 Genetic and phenotypic features of HRS and LP cells

Feature	HRS cells	LP cells
Phenotype		
CD30 expression	Yes	Rare
CD15 expression	Yes (~70 %)[a]	No
B cell receptor expression	No	Yes
Loss of most B cell markers	Yes	Modest
Expression of germinal center (GC) B cell markers (e.g., BCL6, activation-induced cytidine deaminase (AID))	Rarely	Yes
Expression of markers for non-B cells (e.g., CD3, granzyme B, CCL17)	Frequently	No
Putative cell of origin	Defective, pre-apoptotic germinal center B cell	Germinal center B cell
EBV positivity	Yes (~40 %)	No
Signaling pathways		
NF-κB activation	Yes	Yes
JAK/STAT activation	Yes	Yes
Aberrant expression of multiple RTKs	Yes (~60–100 %)	Yes (~40 %)
Genetic lesions		
NFKBIA mutations	Yes (~10–20 %)	No
NFKBIE mutations	Yes (~10 %)	n.a.
TNFAIP3 mutations	Yes (~40 %)	No
REL gains/amplifications	Yes (~50 %)	No
MAP3K14 (NIK) gains/amplifications	Yes (~25 %)	n.a.
BCL6 translocations	Rare	Yes (~50 %)
JAK2, PD-L1, PD-L2, JMJD2C gains/amplification	Yes (~30 %)	No
SOCS1 mutations	Yes (~40 %)	Yes (~50 %)
MHC2TA translocations	Yes (15 %)	n.a.

n.a. not analyzed, *RTK* receptor tyrosine kinase
[a]Numbers in brackets refer to the percentage of positive cases

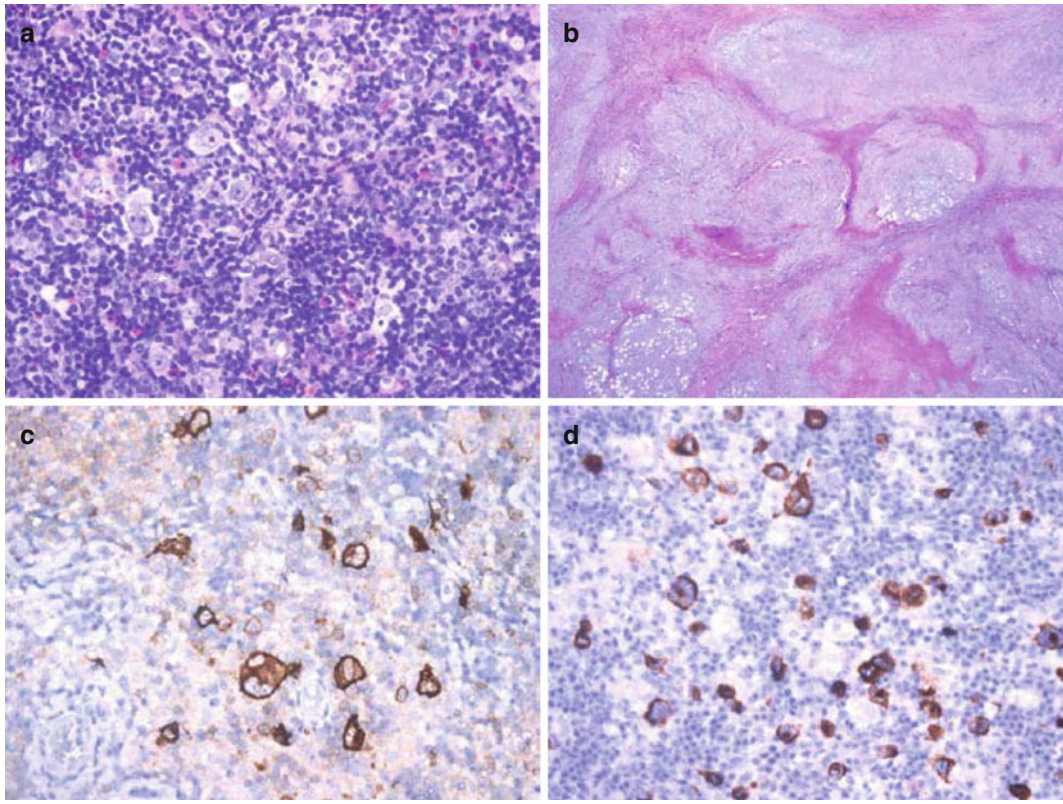

Fig. 3.2 Classical Hodgkin lymphoma (cHL). (**a**) Characteristic Hodgkin and Reed–Sternberg (HRS) cells in a mixed background of small lymphocytes, histiocytes, and eosinophils in a mixed cellularity cHL (MCCHL) (HE, ×400). (**b**) Nodular sclerosis subtype of cHL that demonstrates thick collagen bands surrounding the nodular infiltrates (PAS, ×20). (**c**) CD30 expression in HRS cells (×400). (**d**) Immunohistochemical staining for latent membrane protein 1 (LMP1) shows Epstein–Barr virus (EBV) association of HRS cells (×400)

EBER in situ hybridization, is found in a significant proportion of cHL, but the frequency varies considerably between different histological subtypes and across geographical areas [1]. Whether cHL cases exist with a *bona fide* derivation from the T cell lineage is currently a matter of debate. Single cases have been reported, in which a T cell receptor rearrangement could be proven in the HRS cells [11, 12], but others argue that such cases might represent only mimics of cHL which are not to be included in a disease entity that – based on fundamental principles of current lymphoma classification schemes – is of B cell derivation [13]. HRS cells reside in a cellular background that varies among the different histological subtypes of cHL which will be discussed in the following sections.

3.1.2.1 Nodular Sclerosis Classical Hodgkin Lymphoma

In NSCHL, affected lymph nodes frequently show a markedly thickened capsule and a nodular infiltrate whereby individual nodules are surrounded by broad collagen bands (Fig. 3.2b). HRS cells are present in a background of small lymphocytes and other nonneoplastic cells such as histiocytes and eosinophils. The number of HRS cells can vary significantly between NSCHL cases and also within a single infiltrated lymph node. Occasionally, HRS cells can form sheets that can be associated with necrosis and an intense fibrohistiocytic reaction. Morphologically, HRS cells in NSCHL often show a retraction artifact of the cytoplasmic membrane that appears to be a consequence of formalin fixation, which has

led to the term "lacunar cell variant" of HRS cells. The immunohistochemical phenotype of HRS cells in NSCHL as described above is the classic phenotype; however, association with EBV is less common as compared to other cHL subtypes, especially MCCHL.

3.1.2.2 Mixed Cellularity Classical Hodgkin Lymphoma

HRS cells in MCCHL usually have a classic morphological appearance and are scattered in a background that can contain small lymphocytes, eosinophils, neutrophils, plasma cells, and histiocytes. The infiltration pattern can be diffuse or vaguely nodular; sometimes, the lymph node architecture and especially some B cell areas are partially preserved leading to an interfollicular infiltration pattern. The characteristic features of other histologic cHL subtypes (e.g., the formation of nodular collagen bands) are absent and, thus, MCCHL is sometimes considered as the "wastebasket" of cHL. The EBV association of HRS cells is the highest among all cHL subtypes and can reach 75 % [1].

3.1.2.3 Lymphocyte-Depleted Classical Hodgkin Lymphoma

LDCHL is the rarest histological subtype of cHL (<1 % of cases) and probably the most problematic one to define. It is characterized by an increased number of HRS cells present in the infiltrate and/or depletion of small lymphocytes in the nonneoplastic background population. In some cases, HRS cells are of anaplastic appearance, and in other cases, the background is composed of extensive diffuse fibrosis. However, if the pattern of fibrosis is nodular and therefore characteristic of NSCHL, a given case should be classified as NSCHL, regardless of whether there are a high number of HRS cells. Since the definition of LDCHL has changed over the past decades, some of the established clinical and biological features appear outdated in the context of the current definition. Moreover, with the increase in knowledge and the development of additional immunohistochemical markers, some of the cHL cases that were previously assigned to the LDCHL category would nowadays be included into borderline categories or even different entities [1].

3.1.2.4 Lymphocyte-Rich Classical Hodgkin Lymphoma

In LRCHL, the HRS cells are present in a lymphocyte-rich background that can be nodular or, rarely, diffuse. Often, B cell follicles are partially preserved with recognizable GC, and HRS cells can be found in expanded mantle and marginal zones, thus providing a B cell-rich background. HRS cells in LRCHL may resemble LP cells in LPHL morphologically to such an extent that they are indistinguishable from each other without additional immunohistochemical characterization. It is of significance that eosinophils and neutrophils should be absent from the nodular infiltrates and may only be found in low numbers in interfollicular zones and close to vascular structures. The immunophenotype of the HRS cells is classic, and an EBV association is occasionally observed, though at a lower frequency compared to MCCHL [1].

3.2 Differential Diagnosis

In most instances, the diagnosis of LPHL and cHL is unambiguous on the basis of morphological, clinical, and, especially, immunohistochemical features (Table 3.1). However, a gray area between cHL and diffuse large B cell lymphoma (DLBCL), specifically with primary mediastinal large B cell lymphoma (PMBL), has long been known, and the most recent WHO classification introduced the category of "B cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma" [1]. It is important to note that lymphomas falling into this category are not considered a separate disease entity; rather, it was felt that lymphomas in which there is a discordance between morphological aspects of the infiltrate and the expected immunophenotype should be labeled as "intermediate" to allow a more precise definition of biological and clinical features of

these lymphomas in the future. Frequently, these borderline lymphomas present with large mediastinal masses. Morphologically, they consist of large, pleomorphic B cells that grow in a sheet-like pattern in a background of a fibrotic stroma. A subset of the tumor cells may resemble HRS cells, specifically the lacunar variant, and parts of the infiltrate may correspond to the growth pattern of cHL, particularly the nodular sclerosis subtype. Immunophenotypically, there is often a preserved expression program of cHL including expression of CD30 and CD15, while markers of the B cell lineage that are often downregulated in cHL, such as CD20 and CD79a, are equally expressed in the tumor cells [1]. It is important to note that these gray zone lymphomas appear to be more common in male patients, in contrast to NSCHL and PMBL that are more frequent in females [14]. Clinically, these tumors may behave more aggressively than NSCHL and PMBL; it has to be determined in the future whether treatment regimens for aggressive B cell lymphomas or for cHL are more beneficial.

The differential diagnosis between cHL and Alk-negative anaplastic large cell lymphoma (ALCL) of T cell lineage can usually be resolved using an appropriate panel of immunohistochemical markers including T cell, cytotoxic, and other markers. Problems arise when morphological features favor cHL, but tumor cells lack PAX5/BSAP expression while cytotoxic markers are expressed. As discussed above, it is a matter of current debate whether such cases should be grouped into the cHL category or diagnosed as ALCL. Remarkably, a global gene expression study revealed surprisingly few consistent differences in the gene expression of HRS cells and Alk-negative ALCL cells [15].

Finally, EBV-associated lymphoproliferations, e.g., in the context of a coexisting T cell non-HL as well as EBV-associated DLBCL of the elderly, a subgroup of DLBCL introduced in the new WHO classification [1], can harbor HRS or HRS-like cells and therefore mimic cHL [16]. Besides other morphological and immunohistochemical features and information on the clinical setting, the pattern of EBV infection, determined by LMP1 staining or EBER in situ hybridization, might help to distinguish between these tumors.

3.3 Histogenesis of HRS and LP Cells

3.3.1 Cellular Origin of HRS and LP Cells

The unusual immunophenotype of HRS cells, which does not resemble any normal hematopoietic cell, has hampered the identification of the cellular origin of these cells considerably. Moreover, only few cell lines were available for detailed genetic studies, and the rarity of the HRS cells in the tissue posed a problem for their molecular analysis. Finally, by microdissection of HRS cells from tissue sections and single-cell polymerase chain reaction analysis of these cells, it was clarified that HRS cells derive from B cells in nearly all cases [17, 18]. This is because rearranged immunoglobulin (Ig) heavy (IgH) and light (IgL) chain gene rearrangements were detected in these cells. The detection of identical IgV gene rearrangements in the HRS cells of a given HL case also established the monoclonal nature of these cells, a hallmark of malignant cancer cells. With a few exceptions, somatic mutations were detected in the rearranged V genes of HRS cells [17–20]. As the process of somatic hypermutation, which generates such mutations, is specifically active in antigen-activated mature B cells proliferating in the GC microenvironment in the course of T-dependent immune responses [21], the presence of mutated IgV genes in the HRS cells established their derivation from GC-experienced B cells. A surprising finding was that about 25 % of cases of cHL showed destructive IgV gene mutations, such as nonsense mutations or deletions causing frameshifts that rendered originally functional V region genes nonfunctional [17]. When such mutations happen in normal GC B cells, these cells quickly undergo apoptosis. On this basis, it was proposed that HRS cells in these cases derive from pre-apoptotic GC B cells that were rescued from apoptosis because they harbored or acquired some transforming events [17, 22]. It is important to note that crippling mutations, such as those generating premature stop codons, represent only a small fraction of disadvantageous IgV gene

mutations that cause apoptotic death of GC B cells, and it is therefore likely that also most or even all other cases of cHL are derived from pre-apoptotic GC B cells. Even a few HL with unmutated IgV genes may derive from these precursors, because GC founder cells proliferating in GC become prone to apoptosis before the onset of somatic hypermutation activity [23]. The GC B cell origin of HRS cells was further supported by the molecular analysis of composite lymphomas composed of a cHL and a B cell non-HL. Such cases are often clonally related and show an intriguing pattern of shared as well as distinct somatic V gene mutations [24–26]. This pattern supports the assumption that both lymphomas were derived from distinct members of a proliferating GC B cell clone.

A few cases of cHL appear to originate from T cells, because T cell receptor gene rearrangements were detected in some cases diagnosed as HL and expressing some typical T cell molecules [11, 12]. However, it is debated whether these are true HL (see above). Remarkably, among HL cases with expression of one or more T cell markers, the majority nevertheless derives from B cells [11, 12].

The expression of multiple B cell markers by LP cells of LPHL already indicated a B cell derivation of these cells. Moreover, LP cells express several markers typically expressed by GC B cells, such as BCL6, AID, centerin, and hGAL, and the cells grow in a follicular pattern in close association with typical constituents of normal GC, i.e., follicular dendritic cells and GC-type T-helper cells [2, 3, 5, 6, 27, 28]. This pointed to a close relationship between LP cells and GC B cells. This is indeed supported by the detection of clonally related and somatically mutated IgV genes in these cells [18, 29–31]. As opposed to cHL, the V genes are selected for functionality, and a fraction of cases shows ongoing somatic hypermutation during clonal expansion, a hallmark of GC B cells [18, 29, 30]. Thus, these findings altogether indicate a GC B cell origin of LP cells. A recent large-scale gene expression profiling of isolated LP cells in comparison to the main subsets of mature B cells has led to a further specification of the derivation of LP cells by showing that the gene expression pattern of LP cells resembles that of GC B cells that have already acquired some features of post-GC memory B cells [32].

3.3.2 Relationship of Hodgkin Cells and Reed–Sternberg Cells and Putative HRS Cell Precursors

The relationship of mononucleated Hodgkin cells to multinuclear RS cells and the potential existence of HRS precursor cells have been a matter of debate. Based on the "mixed" phenotype of HRS cells and many numerical chromosomal aberrations in these cells, it has been speculated that HRS cells as such or, specifically, RS cells may derive from cell fusions of different cells (e.g., a B cell and a non-B cell). However, a detailed study of antigen receptor loci revealed that HRS cells do not carry more than two different alleles of these loci, which strongly supports the assumption that these cells do not derive from cell fusions [33]. Several studies of HL cell lines showed that mononuclear Hodgkin cells give rise to RS cells and that the latter have little proliferative activity [34–36]. A recent long-term time-lapse microscopy analysis revealed that mononucleated Hodgkin cells undergo incomplete cytokinesis and re-fusion to give rise to multinucleated RS cells [37].

Two studies reported the existence of a small subpopulation of side population cells among mononuclear Hodgkin cells. Side population cells extrude the Hoechst dye, because they express multidrug transporters, such as MDR1 and/or ABCG2. In several types of cancers, there is an overlap between side population cells and cancer stem cells. Side population cells of cHL cell lines were $CD30^{+}CD20^{-}$ and showed increased resistance against chemotherapeutic drugs [38, 39]. However, it has not yet been determined whether they have a higher capacity to sustain the HRS cell clone in the long term than other mononuclear Hodgkin cells, and the fact that side population cells were not identified in all cHL cell lines analyzed argues against an essential role of these cells for the survival of the HRS cell clone.

Another debated issue relates to the question whether $CD30^{+}$ typical HRS cells represent the

entire tumor clone in HL or whether members of the HRS cell clones exist among small CD30⁻ cells. An initial study for numerical chromosomal abnormalities indeed suggested that such CD30⁻ clone members might exist [40]. However, trisomies of chromosomes as studied in that work are not a stringent clonal marker. Moreover, a molecular analysis of EBV-positive HL cases for members of the malignant clones among small, CD30⁻ EBV⁺ B cells in the HL lymph nodes suggested that the small EBV⁺ B cells rarely, if at all, belong to the HRS cell clones [41]. Recently, two HL cell lines were reported to contain small subpopulations of CD20⁺CD30⁻Ig⁺ B cells coexpressing the stem cell marker aldehyde dehydrogenase (ALDH) [42]. These cells had clonogenic potential and gave rise to the typical HRS cells of these lines. It is important to note that ALDH^{high} cells were also detectable in the peripheral blood of most HL patients, and it was reported that these cells were often clonally related to the HRS cells [42]. However, the clonal relationship between HRS cells and ALDH^{high} peripheral blood B cells was not clearly shown [43], so it remains to be clarified whether ALDH^{high} B cells indeed represent precursors of HRS cell clones. A previous study using a highly sensitive PCR for HRS cell-specific Ig gene rearrangements failed to detect members of the HRS cell clone in the peripheral blood or bone marrow of two HL patients [44].

3.4 Genetic Lesions

HRS cells have a much higher number of chromosomal aberrations, including multiple numerical as well as structural abnormalities, than most other lymphomas [45]. However, it is still unclear whether this is mostly a side effect of some type of genetic instability and whether the expression of specific oncogenes or tumor suppressor genes is recurrently affected by these lesions. When the B cell origin of HRS cells became clear, HRS cells were studied for the presence of chromosomal translocations involving the Ig loci, as such translocations are a hallmark of many B cell lymphomas. Fluorescence in situ hybridization (FISH) studies indeed provided evidence for such translocations in about 20 % of cases, but most of the translocation partners involved remain to be identified [46, 47]. In a few cases, the translocation partners were BCL2, BCL3, REL, BCL6, or MYC [46–49]. Recurrent translocations affecting the major histocompatibility complex (MHC) class II transactivator (MHC2TA) were detected in about 15 % of cHL cases [50]. These translocations appear to cause downregulation of MHC class II expression by HRS cells. In LPHL, translocations of the BCL6 gene have been found in about 30 % of cases [51, 52]. These translocations can involve the Ig loci but also multiple other partners [53].

Due to the difficulty to analyze the few HRS and LP cells for mutations in oncogenes and tumor suppressor genes, only relatively few of such genes have been analyzed so far in these cells. There was a major interest to understand the apoptosis resistance of HRS cells, but it turned out that mutations in the CD95 gene, an important death receptor, as well as in members of the CD95 signaling pathway (FADD, caspase 8, caspase 10) were rare or not found at all [54–56]. Likewise, no mutations were found in the BCL2 family member BAD, and also ATM lesions are very rare [57–59]. The TP53 tumor suppressor gene was mutated in less than 10 % of cases where the exons of TP53 usually carrying mutations were studied in isolated HRS cells [60, 61]. However, recent studies of HL cell lines indicate that HRS cells may additionally carry untypical TP53 mutations and that the frequency of TP53 mutations may therefore be higher than previously thought [62]. MDM2, a negative regulator of TP53, frequently shows gains in HRS cells, which might contribute to impaired functions of TP53 in these cells [63].

HRS cells show constitutive activity of the NF-κB transcription factor (see below), which is essential for the survival of these cells. The mechanisms of this activation were originally not understood. Consequently, members and regulators of this signaling pathway were studied for genetic lesions (Table 3.1). Inactivating mutations in the main NF-κB inhibitor NFKBIA (IκBα) were found in about 10–20 % of HL cases and also in several HL cell lines (Fig. 3.3)

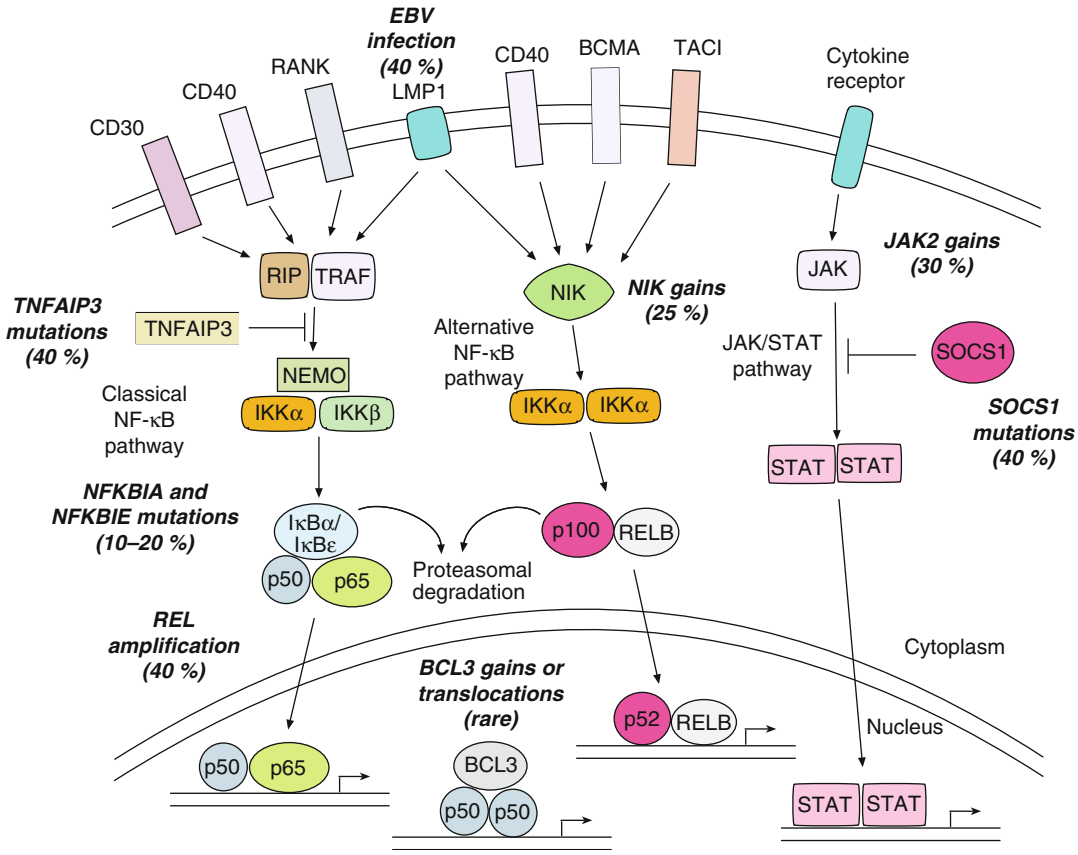

Fig. 3.3 NF-κB and JAK/STAT activity in HRS cells. In the classical NF-κB signaling pathway, stimulation of numerous receptors leads via TNF receptor-associated factors (TRAFs), which are often associated with the receptor-interacting protein (RIP), to the activation of the IKK complex, which is composed of IKKα, IKKβ, and NEMO. The IKK complex subsequently phosphorylates the NF-κB inhibitors IκBα and IκBε. This marks them for ubiquitination and subsequent proteasomal degradation. Thereby the NF-κB transcription factors (p50/p65 or p50/REL heterodimers) are no longer retained in the cytoplasm and translocate into the nucleus, where they activate multiple genes. The signal transduction from TRAFs/RIP to the IKK complex can be inhibited by TNFAIP3, which removes activating ubiquitins from RIP and TRAFs and additionally links ubiquitins to these molecules to mark them for proteasomal degradation. In the alternative NF-κB pathway, activation of receptors such as CD40, BCMA, and TACI causes stimulation of the kinase NIK, which then activates an IKKα complex. Activated IKKα processes p100 precursors to p52 molecules, which translocate as active p52/RELB NF-κB heterodimers into the nucleus. HRS cells show constitutive activity of the classical and alternative NF-κB signaling pathway. This activity is probably mediated by diverse mechanisms, including receptor signaling through CD40, RANK, BCMA, and TACI; genomic REL and MAP3K14 (NIK) amplification; destructive mutations in the TNFAIP3, IκBα, and IκBε genes; and signaling through the EBV-encoded LMP1. The role of CD30 signaling in HRS cells is controversially discussed. HRS cells may also harbor nuclear BCL3/(p50)2 complexes, and in a few cases the strong BCL3 expression appears to be mediated by genomic gains or chromosomal translocations. The JAK/STAT pathway is the main signaling pathway for cytokines. Upon binding of cytokines to their receptors, members of the JAK kinase family become activated by phosphorylation. The activated JAKs then phosphorylate and thereby activate STAT transcription factors. These phosphorylated factors homo- or heterodimerize and translocate into the nucleus where they activate target genes. The main inhibitors of the JAK/STAT pathway are SOCS (suppressor of cytokine signaling) factors, which function by binding to JAK molecules and inhibiting their enzymatic activity and, additionally, by inducing proteasomal JAK degradation. In HRS cells, STAT3, STAT5, and STAT6 are constitutively active. Besides activation of cytokine receptors (e.g., IL13 receptor and IL21 receptor) through cytokines, activation of this pathway is mediated by genomic gains or rare translocations of the JAK2 gene and frequent inactivating mutations in the SOCS1 gene. The frequency of genetic lesions and viral infections affecting NF-κB or STAT activity in classical Hodgkin lymphoma (HL) cases is indicated

[64–67]. One study also detected mutations in another NF-κB inhibitor, NFKBIE (IκBε), in a few cases [68]. Inactivating mutations or deletions in two further negative regulators of NF-κB signaling, CYLD and TRAF3, have also been detected in HL cell lines and a few primary cases, but overall these events are rare [69, 70]. Moreover, HRS cells frequently harbor genomic gains or amplifications of the REL gene [71–73], encoding an NF-κB family member, and a correlation between such gains and strong REL protein expression was found [74]. The MAP3K14 gene, which encodes the NIK kinase, a major activating component of the alternative NF-κB pathway, shows gains or amplifications in about 15 % of cHL [69, 75]. Also the IκB family member BCL3, which acts as a positive regulator of NF-κB activity, is affected by chromosomal gains or translocations in a small fraction of cHL [76, 77]. Recently, somatic and clonal inactivating mutations were found in the TNFAIP3 gene in about 40 % of cHL [78, 79]. TNFAIP3 encodes for the A20 protein, which is a dual ubiquitinase and deubiquitinase that functions as a negative regulator of NF-κB. It inhibits signaling from the receptor-interacting protein (RIP) and TNF receptor-associated factors (TRAF) to the IKK kinases, which are essential mediators of NF-κB signaling. TNFAIP3 mutations were mainly found in EBV-negative cases. Nearly 70 % of EBV$^-$ cases carried TNFAIP3 mutations, indicating that EBV infection and A20 inactivation are alternative pathogenetic mechanisms in HL [79]. As LMP1 of EBV, which is expressed in EBV-positive HRS cells, mimics an active CD40 receptor and signals through NF-κB [80, 81], LMP1 may replace the role of A20 inactivation in EBV$^+$ HL.

As it was recently revealed that also the LP cells of LPHL show strong constitutive NF-κB activity [32], also these cells were studied for mutations in NFKBIA and TNFAIP3, but clonal destructive mutations were not found (Table 3.1) [82].

Genetic lesions were also found in members of the JAK/STAT pathway, which is constitutively activated in HRS and LP cells. In about 40 % of cases analyzed, both HRS and LP cells showed somatic mutations in the SOCS1 gene, which encodes a main inhibitor of STAT signaling (Fig. 3.3) [83, 84]. Furthermore, a fraction of cHL cases show genomic gains or amplifications of the JAK2 locus, which encodes one of the kinases activating the STAT factors (Table 3.1) [72, 85]. Importantly, the genomic gains at 9p24 do not only affect the JAK2 locus but, additionally, the PD-L1, PD-L2, and JMJD2C genes [86, 87]. PD-L1 and PD-L2 are inhibitory receptors for PD1-positive T cells and may hence inhibit a cytotoxic T cell attack on HRS cells. JMJD2C encodes a histone demethylase and plays a role in the epigenetic remodeling of HRS cells. Finally, the JAK gene is in rare instances also deregulated by chromosomal translocations [88].

3.5 Deregulated Transcription Factor Networks and Signaling Pathways

3.5.1 The Lost B Cell Phenotype

Early immunohistochemical studies already revealed that HRS cells usually do not express typical B cell markers, such as CD20, CD79b, or BCR [10, 89–91]. This lack of expression of B cell markers was indeed one of the reasons why the B cell origin of HRS cells was not revealed until genetic studies for Ig gene rearrangements unequivocally demonstrated a B cell identity of these cells (see above). Gene expression profiling studies of HRS cells in comparison to normal B cells then showed that there is a global loss of the B cell-typical gene expression in HRS cells [92]. This downregulation involved all types of genes with important functions in these cells, for example, cell surface receptors (CD37, CD53), components of signaling pathways (SYK, BLK, SLP-65), and transcription factors (PU.B, A-MYB, SPI-B). As plasma cells also show a downregulation of many B cell-typical genes, it had been speculated that HRS cells lost their B cell gene expression and acquired a partial plasma cell differentiation program [2, 93]. However, a gene expression profiling study of microdissected HRS cells revealed that HRS cells have not acquired a plasma cell phenotype [94].

Remarkably, HRS cells have retained the expression of molecules that are involved in antigen-presenting functions and the interaction with $CD4^+$ T-helper cells. HRS cells usually express CD40, CD80, and CD86, and often MHC class II [92, 95]. This indicates that an interaction with T-helper cells is important for HRS cell survival. In line with this view, HRS cells are typically surrounded by CD40L expressing $CD4^+$ T cells [96].

We are now beginning to understand which factors contribute to the lost B cell phenotype of HRS cells. First, several transcription factors that positively regulate the expression of multiple genes in B cells are downregulated, including OCT-2, PU.1, EBF1, ETS1, and BOB.1 [89, 90, 97–99]. The downregulation of ETS1 may often be due to heterozygous deletions of the gene, which have been observed in over 60 % of cHL analyzed [99]. Second, although E2A, a master regulator of the B cell transcription program, is still expressed, HRS cells also show deregulated expression of ID2 and ABF1 [100–102], which bind to E2A and inhibit its function [101]. The physiological role of ABF1 is poorly understood, but ID2 is normally expressed in dendritic cells and natural killer cells and supports the generation of these cells concomitant with suppression of B cell development [103, 104]. Third, HRS cells express activated Notch1, which normally induces T cell differentiation in lymphocyte precursors and suppresses a B cell lineage differentiation of such cells [105, 106]. Activation of Notch1 is probably caused by interaction with its ligand Jagged-1, which is expressed by other cells in the HL microenvironment [106], and by high level expression of the Notch coactivator mastermind-like 2 (MAML2) [107]. Moreover, HRS cells have downregulated the Notch1 inhibitor Deltex1 [105]. Fourth, STAT5A and STAT5B are activated in HRS cells and have been reported to induce an HRS cell-like phenotype in normal B cells [108]. Constitutive active STAT5 induced the expression of CD30 and of the T cell transcription factor GATA3 in the B cells and led to the downregulation of BCR expression. Aberrant GATA3 expression in HRS cells is furthermore mediated by Notch1 and NF-κB activity in HRS cells [109]. Fifth, the downregulation of multiple B cell genes in HRS cells is further caused by epigenetic mechanisms, as DNA methylation has been detected for numerous such genes [110–112]. Sixth, HRS cells express several transcription factors that have important roles in hematopoietic stem cells and early lymphoid precursors, including GATA2, BMI1, RING1, and RYBP [113–116]. The expression of these factors may contribute to a "dedifferentiated" phenotype of HRS cells.

Surprisingly, PAX5, the main B cell lineage commitment and maintenance factor, is still expressed in HRS cells, albeit at reduced levels [8]. As many of its direct target genes are not expressed, it is likely that PAX5 activity is inhibited. Notch1 is a candidate for this inhibition [105]. It may also be that PAX5 target genes are not expressed because other transcription factors needed for the efficient expression of these genes are missing.

Expression of the myeloid-specific colony-stimulating factor 1 receptor (CSF1R) by HRS cells is a further important example of aberrant expression of a non-B cell gene in HRS cells [117]. CSF1R expression promotes HRS cell survival. The mechanism of its deregulated expression is remarkable because this is mediated by derepression of an endogenous long terminal repeat upstream of the CSF1R gene that replaces the function of the normal CSF1R promoter [117].

The downregulation of many B cell transcription factors that also suppress the expression of non-B cell lineage genes, combined with the upregulated expression of genes promoting expression of genes of other hematopoietic cell types (e.g., Notch1, ID2), not only explains the lost B cell phenotype of HRS cells but also the heterogenous expression of genes specifically expressed by dendritic cells, T cells, or other cell types. It is an intriguing question whether the lost B cell phenotype of HRS cells is related to their origin from crippled GC B cells. Perhaps, due to the stringent selection of B cells for expression of a functional BCR (a high-affinity one in the GC), there is a selection in HRS cell pathogenesis downregulating the B cell gene expression program to escape the selectional forces that induce apoptosis in GC B cells with unfavorable IgV gene mutations. The observa-

tion that enforced reexpression of PU.1 in HL cell lines induces apoptosis is in line with this view [118]. However, the lost B cell phenotype could also be a side effect of so far unknown transforming events.

3.5.2 Constitutive Activation of Multiple Signaling Pathways

It is obvious that tumor cells need to activate and deregulate signaling pathways and transcription factors that promote their survival and proliferation. Nevertheless, it is striking how many of such pathways are constitutively activated in HRS cells, and cHL appears to be rather unique among lymphoid malignancies in the extent to which multiple signaling pathways contribute to the survival and expansion of HRS cells. It has already been mentioned above that HRS cells show constitutive NF-κB activity. This activity is essential for HRS cell survival [119] and is most likely not only mediated by genetic lesions (see above) but also by signaling through receptors. NF-κB factors of both the canonical pathway (p50/p65) and the noncanonical NF-κB pathway (p52/RelB) are activated (Fig. 3.3). HRS cells express the TNF receptor family members CD30, CD40, RANK, TACI, and BCMA, which activate NF-κB, and cells expressing the respective ligands are found in the HL microenvironment [96, 120–124]. There are, however, conflicting data about the role of CD30 in NF-κB activation [125, 126]. In EBV-positive cases of cHL, the virally encoded LMP1 mimics an active CD40 receptor and hence also contributes to NF-κB activation [127].

Another central signaling pathway, which is like NF-κB activated both by genetic lesions as well as by ligand-mediated receptor triggering, is the JAK/STAT pathway (Fig. 3.3). This is the main signaling pathway for cytokines. Activation of cytokine receptors causes activation of JAK kinases which in turn phosphorylate and thereby activate STAT transcription factors. The phosphorylated STAT factors dimerize and then translocate into the nucleus where they activate transcription of target genes. HRS cells show activation of STAT3, STAT5, and STAT6 [108, 128–130]. The activation of STAT6 is at least partly mediated by signaling through IL13. As HRS cells express IL13 and its receptor, STAT6 activation can be mediated through an autocrine stimulation loop [131, 132]. Signaling through the IL21 receptor contributes to STAT3 and STAT5 activation in HRS cells, which is also enhanced by the NF-κB activity in the cells [108, 133, 134]. As mentioned above, STAT5 activity may contribute to the lost B cell phenotype of HRS cells. Inhibition of STAT activity in HL cell lines resulted in reduced proliferation of the cells, further supporting an important pathogenetic role of this signaling pathway [128, 129, 131].

Receptor tyrosine kinases (RTK) are important regulators of cell growth, survival, and proliferation. In multiple cancers, specific RTK are activated, often by somatic mutations [135]. In contrast, HRS cells show multiple activated RTK, and their activation does not appear to be due to activating mutations but at least partly to ligand-mediated stimulation [136]. RTK that are often expressed in varying combinations in HRS cells include PDGFRA, DDR2, EPHB1, RON, TRKA, TRKB, CSF1R, and MET [117, 136, 137]. The expression of most of these is aberrant, as they are not expressed by normal GC B cells [117, 136]. They are also usually not expressed by other B cell non-HL, showing that this is a specific feature of HL among B cell lymphomas [136, 138]. Expression of multiple RTKs is most pronounced in EBV-negative cases of cHL, suggesting that EBV activates pathways in HRS cells replacing the function of RTKs [139]. For PDGFRA, TRKA, and CSF1R, a growth-inhibitory effect has been shown upon their inhibition in HL cell lines, giving a first indication that the activity of RTKs is important for HRS cell proliferation [117, 136, 140].

Signaling through various receptors is mediated by the mitogen-activated protein kinase (MAPK)/ERK pathway. In HRS cells, the serine/threonine kinases ERK1, ERK2, and ERK5 are activated [141, 142]. Inhibition of their activity has antiproliferative effects on HL cell lines [142]. Signaling through CD30, CD40, and RANK may contribute to the stimulation of this pathway [142].

The transcription factor AP-1 acts as homo- or heterodimers of Jun, Fos, and ATF components. In HRS cells, c-Jun and Jun-B are overexpressed and constitutively active [143]. The overexpression of Jun-B is mediated by NF-κB [143]. AP-1 induces many target genes and promotes proliferation of HRS cells. Target genes of AP-1 include CD30 and galectin-1, the latter of which has immunomodulatory functions [144, 145].

Finally, also the phosphatidylinositol-3-kinase (PI3K)/AKT pathway, which is a main promoter of cell survival, shows activity in HRS cells [146, 147]. AKT is a serine/threonine kinase that is activated in HRS cells, as evident from its phosphorylated state and phosphorylation of known target proteins [146, 147]. Inhibition of AKT in HL cell lines causes cell death, suggesting an important role of active AKT in HRS cell survival [146, 147]. PI3K may be activated in HRS cells by signaling through CD30, CD40, RANK, and RTK. Moreover, downregulation of the AKT inhibitor INPP5D in HRS cells may further contribute to strong AKT activity in these cells [94].

While we have a relatively detailed insight into signaling pathways active in HRS cells, less is known about signaling pathways constitutively active in LP cells of LPHL. However, LP cells also show a high constitutive activity of NF-κB [32]. RTKs are partly also aberrantly expressed by these cells [136], and activation of the JAK/STAT pathway has been observed [83].

In conclusion, HRS cells are characterized by the deregulated and constitutive activation of multiple signaling pathways and transcription factors that contribute to the survival and proliferation of these cells. The multitude of different stimulated pathways appears to be rather unique among human B cell lymphomas. Often, these pathways are activated by common mechanisms, and they may interact in numerous ways.

3.6 Antiapoptotic Mechanisms

With a presumed origin from pre-apoptotic GC B cells, it is critical to understand through which mechanisms HRS cell escape from apoptosis. A number of factors contributing to HRS cell survival have already been discussed in the previous section: constitutive activity of NF-κB, STAT, PI3K, Notch1, AP-1, RTK, and ERK. Several specific inhibitors of the two main apoptosis pathways deserve specific mentioning. Although HRS cells express the CD95 death receptor of the extrinsic apoptosis pathway as well as its activating ligand, HL cell lines are resistant to CD95-mediated death induction, suggesting a specific inhibition of this pathway [148–150]. As mentioned above, this resistance is neither due to mutations in the CD95 receptor itself nor in its interaction partners FADD, caspase 8, or caspase 10. However, HRS cells show strong expression of the CD95 inhibitor cFLIP (cellular FADD-like interleukin 1b-converting enzyme-inhibitory protein), and this factor impairs CD95 signaling in HRS cells [148, 149]. Inhibition of the intrinsic (mitochondrial) apoptosis pathway is probably mediated through strong expression of the anti-apoptotic factors BCLXL and XIAP (X-linked inhibitor of apoptosis), and downregulation of the pro-apoptotic factor BIK [94, 151, 152]. BCLXL inhibits apoptosis at the level of the mitochondrial apoptosis induction, whereas XIAP inhibits activity of caspases 3 and 9, which are downstream executioners of the mitochondrial apoptosis program. Although HRS cells also express pro-apoptotic Smac, which can inhibit XIAP, the cells show an impaired release of Smac from the mitochondria into the cytoplasm [153]. As mentioned above, HRS cells express high levels of the pro-apoptotic TP53 factor, but resistance to TP53-mediated apoptosis appears to be rarely due to inactivating mutations in the TP53 gene. An important factor for the inhibition of TP53 activity is MDM2, which is expressed at high levels in HRS cells [154]. The functional role of MDM2 as an TP53 inhibitor in HRS cells is supported by the fact that HL cell lines expressing wild-type TP53 are rendered apoptosis-sensitive toward pharmacological apoptosis inducers upon inhibition of MDM2 by its antagonist nutlin 3 [155, 156].

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Microenvironment, Crosstalk, and Immune Escape Mechanisms

4

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Contents

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4.1 Microenvironment

4.1.1 Hodgkin Lymphoma Subtypes

When discussing the microenvironment in Hodgkin lymphoma (HL), it is important to recognize the different HL subtypes described by the WHO classification [1, 2]. The classical HL (cHL) subtypes are defined in large part by the composition of the reactive infiltrate (Table 4.1). The most prevalent subtype is the nodular sclerosis type that consists of a nodular background with thick fibrotic bands, usually with a thickened lymph node capsule. In addition to the lacunar type of Hodgkin/Reed–Sternberg (HRS) cells, there is a microenvironment consisting of T cells, eosinophils, and histiocytes, with a variable admixture of neutrophils, plasma cells, fibroblasts, and mast cells. The second most common subtype is mixed cellularity, which is defined by the presence of typical HRS cells and a diffuse infiltrate of T cells, eosinophils, histiocytes, and plasma cells, sometimes with the formation of granuloma-like clusters or granulomas (Fig. 4.1). Lymphocyte-rich cHL also comprises typical HRS cells in a nodular or diffuse microenvironment and small B and/or T lymphocytes dominating the background, sometimes with admixture of histiocytes. Granulocytes are not a component in this subtype. The rare lymphocyte-depleted subtype harbors a high percentage of HRS cells in a background consisting of fibroblasts and a low number of T cells. Nodular lymphocyte predominance (NLP)

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_4, © Springer International Publishing 2015

Table 4.1 Composition of the microenvironment in different Hodgkin lymphoma (HL) subtypes

Subtype	EBV (%)	Background	T cells	Other cells
Nodular sclerosis	10–40	Nodular+fibrosis	CD4 > CD8, Th2, Treg > Th1	Eosinophils, histiocytes, fibroblasts, B cells, mast cells (neutrophils)
Mixed cellularity	75	Diffuse	CD4 > CD8, Th2, Treg > Th1	Eosinophils, histiocytes, plasma cells, B cells
Lymphocyte rich	40–80	Nodular or diffuse	CD4 > CD8	Histiocytes
Lymphocyte depleted (including HIV+)	80–100	Diffuse	–	Fibroblasts
Nodular lymphocyte predominant	0	Nodular (+diffuse)	Th2, CD57+ Treg, CD4+/8+	Histiocytes, B cells

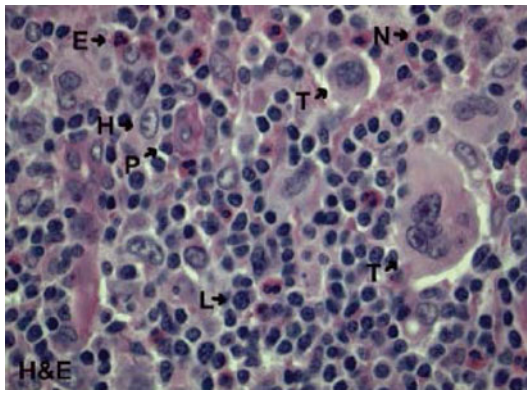

Fig. 4.1 The microenvironment in mixed cellularity classical Hodgkin lymphoma. *T* tumor cell, *L* (T–) lymphocyte, *H* histiocyte, *E* eosinophil, *N* neutrophil, *P* plasma cell. Hematoxylin and eosin staining

HL is considered a separate entity. The morphology may closely resemble that of the nodular variant of the classical lymphocyte-rich subtype, both involving follicular areas with many small B cells. However, the nature of the tumor cells and the T cells is different. In the cHL subtypes, the HRS cells are transformed post germinal center B cells with a loss of B cell phenotype, while in LPHL the lymphocyte-predominant (LP) cells have a germinal center B cell phenotype. The T cells in cHL have features of paracortical T cells, while those in LPHL are similar to germinal center T cells [3, 4].

4.1.2 Epstein–Barr Virus

The presence of latent Epstein–Barr virus (EBV) genomes in HRS cells appears to influence the composition of the microenvironment. Positive EBV status is strongly associated with the mixed cellularity subtype (~75 % EBV+) and by definition is absent in LPHL. Depending on the geographic locale, EBV is present in the HRS cells in 10–40 % in nodular sclerosis cases. The percentage of EBV+ classical lymphocyte-rich cases is not very clear but is probably between 40 and 80 %. EBV infects more than 90 % of the world population and establishes a lifelong latent infection in B cells in its host. Potent cytotoxic immune responses keep the number of EBV-infected B cells at approximately 1/100,000 B cells and usually prevent EBV-driven malignant transformation in immunocompetent individuals. Accordingly, EBV-associated cHL cases contain slightly more CD8+ cytotoxic T cells in the reactive background compared to non-EBV-associated cHL cases [5].

4.1.3 Human Immunodeficiency Virus

In patients with an impaired immune response, cHL occurs more frequently. After solid organ transplantation, there is a small increase in the incidence of cHL that can largely be attributed to EBV-positive cHL. Human immunodeficiency virus (HIV)-infected individuals have an approximate 10 times increased risk of developing cHL [6]. In comparison to non-HIV-associated cHL, these tumors are more often EBV-associated, mixed cellularity, and lymphocyte depletion subtypes and usually contain more tumor cells. This indicates a

functional defect in the immune response, in particular to EBV, presumably caused by the impairment of CD4+ T cells by HIV. On the other hand, the importance of CD4+ T cells for supporting the growth of HRS cells is also illustrated in HIV-positive patients, because an increase in HIV-associated cHL incidence has been observed after the introduction of highly active antiretroviral therapy (HAART) [7] (Fig. 4.4).

4.1.4 T Cell Subsets in cHL

A unifying feature of the reactive infiltrate in virtually all cHL subtypes is the presence of large amounts of CD4+ T cells. Besides being widely distributed in the background, these CD4+ T cells form a tight rosette around the tumor cells. T cells within these rosettes often have a distinct phenotype, different from the phenotype of the T cells that are located further away from the cHL tumor cells (Fig. 4.2).

In general, CD4+ T cells can be divided into naive (CD45RA+) and memory (CD45RO+) subsets depending on whether they have previously been stimulated by antigen. A large subset of CD4+ T cells consists of the so-called helper T (Th) cells; these cells play an important role in helping other cells to induce an effective immune response. Th cells can be further divided into Th0 (naive), Th1 (cellular response), Th2 (humoral response), Th17 (IL-17 producing), and Treg (regulating other responses) cells. The Treg cells can be further divided into Th3 (transforming growth factor-β (TGF-β)-producing), Tr1 (IL-10-producing), and

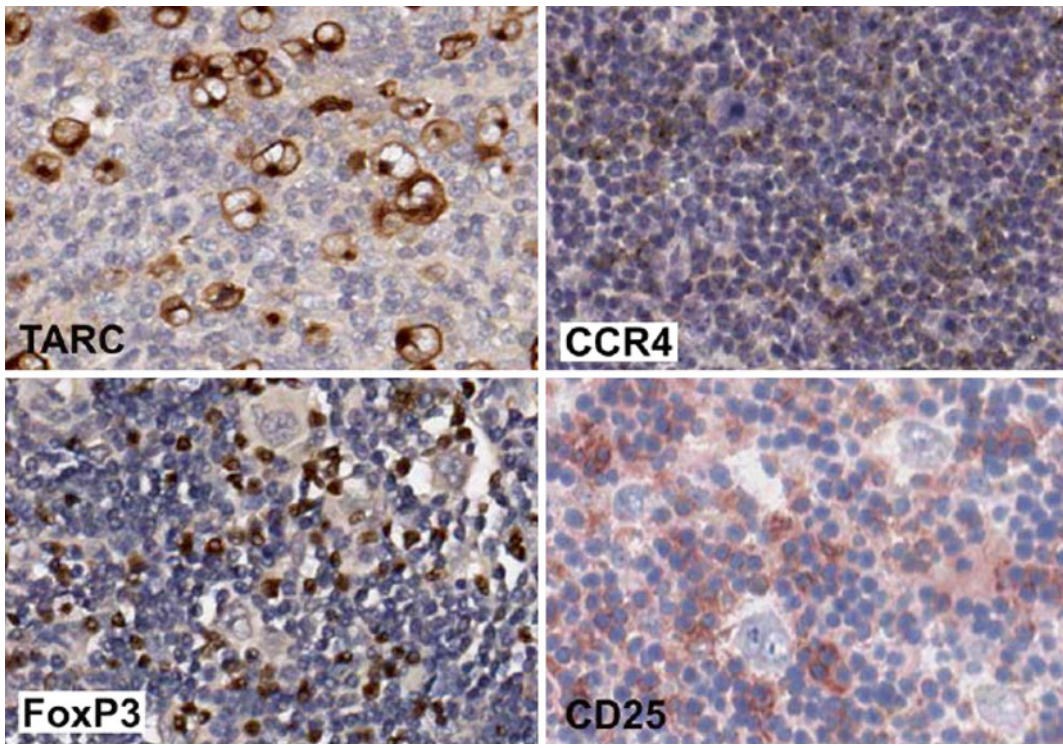

Fig. 4.2 Shaping the microenvironment in classical Hodgkin lymphoma (HL). Immunohistochemistry of classical HL cases. In the *upper panel*, *left*, strong and specific staining of Hodgkin/Reed–Sternberg (HRS) cells for chemokine CCL17 (TARC). This chemokine attracts CCR4+ lymphocytes (*upper panel*, *right*). A large proportion of reactive T cells are Treg cells, as shown by positive staining for transcription factor FoxP3 (*lower panel*, *left*) and activation marker CD25 (*lower panel*, *right*)

CD4+CD25+ Treg (originating from the thymus) subpopulations. Some, but not all, Treg cells express the transcription factor FoxP3.

The T cells in cHL consist mainly of CD4+ T cells that have a memory phenotype (CD45RO+) and express several activation markers including CD28, CD38, CD69, CD71, CD25, and HLA-DR, as well as markers like CD28, CTLA-4, and CD40L. However, these T cells lack expression of CD26 [8]. This lack of CD26 expression is most striking in the areas surrounding the tumor cells. CD26, dipeptidyl peptidase IV, regulates proteolytic processing of several chemokines, e.g., CCL5 (RANTES), CCL11 (eotaxin), and CCL22 (MDC) [9]. CD26 is also associated with adenosine deaminase (ADA) and with CD45RO and, when interacting with anti-CD26 antibodies, leads to enhancement of T cell activation through the T cell receptor [10]. CD26 is preferentially expressed on CD4+CD45RO+ cells and is normally upregulated after activation. However, CD26 cannot be upregulated on the CD26-negative cells from cHL lesions. In general, a high CD26 expression level correlates with a Th1 subtype of cells.

The transcription factor expression pattern indicates that the CD4+ T cells in cHL are predominantly Th2 (c-Maf) and Treg (FoxP3) [3, 11]. The CD4+CD26– T cell subset in cHL has reduced mRNA levels of Th1- and Th2-associated cytokines in comparison to the CD4+CD26+ T cells from cHL and CD4+ T cells (both CD26– and CD26+) in reactive lymph nodes [12]. Based on much higher mRNA expression levels of IL-2RA (CD25), CCR4, FoxP3, CTLA4, TNFRSF4 (OX-40), and TNFRSF18 (GITR) observed in the CD4+CD26– T cells from cHL, it has been postulated that these cells have a Treg phenotype (Fig. 4.2). In addition, mildly enhanced IL-17 levels can be observed both in CD4+CD26– and CD4+CD26+ T cells from cHL in comparison to the T cells from the tonsil. Upon stimulation, the CD4+CD26– T cells fail to induce expression of cytokines, suggesting that the T cell population rosetting around the HRS cells or located in the direct vicinity of the HRS cells have an anergic phenotype [12]. Immunohistochemistry for several Treg-associated molecules demonstrates that the rosetting T cells in cHL express GITR, CCR4, and CD25, but not FoxP3. Scattered FoxP3-positive cells are present in the infiltrate but only rarely in the direct vicinity of the HRS cells, and CTLA-4 shows a more diffuse presence [12]. Likewise, a small number of scattered IL-17-positive cells can be found in the reactive infiltrate. Anergy in T cells is normally induced by lack of costimulation through CD80/CD86, activation by superantigens, or the effect of cytokines like TGF-β and IL-10. The anergic state in cHL is probably not caused by the lack of costimulatory molecules since CD80 and CD86 as well as several other costimulatory molecules are highly expressed on the HRS cells [13, 14]. However, besides CD28, the surrounding lymphocytes express CTLA-4, and HRS cells frequently produce TGF-β and IL-10 which can cause anergy of the surrounding T cells. Although the vast majority of studies indicate that the CD4+ T cells in cHL are (anergic) Th2 cells and Treg cells, a single recent study by flow cytometry of whole lymph nodes showed a predominant Th1-type pattern. In this study there were high numbers of T-bet (Th1-type)-positive cells in tissue by immunohistochemistry, with increased levels in EBV+ cHL [15].

4.1.5 T Cell Subsets in LPHL

The CD4+ T cells in LPHL resemble the CD4+ T cells in cHL, regarding the expression of CD45RO, CD69, CTLA4, and CD28 and lack of CD26. However, these T cells do not express CD40L, and a significant proportion of the cells that immediately surround the LP cells express CD57 and PD-1 [16]. Similar to the Th2 cells in cHL, the rosetting cells in LPHL strongly express the Th2-associated transcription factor c-Maf (Fig. 4.3; [3]).

Characterization of the CD4+CD57+ T cell subset shows lack of IL-2 and IL-4 mRNA but elevated interferon-γ (IFN-γ) mRNA levels in comparison to CD57+ T cells from the tonsil. Stimulation of these cells fails to induce upregulation of IL-2 and IL-4 mRNA levels [17], which is similar to the lack of cytokine induction upon

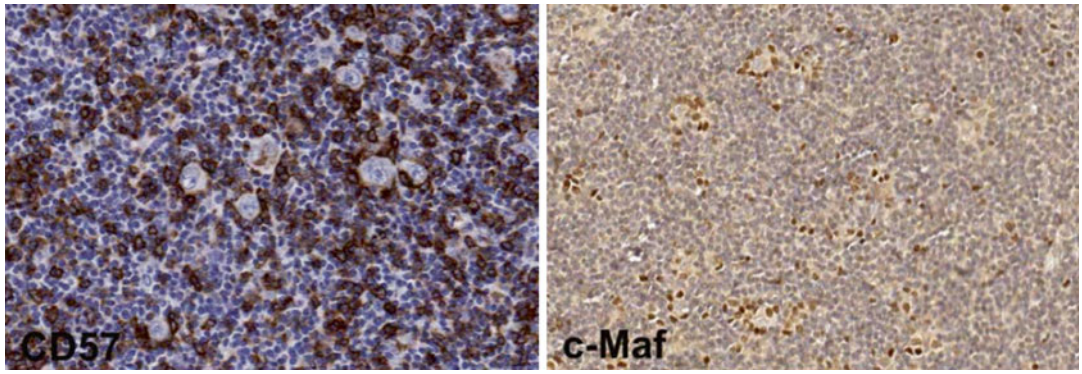

Fig. 4.3 T cells in nodular lymphocyte-predominant Hodgkin lymphoma (LPHL). Immunohistochemistry of a case of LPHL. A variable but usually high amount of reactive T cells express CD57, and as in this case these cells can encircle the tumor cells (*panel*, *left*). The CD57+ T cells also express transcription factor c-Maf, indicating a Th2-type nature (*panel*, *right*)

stimulation of the CD26− T cells in cHL. The normal counterpart of CD4+CD57+ T cells is found almost exclusively in the light zone of reactive germinal centers. These CD57+ T cells also lack CD40L expression. CD57 is known as an activation marker, but it has also been demonstrated to be a marker for senescent cells. Senescence is the phenomenon by which normal diploid cells lose the ability to divide, normally after about 50 cell divisions.

In LPHL, a population of CD4+CD8+ T cells has been reported in more than 50 % of patients. The function of these cells in LPHL is currently unknown, but in other settings these cells have immunoregulatory properties [18].

4.1.6 Fibrosis and Sclerosis

The presence of bands of collagen surrounding nodules and blood vessels is typical of the nodular sclerosis subtype. Several factors can induce the activation of fibroblasts and the subsequent deposition of extracellular matrix proteins. The Th2 cells in cHL might provide a profibrogenic microenvironment by the production of the Th2 cytokine IL-13. IL-13 is expressed at a higher level in nodular sclerosis than in mixed cellularity cHL. Moreover, the percentage of IL-13 receptor-positive fibroblasts is increased in nodular sclerosis cHL cases [19]. IL-13 stimulates collagen synthesis in vitro and also stimulates the production of TGF-β, another potent stimulator of fibrosis. TGF-β can interact with basic fibroblast growth factor (bFGF) to cause fibrosis in cHL. In a mouse model for fibrosis, the simultaneous application of TGF-β and bFGF causes persistent fibrosis [20]. Both TGF-β and bFGF are produced by the HRS cells as well as the reactive background [21, 22]. TGF-β and bFGF are both produced more prominently in nodular sclerosis than in mixed cellularity cHL [23], which is consistent with this concept. The third factor that stimulates fibroblasts in cHL is the engagement of CD40. CD40, a member of the tumor necrosis factor receptor (TNFR) superfamily, can be upregulated on fibroblasts by IFN-γ, and its ligand CD40L is present on activated T cells, mast cells, and eosinophils present in the cHL microenvironment.

4.1.7 Eosinophils, Plasma Cells, Mast Cells, and B cells

The presence of eosinophils in the reactive infiltrate can be promoted by both IL-5, produced by Th2 cells, and by IL-9. In cHL patients with eosinophilia in the peripheral blood, IL-5 and IL-9 have been reported to be expressed by the HRS cells [24]. In addition, eosinophils are attracted to cHL tissues by the production of the

chemokine CCL11, especially in nodular sclerosis cHL. CCL11 levels can be enhanced by the production of tumor necrosis factor-α (TNF-α) by the HRS cells, which in turn can induce CCL11 production in fibroblasts. This process is specific for cHL since other lymphomas with tissue eosinophilia show no expression of CCL11 [25]. HRS cells also produce CCL28 (MEC), and expression of CCL28 correlates with the presence of eosinophils and plasma cells in cHL. CCL28 attracts eosinophils by signaling through the chemokine receptor CCR3 and attracts plasma cells through CCR10 [26]. CCL5 is produced at high levels by the reactive infiltrate in cHL and can attract eosinophils as well as mast cells. CCL5 and IL-9 may both contribute to the attraction of mast cells in cHL [27]. The stimulation and recruitment of eosinophils in cHL can be illustrated in bone marrow biopsies that often show reactive enhancement of granulopoiesis with many eosinophils in the absence of bone marrow HRS cells. IL-6 has been shown to be produced by HRS cells in some cases of cHL, and this may explain the presence of variable amounts of plasma cells [28]. B cells that express CD20, CD21, IgM, and bcl-6 can be found in cHL [29]. It is possible that these cells are remnants of the original lymph node B cell areas.

4.2 Crosstalk Between HRS Cells and Microenvironment (Fig. 4.4)

4.2.1 Factors Supporting Tumor Growth

It is likely that HL tumor cells originate from a precursor B cell that has become addicted to

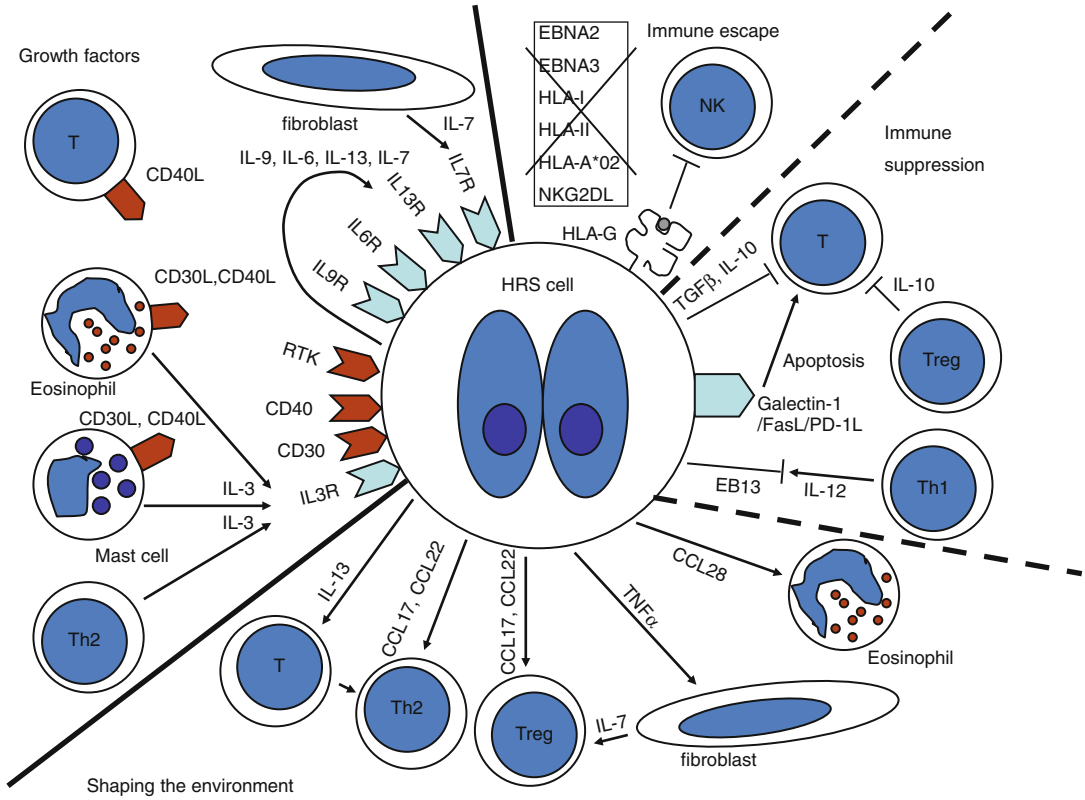

Fig. 4.4 Schematic overview of the crosstalk between Hodgkin/Reed–Sternberg (HRS) cells and the microenvironment. Hodgkin lymphoma tumor cells attract specific cell subsets by chemokines, are dependent on growth factors, and use mechanisms of immune suppression and immune escape. *Arrows* indicate stimulating effects; the other lines indicate inhibitory effects

activating and growth-supporting stimuli during a deregulated immune response. Many additional events are needed to account for the highly deregulated malignant phenotype of HRS and LP cells. Although the tumor cells attain multiple alternative mechanisms to circumvent the dependence on growth-stimulating signals from the reactive infiltrate, they usually are not self-sufficient at the time of diagnosis. This is reflected by the inability to grow cell lines from primary HL cell suspensions.

IL-3 can function as a growth factor for B cells and is produced by activated Th2 cells, mast cells, and eosinophils. Its functions include protection against apoptosis and stimulation of proliferation. Most HRS cells in cHL cases express the IL-3 receptor, and exogenous IL-3 promotes cell growth in cHL cell lines. Costimulation of IL-3 with IL-9 results in further enhancement of cell growth [30]. There is no evidence for the production of IL-3 by HRS cells themselves, so this signaling pathway depends on the reactive infiltrate. IL-7 is most likely an autocrine as well as a paracrine growth factor for HRS cells, since HRS cells express both the IL-7 receptor and produce IL-7 [31]. Moreover, fibroblasts isolated from cHL tissue are able to produce IL-7 [32]. cHL cell lines produce very little IL-7 themselves, but anti-IL-7 has some effect on cell growth. Addition of IL-7 results in an increase in proliferation and protection against apoptosis. Other growth factors important for HRS cells are IL-9, IL-13, and, possibly, IL-6. IL-9 is expressed by the tumor cells and not in the infiltrate, and the IL-9 receptor is expressed on the tumor cells and mast cells. IL-9 supports tumor growth in cell lines and is an autocrine factor in cHL tissue [27]. IL-13 produced by HRS cells as well as the surrounding T cells drives proliferation and is mostly autocrine [33]. IL-6 is mainly produced by the HRS cells and occasionally by the infiltrating cells [28]. In general, IL-6 is found at higher levels in EBV+ cases [34]. IL-6 might have an autocrine effect although neutralizing antibodies have no effect on the growth of cHL cell lines.

HRS cells express several members of the TNFR superfamily including CD30, which has been used as a marker for cHL since the early 1980s. The CD30 ligand (CD30L) is expressed on eosinophils [35] and mast cells [36] that are present in the cHL infiltrate. Circulating eosinophils in cHL patients also have increased expression levels of CD30L [35]. Binding of CD30L to CD30 causes enhanced secretion of IL-6, TNFα, and lymphotoxin-α; increased expression of ICAM-1 and B7; and, possibly, increased clonogenic growth and protection against apoptosis [37]. Another TNFR expressed on HRS cells is CD40. CD40 is generally found on B cells, and B cells can be activated through CD40. In vitro rosetting of activated CD4+ lymphocytes around HRS cells is mediated through the CD40L adhesion pathway [38]. Engagement of CD40 is important for the prevention of apoptosis. Similar to stimulation of CD30, stimulation of HRS cell lines with CD40L causes enhanced secretion of several cytokines and upregulation of costimulatory molecules [37].

Several receptor tyrosine kinases (RTKs) are expressed by HRS cells and can have a role in cell growth. Their ligands are expressed in the microenvironment or by the HRS cells themselves. PDGFRA has a role in cell growth, since inhibition of PDGFRA signaling by imatinib blocks proliferation. Its ligand, PDGFA is also produced by the HRS cells [39]. DDR1 [40] and DDR2 [39] can protect HRS cells from cell death by binding to collagen, which is present in the immediate surroundings of the HRS cells. Knockdown of DDR1 decreases survival of the L428 cHL cell line [40]. TRKA is the receptor for NGF which is expressed by granulocytes [39], and TRK inhibition can decrease survival of cHL cell lines [41]. EPHB1 and its ligand ephrin-B1 are both expressed by the HRS cells [39]. HGF receptor c-Met is expressed on HRS cells, and inhibition causes G2/M cell cycle arrest. HGF is produced by the tumor cells in a small group of patients and by dendritic reticulum cells [42]. PDGFRA, DDR2, EPHB1, RON, TRKA, and TRKB are found especially in EBV– HL [43], while DDR1 is upregulated by LMP1 [40].

Another receptor, Notch1 is an upstream regulator of NFκB [44]. It is strongly expressed by HRS cells, and stimulation via Jagged1 induces proliferation and survival of cHL cells [45].

4.2.2 Shaping the Environment

In addition to the production of several growth factors, HRS cells also produce large amounts of chemokines to attract specific beneficial or non-reacting cells. The lack of CD26 on the T cells surrounding the HRS cells may result in an incapability to cleave the chemokines and thereby modulate the chemotaxic effects exerted by the HRS cells. The attraction of a specific population of cells is an important immune escape mechanism exerted by the tumor cells.

The most abundant and cHL-specific chemokine is CCL17 (TARC); it binds to CCR4 on Th2 cells, Treg cells, basophils, and monocytes. CCL17 is highly expressed by HRS cells in the vast majority of cHL patients and not in LPHL or non-Hodgkin lymphomas [46, 47]. CCL17 levels can be measured in serum and are a sensitive and specific marker reflecting cHL tumor burden [48–51]. High expression levels of CCL17 might explain the influx of lymphocytes with a Th2- and Treg-like phenotype, and CCL17- positive cases are indeed associated with a higher percentage of CCR4-positive cells (Fig. 4.2; [47, 52]). In turn, Th2-type cytokines (IL-4, IL-13) can induce the production of CCL17 by HRS cells. CCR4-positive lymphocytes are found especially in the rosettes immediately surrounding the HRS cells [12, 53]. CCL22 is another chemokine that has a similar function as CCL17. High CCL22 protein expression levels were found in the cytoplasm of HRS cells in 90–100 % of cHL patients and also in tumor cells in the majority of LPHL and non-HL patients [54–57]. CCL22 production can also be stimulated by Th2 cytokines, IL-4 and IL-13, and may serve to reinforce the attraction of Th2 and Treg lymphocytes, initiated by CCL17. Stimulation of the IL-21 receptor on HRS by IL-21 activates STAT3, which can induce CCL20 (MIP3α) production. CCL20 in turn attracts memory T cells and Treg cells [58]. HRS cells express both IL-21 and the IL-21 receptors, indicating the presence of an autocrine signaling loop. The expression of some chemokines is more pronounced in EBV+ cHL (i.e., CXCL9 and CXCL10), and perhaps as a result the composition of the reactive background is somewhat different from that in EBV– cHL, with a slightly higher proportion of CD8+ T cells in EBV+ cases.

In addition to attracting specific cell subsets by chemotaxis, HRS cells also shape their environment by inducing differentiation of specific T cell subsets that are favorable for HRS cell survival and growth. The expression of IL-13 by the HRS cells stimulates differentiation of naïve T cells to Th2 cells [33]. The production of IL-7 by HRS cells and fibroblasts can induce proliferation of Tregs [32]. Also, cHL cell lines with antigen-presenting functions like KMH2 and L428 have been shown to promote the differentiation of Treg-like cells in vitro (expressing CD4, CD25, FoxP3, CTLA4, and GITR and producing large amounts of IL-10). Interestingly, these cell lines can also induce the formation of CD4+ cytotoxic cells (expressing granzyme B and TIA-1) that can kill tumor cells directly, suggesting that CD4+ CTLs have the potential to attack tumor cells in vivo [59].

4.2.3 Immune Suppression

Because normal B cells are professional antigen-presenting cells, HRS cells are expected to present antigens to the immune system, at least early in disease pathogenesis. Indeed, most components of the HLA class I and HLA class II antigen-presenting pathways have been detected in the HRS cells at the time of diagnosis. However, Th1 cells are not actively attracted by the HRS cells, and CD8+ CTLs are relatively scarce. Moreover, HRS cells have gained the capacity to prevent CTLs from attacking by producing high amounts of the strongly immunosuppressive cytokines TGF-β and IL-10. TGF-β is produced by HRS cells in nodular sclerosis cHL [21, 22], whereas IL-10 is more frequently found in EBV+ (mixed cellularity) cHL [60, 61]. In normal cells, TGF-β is produced in an inactive form, which can be activated by acidification. TGF-β produced by cHL cell line L428 is active at a physiological pH and has a high molecular weight [62]. The same high molecular weight form of TGF-β can also be found in the urine of

cHL patients [63] indicating that in patients HRS cells are able to produce the active TGF-β form.

The Tregs that are present in the microenvironment of cHL are highly immunosuppressive and contain Tr1 (IL-10 producing Tregs) as well as CD4+CD25+ Tregs. IL-10, cell–cell contact, and CTLA4 play a main role in executing their immunosuppressive function [64]. In addition, HRS cells express galectin-1, an animal lectin, which can cause apoptosis in activated T cells and contributes to the elimination of an effective antitumor response in cHL [65]. HRS cells also express FAS and the FAS ligand. There are some mechanisms protecting the HRS cells from apoptosis induction, such as FAS mutations in a small proportion of cases and c-FLIP overexpression in all cases [66]. Presumably, activated Th1 and CD8 cells expressing FAS are driven into apoptosis by the FAS ligand expression on the HRS cells. Also, HRS cells were found to express PD-1 ligand, induced by a selective amplification of 9p24.1 [67], AP-1 activation, the presence of LMP-1 [68], or chromosomal translocations involving the CIITA locus [69]. The rosetting lymphocytes are rarely PD-1 positive, and their numbers are significantly lower in cases with PD-1 ligand gain [70]. In LPHL, the rosetting lymphocytes express PD-1 [16], but LP cells do not express PD-1 ligand. In EBV+ cHL, the Th1-inducing cytokine IL-12 is expressed in T cells surrounding the HRS cells, and its presence suggests that these T cells have the potential to induce antitumor activity [71]. However, an EBV-induced IL-12-related cytokine called EBI3 can block this Th1 response and is produced by HRS cells [72].

4.3 Immune Escape Mechanisms (Fig. 4.4)

4.3.1 Antigen Presentation

The importance of antigen presentation in the pathogenesis of cHL has been suggested by the association of specific HLA subtypes with increased cHL incidence. cHL is more common in Caucasians as compared to Asians, and about 4.5 % of cHL cases occur in families [73, 74]. A three- to sevenfold increased risk has been observed in first-degree relatives and siblings. In monozygotic twins, the cotwin has an approximate 100-fold increased risk of developing cHL compared to dizygotic twins [75]. From the 1970s, a number of serological HLA types have been associated with the occurrence of cHL. More recently, a genetic screen of the entire HLA region showed a strong association between the *HLA-A* gene and EBV+ cHL and the HLA class II region with EBV– cHL [76, 77]. At present, three independent genomewide association studies have confirmed that the HLA region is the strongest genetic susceptibility locus in cHL [78–80]. In EBV+ cHL, it can be hypothesized that this association is related to insufficient presentation of EBV antigenic peptides. These antigenic peptides most likely are derived from the latency type II genes that are expressed in cHL, i.e., LMP1, LMP2, and EBV-related nuclear antigen 1 (EBNA1). EBV partially escapes cytotoxic immune responses by downregulating immunodominant latent genes (*EBNA2* and *EBNA3*). In addition, the glycine–alanine repeat in EBNA1 largely prevents its presentation by HLA class I by blocking its degradation into antigenic peptides through the proteasome [81]. However, subdominant immune responses to LMP2 and to a lesser extent LMP1 are present in the healthy EBV-infected population [82]. In fact, adoptive immunotherapy in relapsed EBV-associated cHL has been used in some small studies with success, although limited. In these studies, peripheral blood from cHL patients was used to create EBV-specific cytotoxic T cell lines in vitro, and these were reinfused. Some objective responses were observed (3/11 and 5/6), with better responses if the CTLs were specifically targeted to LMP2 [83, 84] (Fig. 4.4).

Interestingly, the genetic association of the *HLA-A* gene with EBV+ cHL is attributed to the presence of the HLA-A*01 type and absence of the HLA-A*02 type [85]. HLA-A*01 is known to have a low affinity for LMP2- and LMP1-derived antigenic peptides, while HLA-A*02 can present these peptides very well. This suggests that EBV+ cHL is more likely to occur after

primary EBV infection if an individual's set of HLA class I molecules cannot properly present LMP2 and LMP1 to the immune system.

4.3.2 HLA Expression

Paradoxically, HLA class I and class II expression by HRS cells is usually retained in EBV+ cHL patients, whereas in EBV– cHL patients these molecules are frequently downregulated. Defects in the antigen-presenting pathways are very common in solid malignancies (HLA class I), as well as in many B cell lymphomas (HLA class I and class II), and are an obvious mechanism to escape from antitumor immune responses. Especially downregulation of HLA class I is a common immune escape mechanism in EBV– cHL, with less than 20 % of cases still expressing cell surface HLA class I on the HRS cells at the time of diagnosis [86]. Different mechanisms are involved in this downregulation because immunohistochemistry has shown complete absence of HLA class I or retention of HLA class I heavy chains within the cytoplasm. This retention in the cytoplasm is usually accompanied by an absence of β2-microglobulin expression, which is necessary for HLA class I assembly and transport to the cell surface. The different mechanisms may indicate that downregulation of HLA class I is based on clonal selection by continuous cytotoxic immune responses. This may be related to the presence of antigenic peptides that are associated to malignant transformation or disease progression. However, downregulation of HLA class I generally induces activation of natural killer (NK) cells. These cells contain HLA class I–specific inhibitory receptors and are sparse in the reactive infiltrate of cHL. The inhibitory receptors can also be engaged by a nonclassical HLA class I–like molecule known as HLA-G. In about two thirds of HLA class I–negative cHL cases, the HRS cells indeed express HLA-G [87]. Besides NK cell inhibition, HLA-G might also induce Treg cells and inhibit cytotoxic T cell responses. Another immune escape mechanism consists of the proteolytic cleavage of MHC class I–related chain-A (MIC-A) by ERp5 and ADAM10, which are both expressed by HRS cells. MIC-A is a membranous ligand for the activating NKG2D receptor present on cytotoxic T cells. In addition, the NKG2D receptor expression by these cytotoxic T cells is reduced in the presence of TGF-β [88].

4.3.2.1 HLA Class I Expression

In contrast to EBV– cHL, 70–80 % of EBV+ cHL patients show cell surface expression of HLA class I and β2-microglobulin at the time of diagnosis. This expression is usually particularly strong in mixed cellularity subtype cases [5, 86]. Upregulation of HLA class I has been attributed to LMP1, but the function of this upregulation is enigmatic, since it should make latent EBV-infected B cells more susceptible to immune recognition. In fact, in primary lytic EBV infection, the HLA class I antigen-presenting pathway is strongly inhibited by EBV proteins [89]. When the virus goes into latent infection, this immune escape mechanism is no longer available. As the lytic gene products are switched off, the expression and function of HLA class I and class II are restored. Importantly, the cHL-associated EBV latent gene products LMP1, LMP2, and EBNA1 are necessary for EBV-infected B cells to go through the germinal center reaction. At that time HLA class I and class II antigen-presenting functions might also be essential for B cell survival. It is generally accepted that HRS cells derive from germinal center B cells, and in EBV+ cHL it is likely that the tumor cell precursor expresses LMP1, LMP2, EBNA1, HLA class I, and HLA class II.

4.3.2.2 HLA Class II Expression

HLA class II cell surface expression on HRS cells is lost in approximately 40 % of all cHL patients [86]. In addition, translocations involving CIITA have been found in 15 % of cHL patients and may result in subtotal downregulation of HLA class II expression [69]. The absence of HLA class II is weakly related to extranodal disease, EBV-negative status, and absence of HLA class I cell surface expression. Lack of HLA class II expression has been associated with adverse failure–free survival and relative survival

and is independent of other prognostic factors [86]. It can be hypothesized that antigen presentation in the context of HLA class II is involved in recruitment and activation of CD4+ T cells early in cHL pathogenesis. Under the influence of immunomodulating mechanisms, these T cells are important in providing trophic factors for HRS cells and also have a role in inhibiting Th1 responses. In the initial stages of cHL pathogenesis, HRS cells are probably highly dependent on the reactive infiltrate and expression of HLA class II, but as the lymphoma develops this dependency may weaken because of alternative trophic and immunosuppressive strategies. Thus, downregulation of HLA class II without loss of viability of HRS cells might occur when the HRS cells have grown less dependent on the reactive infiltrate. This is supported by the association of downregulation of HLA class II with extranodal disease [86].

4.4 Prognostic Impact of the Microenvironment

Several research groups studied the cHL reactive infiltrate in relation to prognosis. Gene expression profiling of whole tissue and subsequent validation by immunohistochemistry showed that high numbers of CD68-positive cells are related to adverse outcome [90]. These CD68-positive cells reflect tumor-associated macrophages and probably also other cell types in the microenvironment. Patients with a higher degree of mast cell infiltration or with tissue eosinophilia have an adverse failure–free survival, probably because the CD30L expression by these cell types is advantageous to the HRS cells [35, 36].

Large numbers of Th2 cells in the microenvironment, as determined by c-Maf expression, correlate with improved disease-free survival [9]. Also, increased numbers of infiltrating Treg cells seem to correlate with improved survival as this effect was observed in two out of three studies [11, 91, 92]. Accordingly, a high percentage of activated CTLs (CD8+/granzyme B+ T cells) is a strong indicator of unfavorable clinical outcome [93]. A high ratio of FoxP3 to CTL markers, granzyme B [92] or Tia-1 [91], gives the best predictive value for a good prognosis. These results are unexpected since in other malignancies the presence of Tregs and the absence of CTLs are associated with adverse prognosis. One explanation might be that HRS cells are expected to behave more aggressively as they develop a stronger independency from the reactive infiltrate. In this situation a hostile microenvironment is allowed because the HRS cells have acquired alternative immunoevasive strategies. This theory fits with the adverse prognostic impact of the absence of HLA class II expression.

Conclusion

The microenvironment is a fundamental component of the tumor mass and an essential pathogenetic factor in cHL and LPHL. It supplies the tumor cells with growth factors and inhibits antitumor immune responses. In fact, it could be stated that "the infiltrate consists not of 'innocent bystanders' but of guilty opportunists" [27]. As the tumor cells and the reactive infiltrate grow up together, there is an extensive crosstalk between these two components. The tumor cells actively attract and shape their environment for their own benefit and make use of a number of mechanisms to fend off antitumor immune responses.

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What Will We Learn from Genomics and Proteomics in Hodgkin Lymphoma?

5

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5.1 Introduction

Genome-wide strategies have been developed in recent years to comprehensively detect changes on the DNA, RNA, and proteins. These technologies are in constant flux, as improvements in nanotechnology combined with innovation in the fields of genomics and bioinformatics improve our ability to examine single cells at a resolution not seen previously. Next-generation sequencing technology and microarray approaches allow an unparalleled ability to explore genomes, transcriptomes, and proteomes at a depth of coverage and resolution at which novel discovery is possible. The phenotypic consequences of these genetic changes can now be more fully understood. By applying these technologies to Hodgkin lymphoma, major advances have been made and more yet to be realized, all of which improve our understanding of the complex biology of this unique cancer. Despite major advances, numerous obstacles remain that prevent direct clinical translation and meaningful improvements in diagnosis, predicting prognosis, and patient care. For both scientists and clinicians interested in the pathogenesis of Hodgkin lymphoma and the identification of new targets for

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_5,

therapy, these obstacles include: (a) the scarcity of the malignant Hodgkin Reed–Sternberg (HRS) cells in diagnostic biopsies, (b) the complex interaction of these cells with non-neoplastic immune cells in the tumor microenvironment, (c) the lack of good in vitro and animal models, (d) sophisticated bioinformatics tools required to properly analyze the large amounts of data that result from high-resolution genomic experiments, and, finally, (e) systematic clinical data and/or randomized clinical trial material needed to translate novel findings into clinically useful biomarkers.

The focus of this chapter is largely a subject of speculation. Before peering into the future and addressing the question of "what will we learn from genomics and proteomics," we will first examine what useful data these approaches have already provided. We will then turn our attention to a discussion of whether these strategies will ultimately lead to significant insight that will result in unraveling the biology of Hodgkin lymphoma, with the goal of developing new therapies that translate into cures and improved quality of life for patients suffering from this disease.

5.2 What Have We Learned Thus Far?

5.2.1 HRS Cells or the Microenvironment?

The clinical and pathological features of cHL reflect an abnormal immune response that is thought to be due to expression of a variety of cytokines by the HRS cells altering the surrounding microenvironment [1]. Cytokines are low-molecular-weight proteins with a wide variety of functions that work either in a paracrine manner to modulate the activity of surrounding cells or in an autocrine fashion to affect the cells that produce them. Furthermore, it is a widely accepted concept that the overexpression of Th2 cytokines and TGFβ leads to a microenvironment that suppresses cell-mediated immunity and in return favors HRS cell survival highlighting the bidirectional crosstalk of cells involved in the pathogenesis of HL [2, 3]. Dissecting and simplifying this complex interaction of the malignant HRS cells with their microenvironment, two types of experiments have been performed, including those focusing on (1) cell lines and enriched HRS cells (by microdissection or fluorescence-activated flow sorting) and (2) the reactive microenvironment. In addition, targeted and genome-wide association studies focusing on single nucleotide polymorphisms have established a link to the host-specific genetic background modulating Hodgkin lymphoma susceptibility and treatment outcome [4–8].

5.2.2 Copy Number Variations (CNV)

Studies of copy number variations using conventional chromosomal comparative genomic hybridization (CGH) helped to establish the clonal relationship of HRS cells and revealed that many cases shared common chromosomal imbalances during tumor evolution. In detail, a Hodgkin lymphoma characteristic profile of recurrent copy number gains and losses has been described, including gains of chromosomes 2p, 9p, 16p, and 17q and losses of 13q, 6q, and 11q [9–11]. Both studies for the first time used laser capture microdissection followed by whole-genome amplification (WGA). In one of these studies, the authors also found a correlation of 13q losses with poor outcome [11]; however, the major contribution of these data encompassed an improved understanding of the underlying pathobiology as exemplified by the detailed characterization of the two most prominent alterations, gains of 2p and 9p, recognizing the oncogenes *c-REL* and *JAK2* as putative target genes [12–14]. While these studies were primarily limited because of low resolution (approx. 2–5 Mb for high-level amplifications and 10–20 Mb for deletions), the two most recent studies used oligonucleotide and BAC arrays providing a much higher resolution. In these studies, novel copy number changes were identified including amplification of *STAT6*, *NOTCH1*, *JUNB*, *IKBKB*, *CD40*, *and MAP3K14* [11, 15]. Remarkably, the smallest detected deletion spanned only 156 kb targeting

CDKN2B emphasizing the improved detection sensitivity over conventional chromosomal CGH. Furthermore, for the first time a correlation of chromosome 16p gains with primary treatment failure could be described [11]. Interestingly, in the therapy-resistant HL cell line, KMH2 genomic gains and overexpression of the multidrug resistance gene *ABCC1* mapping to cytoband 16p13.11 were found contributing to the drug resistance phenotype of this cell line.

Characterization of commonly used Hodgkin lymphoma cell lines by high-resolution copy number analysis further contributed to the inventory of imbalances found in relapsed Hodgkin lymphoma [16].

5.2.3 Gene Expression Profiling

Overall, gene expression profiling experiments have contributed substantially to an improved understanding of the disease with respect to the inherent phenotypic features of the malignant HRS cells and the specific composition of the microenvironment. Furthermore, first steps could be made to establish outcome correlations with the potential to improve treatment outcome prediction. However, many questions remain including often contradictory results derived from different patient cohorts. Focusing on HRS cells, the first major contribution of gene expression profiling was made by investigating Hodgkin lymphoma cell lines. These pivotal studies first established a transcriptome-wide view of the malignant cell compartment describing a unifying gene signature for classical Hodgkin lymphoma [17]. Together with other important similar studies, this gene expression work helped to elucidate the loss of B cell signature phenotype and the deregulated expression of transcription factor networks in comparison to the normal germinal center B cell counterparts [18–21]. Most recently, major advances have been made examining microdissected HRS cells from clinical biopsy material that further characterized transcriptional changes in primary cells [22–25]. Steidl and colleagues identified significant phenotypic heterogeneity within classical Hodgkin lymphoma and described for the first time genome-wide association with treatment outcome [24] (Fig. 5.1). Specifically, a macrophage-like expression signature derived from HRS cells was reported to be significantly associated with treatment failure, and in a subsequent in situ hybridization-based study using an independent validation cohort, an outcome correlation with *CSF1R* as a representative of this signature could be confirmed. The second study by Tiacci and colleagues added significant texture to the primary HRS cell expression phenotype emphasizing the differences in comparison to HL-derived cell lines [25]. Furthermore, two molecularly distinct cHL subtypes were discovered related to the transcription factor activity of NOTCH1, MYC, and IRF4. Another study for the first time also focused on gene expression profiling of microdissected cells from nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) describing a close relationship to classical Hodgkin lymphoma and T cell–rich B cell lymphoma [22].

Focusing on the Hodgkin lymphoma microenvironment, a number of genome-wide gene expression studies have been published to date analyzing whole tissue lymph node biopsy material. Since the HRS cells are largely outnumbered by reactive cells in most biopsies, these studies on whole frozen biopsies are regarded as a reflection of the microenvironment [26–29]. However, some of these data provide evidence that at least parts of the apparent signatures are derived from HRS cells [27, 29]. In one study a specific gene expression signature could be linked to EBV positivity with genes overexpressed indicative of an increased Th1/antiviral response in comparison to the EBV-negative cases [28]. In addition to a better characterization of certain Hodgkin lymphoma subtypes defined by specific gene signatures, these experiments also allowed for the study of outcome correlations using supervised analyses. All studies have used dichotomized clinical data sets based on slightly different definitions of clinical extremes according to the outcome after systemic treatment (i.e., treatment success versus treatment failure). However, these types of analyses have in part yielded conflicting results regarding the specific

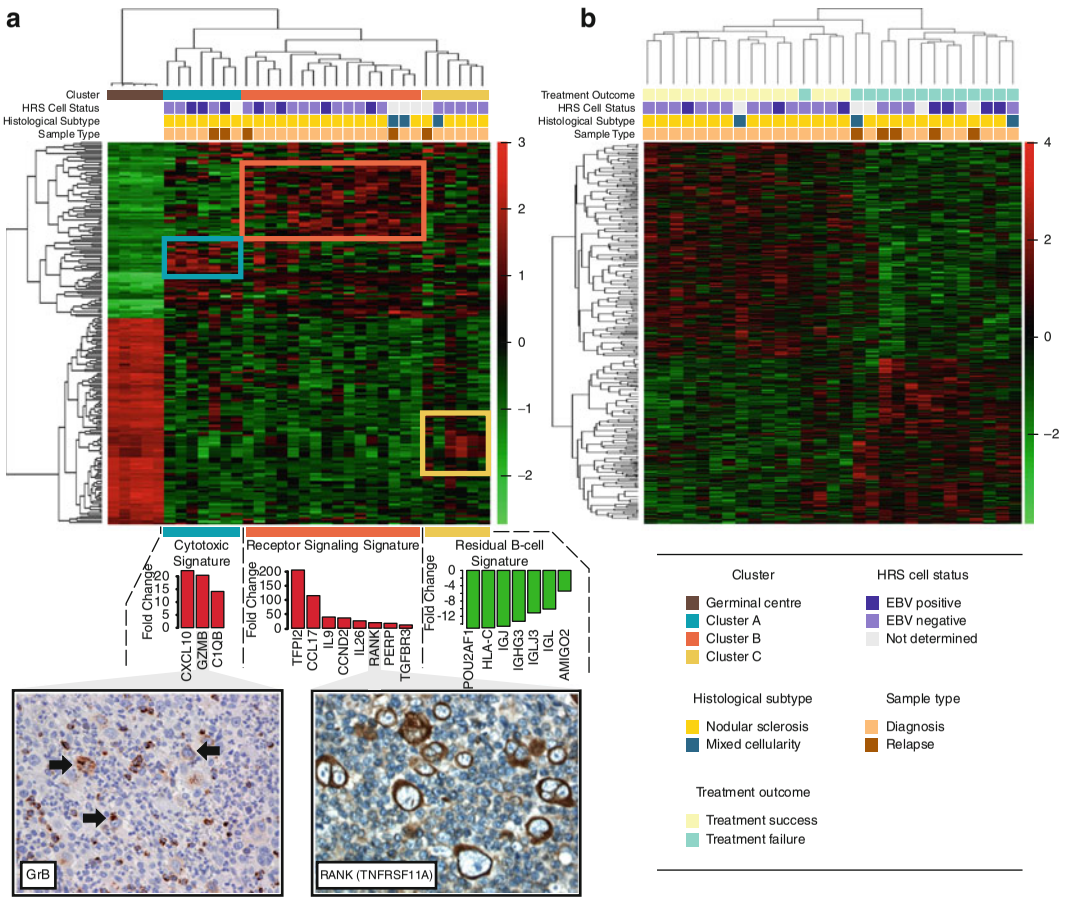

Fig. 5.1 Expression profiling of 29 samples of microdissected Hodgkin Reed–Sternberg cells. (**a**) Unsupervised hierarchical clustering of gene expression profiles is shown using high variance genes. *Red* indicates relative overexpression, *green* relative underexpression. Patient clusters, histological subtype, EBV positivity of HRS cells by EBER in situ hybridization, and sample type are shown. The average fold changes of genes representative of the three main signatures are shown in the bar plots. Representative immunohistochemistry images are depicted demonstrating cytoplasmic positivity of Granzyme B (GrB, *black arrows*) and RANK in HRS cells. (**b**) Unsupervised hierarchical clustering of the cohort using the most differentially expressed genes between primary treatment failure and success. Treatment outcome, histological subtype, EBV positivity of HRS cells by EBER in situ hybridization, and sample type are shown. Cases cluster according to the outcome groups (two main clusters)

signatures that best define these clinical extremes. While one study found overexpression of genes involved in fibroblast activation, angiogenesis, extracellular matrix remodeling, and downregulation of tumor suppressor genes to be linked with an unfavorable prognosis, another study found a correlation of fibroblast activation, fibroblast chemotaxis, and matrix remodeling with improved outcome [26, 27]. While small sample sizes in both studies might have hampered interpretation, a more recent study investigated gene expression profiles of 130 patients including 38 patients whose primary treatments failed [29]. This study validated previously reported outcome correlations and furthermore showed that a gene signature of macrophages was linked to primary treatment failure. In a number of immunohistochemistry-based follow-up studies, multiple groups demonstrated that the enumeration of CD68+ macrophages in lymph node biopsies was a strong and independent predictor of disease-specific survival [30]. Specifically, an elegant retrospective study using Intergroup E2496 trial material (comparing ABVD to the Stanford V regimen) showed that both high abundance of CD68+ and CD163+ cells was correlated with shorter progression-free and overall survival independent of the IPS [31]. Importantly, the latter study used a computer-based scoring algorithm (Aperio) and systematically derived scoring thresholds that were tested in an independent validation cohort. Maximizing the concept of combining markers for building outcome predictors, a recent study used the same E2496 trial material to train a predictive model using intermediate density digital gene expression profiling developed in and applicable to routinely collected formalin-fixed paraffin-embedded tissue [32]. In this study the authors developed a 23-gene predictive model and associated thresholds to distinguish high-risk from low-risk advanced-stage Hodgkin lymphoma using overall survival as the end point. Encouragingly, when applied to an independent cohort treated with ABVD chemotherapy, the model validated the results in the E2496 training cohort identifying the patient at high risk of death. Follow-up studies are needed to further validate and implement the predictor for potential routine clinical use, risk stratification, and assessment as a predictive biomarker possibly guiding initial treatment decisions.

5.2.4 Proteomics

Proteomic studies in lymphoid malignancies and in Hodgkin lymphoma in particular are still in its infancy. The application of proteomic techniques has been shown to be a useful tool for the detection of biomarkers in other diseases; however, clinically relevant findings are largely lacking in Hodgkin lymphoma [33]. Two approaches have been chosen thus far, one using total cell lysates, the other analyzing the secretome of HRS cells [34–37]. These studies were aimed at developing novel candidate biomarkers and diagnostic tools by identifying specific protein profiles linked to certain lymphoma entities, but also sought to determine an inventory of secreted proteins that are critically involved in the crosstalk of HRS cells with their microenvironment. While these experiments demonstrated the feasibility of proteomic studies in HL cell lines, the literature is still lacking studies using primary lymph node tissues in this disease. Furthermore, reproducibility of proteomics experiments in particular reproducibility of time-of-flight mass spectrometry (TOF-MS) is of general concern for its potential clinical applicability [38]. However, recently developed proteomic approaches using nanoscale reversed-phase liquid chromatography–tandem mass spectrometry (LC-MS/MS) has shown to be a major advance by identifying a large number of secreted proteins using Hodgkin lymphoma cell lines, including candidate molecules such as CCL5, CCL17, CTCS, CTSS, CX3CL1, and MIF. Moreover, these results were validated using independent techniques including enzyme-linked immunosorbent assays (ELISA) and immunohistochemistry (IHC) [36]. Additional efforts are needed to translate these findings into clinically useful biomarkers in Hodgkin lymphoma.

5.3 What Will We Learn?

Meaningful separation of clinical Hodgkin lymphoma cases into limited versus advanced-stage disease, classical Hodgkin lymphoma versus nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), and finally distinguishing patients based on the International prognostic scoring (IPS)

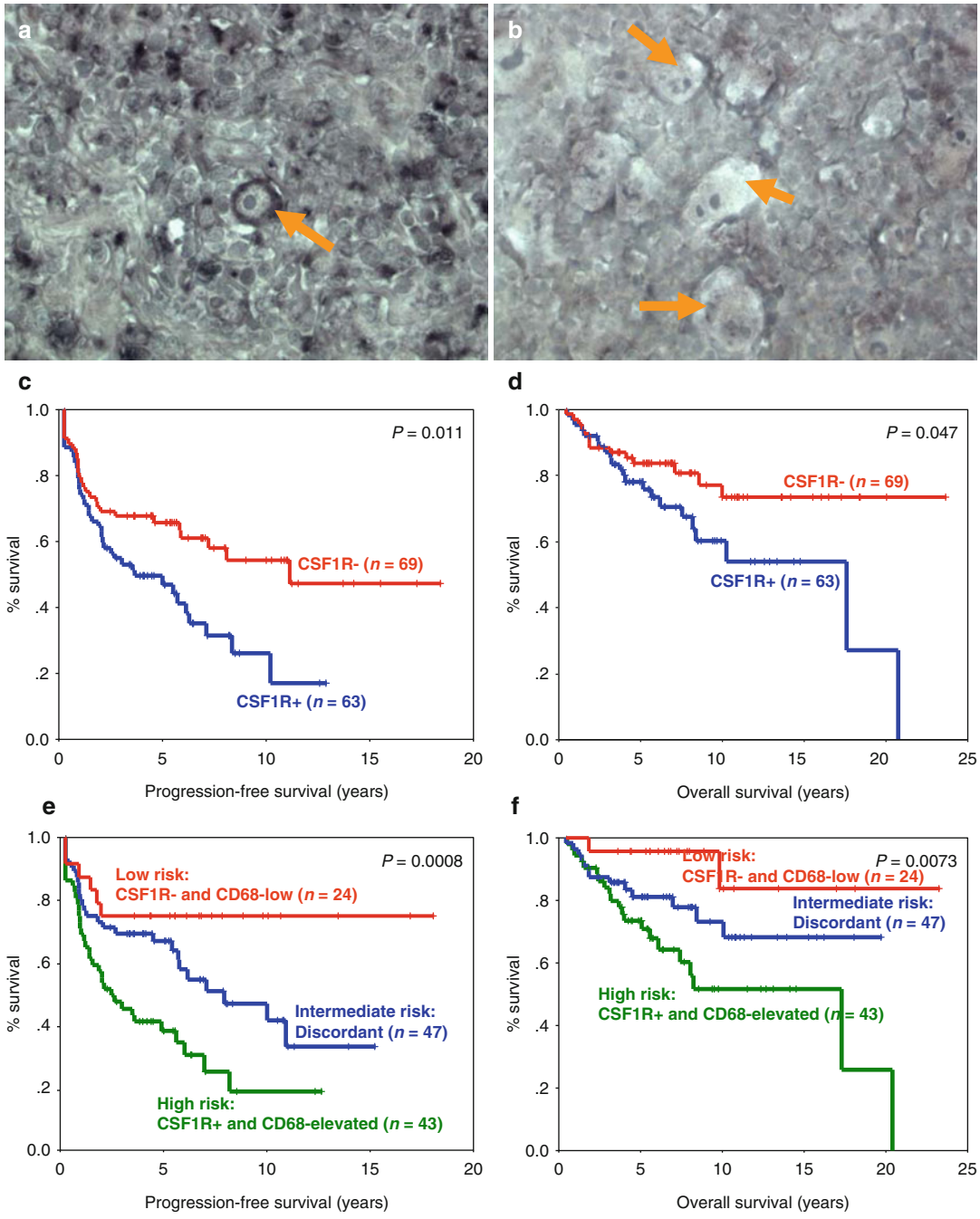

Fig. 5.2 (**a**–**f**) mRNA in-situ hybridization in Hodgkin-Reed Sternberg cells identifies patients with inferior progression-free and overall survival

for advanced-stage disease are still considered the gold standard for risk assessment and stratification used to guide treatment decisions. Despite advances in genomics and proteomics research, none of the findings derived from the various aforementioned platforms have found their way into clinical practice in the form of accepted biomarkers. Similarly, the goal of developing novel targeted therapies has essentially not been achieved with the exception of brentuximab vedotin [39]. However, as many necessary steps in this direction have already been made, we can hopefully anticipate important advances in the near future. In the following discussion we will substantiate our optimism and discuss the "ingredients" required for successful clinical translation of genomic and proteomic discovery (Fig. 5.2).

5.3.1 Enrichment Strategies for the Malignant HRS Cells

Research in Hodgkin lymphoma has moved beyond the investigation of whole lymph node biopsies and Hodgkin lymphoma cell lines. Many studies have demonstrated using laser capture microdissection [9, 22, 40] or fluorescence-activated cell sorting (FACS) [41, 42] that the study of isolated HRS cells separated from their microenvironment is both feasible and of value for improved biological understanding. In particular, the technical approach of enriching for HRS by flow sorting has been "revitalized" and can be added to the inventory of methods needed to isolate and study the malignant cell compartment. Although flow sorting in general is an established method used to purify small cell populations, only recently have HRS cells been successfully enriched using a cocktail of unlabeled antibodies to adhesion molecules that block the interaction of HRS cells with rosetting T cells, unmasking HRS cell antigens such as CD15 or CD30. Of note, a very recent study used these enrichment techniques for a whole-exome sequencing study of HRS cell samples enriched from 10 classical Hodgkin lymphoma cases [43].

Successful application of novel genome-wide applications, however, will be dependent on sophisticated strategies to amplify often small amounts of nucleic acids derived from a small number of enriched HRS cells. Taking advantage of large numbers of clinical samples should allow outcome correlations to be realized. Combining enrichment strategies with state-of-the-art genomic platforms including single nucleotide polymorphism (SNP) analyses, gene expression profiling, and whole-genome or whole-transcriptome analysis would seem to be a likely paradigm for new gene discovery tools in the future.

5.3.2 Hodgkin Lymphoma Genomics in the Future: What Platforms?

Significant technological advances have been made in the recent past. At the level of the genome, the most striking improvements have been made by introducing massively parallel sequencing approaches (whole-genome and whole-transcriptome sequencing), so-called next-generation sequencing, that allow for genome-wide genotyping at base pair resolution with unprecedented depth of genomic coverage. This technology not only maximizes resolution but also provides the sensitivity for detecting single nucleotide variants, genomic insertions, deletions, and translocations. Similarly, at the transcriptome level (entirety of the transcribed genome) this technology will lead to the detection of novel gene mutations and fusion transcripts and an improved understanding of RNA editing and the role of noncoding RNAs. Two studies in Hodgkin lymphoma using next-generation sequencing technology have been published to date [44, 45], reporting structural rearrangements and gene fusions involving the *CIITA* and *PDL1*/*PDL2* genes in Hodgkin lymphoma cell lines. The studies demonstrate the discovery potential of next-generation sequencing and specifically elucidated the genomic basis of immune privilege in Hodgkin lymphoma and related entities. Going beyond these initial studies, the field anticipates the description of the entire mutational landscape of somatic changes in primary HRS cells based on this technology

in the very near future [43]. Using integrative approaches, additional experimental and analytical methods investigating tumor genomes will be needed to examine copy number and gene expression changes, as well as epigenetics, and to comprehensively describe the molecular features of HRS cells. All of these approaches are still largely unexplored in primary Hodgkin lymphoma samples, and their routine application to small numbers of enriched HRS cells will be technically challenging, although doable in principle based on the most recent reports.

5.3.3 Data Integration

Gene expression profiling studies and array CGH have yielded valuable information about the specific biology of HRS cells and their microenvironment, but ideally both orthogonal data types have to be examined simultaneously using integrative bioinformatics approaches. In Hodgkin lymphoma cell lines, the consequence of genomic copy number changes that might underlie altered gene expression changes has already been explored [46], and recently another study has systematically reported copy number–gene expression correlations on a genome-wide scale in 29 primary HRS cell samples [24] (Fig. 5.3). In this study, the authors reported significant correlations for 216 genes including *REL*, *TNFAIP3*, *CD274*, *JMJD2C*, *TNFRSF17*, *FOXO3*, and *WNT3*, highlighting the importance of these genes in the pathogenesis of Hodgkin lymphoma. Moreover, integrative approaches will be required to correlate findings in the malignant cells to findings in the nonmalignant cellular compartment. Experimental designs using matching genome-wide profiles of the same cases will allow for data integration and an in-depth look at the multiple interactions between neoplastic HRS cells and the microenvironment at the molecular level. These analyses have the potential to detect common patterns of deregulated gene expression that might reflect specific ligand–receptor interactions and cytokine expression patterns. Moreover, linkage of all of these findings to treatment outcome will be useful for further biomarker discovery and will likely shed more light on the specific cellular interactions found in patients who are destined to fail primary or subsequent treatments.

5.3.4 Biobanking and Large Correlative Databases

Translation of genomics findings into clinically useful biomarkers is not possible without the availability of well-annotated clinical data and linked frozen biopsy samples. These large correlative databases will undoubtedly provide the foundation for translational genomics for years to come. Linkage of fresh frozen lymph node specimens, peripheral blood lymphocyte collections representing constitutional or host genetics, formalin-fixed material, classical cytogenetic and cell culture material, and archived single-cell suspensions all linked with clinical parameters, particularly treatment outcome data, will be crucial for the discovery of novel biomarkers, predictive factors, and revised pathological classifications. Ideally, collection of this material must be included in the design of randomized phase III clinical trials where important clinical questions are being addressed. Clearly this represents a major challenge, both in terms of logistics and funding, but must be made an important objective for all clinical trial groups into the future.

A parallel strategy should also be considered using population-based registries, where some of the pitfalls associated with accrual to clinical trials, such as selection and referral bias, are avoided. The experience at the British Columbia Cancer Agency shows that a centralized and representative population-based collection of lymph node material and clinical data provides an ideal platform to assess biomarkers using a retrospective approach. Advantages include large numbers of study cases, lack of substantial selection bias, standardized and homogenous treatment of the study cohorts, and standardized diagnostic procedures. However, special attention has to be paid to ethical considerations in the era of whole-genome sequencing as systems have to be in place that respect privacy rights and genomic analysis of diagnostic material that has been initially col-

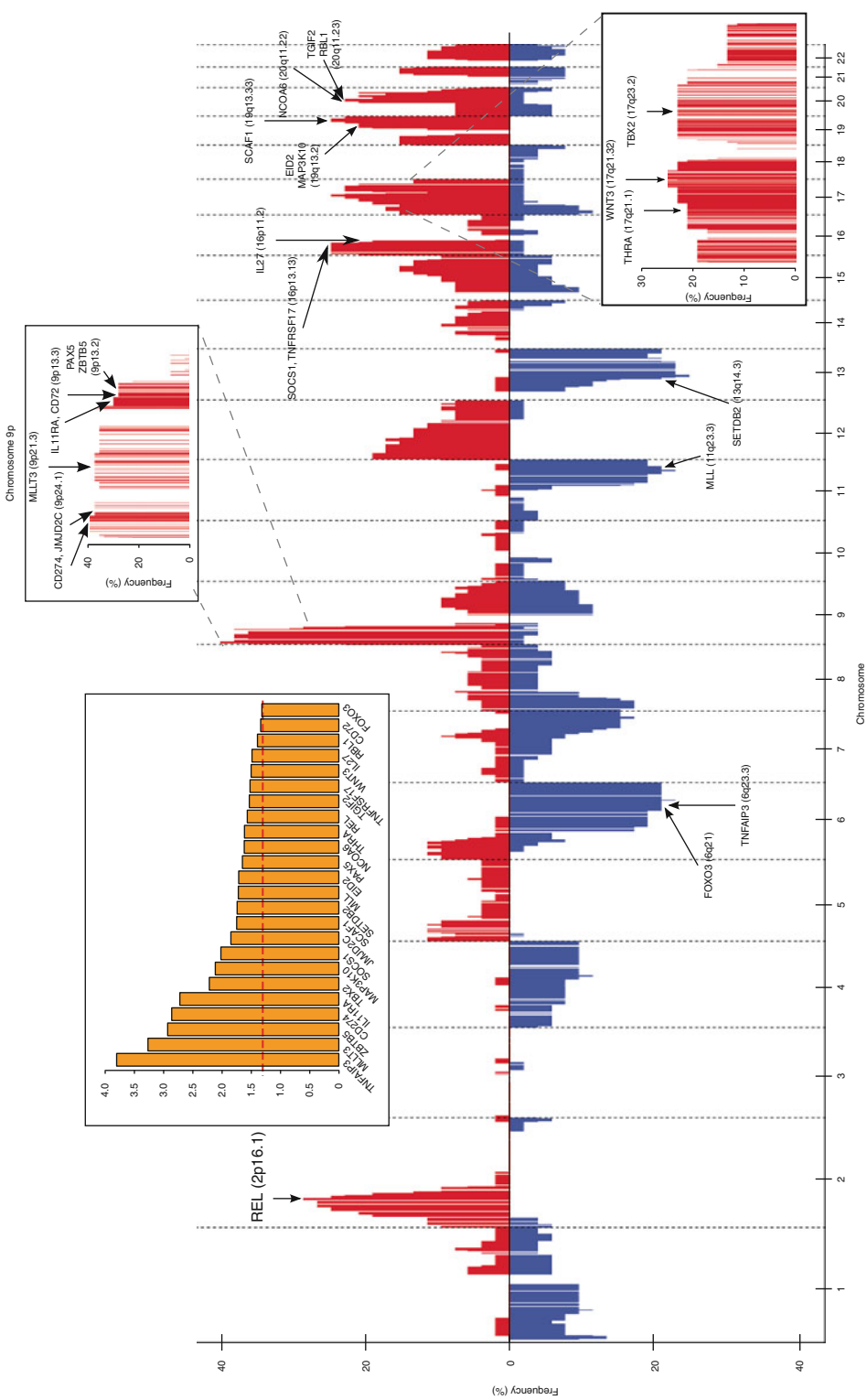

Fig. 5.3 Integrative analysis of copy number and gene expression in microdissected Hodgkin Reed–Sternberg cells ($n = 29$). Genome-wide copy number data are represented by chromosomal position (x-axis), and the relative frequency of imbalances is shown on the y-axis. Chromosomal gains are shown in *red*, deletions are shown in *blue*. A selection of genes in regions of frequent imbalances and with significant correlations between copy number and gene expression is highlighted in the *vertical yellow bar* plot. The *horizontal red dotted line* indicates the p-value threshold of significance. Target genes are also highlighted on the copy number plot by *arrows* (cytoband). High-resolution views (*boxes*) of chromosome 9p and 17q are provided to assist in visualizing multiple adjacent genes

lected for different purposes. With respect to Hodgkin lymphoma, the merging of genomics and proteomics data with established clinical risk factors and clinical outcome correlations of patients that have been homogenously treated will undoubtedly lead to major improvements in outcome prediction.

Systematic and comprehensive biobanking would include snap-freezing lymph node material obtained at the time of relapse, an inventory that has not been properly collected and thus has been largely unexamined in the published literature. While the past most studies have focused on pretreatment diagnostic biopsies, a detailed investigation of relapse biopsies will likely answer questions related to disease progression and the development of therapy resistance. Moreover, genome-wide approaches using paired pretreatment and relapse biopsies are ideally suited to investigate clonal evolution and tumor progression under the influence of therapy.

5.3.5 Interdisciplinary Research

Genomics research in the modern era requires interaction of researchers on many different levels. Fundamental infrastructures for sample acquisition and selection by hematologists, clinical oncologists, and hematopathologists are essential prerequisites; however, data generation in state-of-the-art-equipped genome research centers and its proper processing and analysis is becoming increasingly critical. Development and application of specific algorithms and models by specialized bioinformatics research teams are needed to handle and make interpretable large amounts of data generated in genomewide single nucleotide polymorphism or whole-genome sequencing experiments. Furthermore, biological and clinical interpretation of genomics research as well as validation of the results by interdisciplinary research groups remains equally critical. In summary, close interaction of clinicians, pathologists, basic genome researchers, and bioinformaticians provides the important ingredients for novel discoveries in translational research. Thus far, the fruits of interdisciplinary research in lymphoma are best evidenced by the revised WHO classification of tumors of hematopoietic and lymphoid tissues [47] in which much emphasis has been placed on defining entities that can be recognized by (1) pathologists according to morphology, immunophenotype, and genetic features and (2) clinicians who have to ensure its utility and acceptance in daily practice. In the case of Hodgkin lymphoma, biological and clinical studies have led to the subclassification into NLPHL and cHL, histological distinctions that affect treatment decisions and subsequent clinical management. No genomics data generated thus far have led to a change or refinement of this distinction. However, overlap of Hodgkin lymphoma with related lymphoma entities exists, including T cell/histiocyte-rich large B cell lymphoma (TCRBCL) and NLPHL, primary mediastinal large B cell lymphoma (PMBCL) and nodular sclerosis Hodgkin lymphoma, or anaplastic large cell lymphoma and classical Hodgkin lymphoma, where gene expression studies of microdissected cells have already yielded further insight into the relatedness of these diseases [22, 48, 49]. We hypothesize that genomics and proteomics approaches will increasingly refine the similarities and differences at the molecular level and ultimately provide the molecular underpinnings of modified classifications in the future. As a consequence, new molecularly defined diseases will likely be recognized with the possibility of candidate gene discovery and new targeted therapies becoming routine in clinical practice.

5.4 Will These Advances Lead to a Cure of Hodgkin Lymphoma?

Currently, Hodgkin lymphoma is a very treatable disease, and the majority of patients are cured following primary therapy. However, current therapies fail to cure about 20 % of patients, and reasonable estimates suggest that a similar proportion of patients are overtreated [50], which suggests that the clinical management of Hodgkin lymphoma is far from being satisfactory for typi-

cally young patients who suffer from relapse or "off-target" therapy effects. Thus, an answer to this provocative question is not only contingent on further characterization of treatment failure and its underlying mechanisms but also on strategies to reduce treatment and the far too frequent occurrence of treatment-related long-term sequelae. These two clinical scenarios dictate that we focus on strategies aiming at improved overall survival: (1) the development of prognostic/predictive biomarkers used for risk stratification and rational selection of existing drug combinations and (2) the definition of unfavorable subtypes according to underlying pathobiology and the development of targeted therapy against these important subgroups. To realize both goals, the analysis of the whole genome, transcriptome, or proteome seems ideally suited as discovery platforms with the potential to discover candidate molecules and molecular pathways that are drugable or, alternatively, reliably predict treatment failure with the use of existing therapies.

At the present time, gene expression profiling and aCGH profiles have been linked to treatment outcome, but none of these findings has yet led to improvements in our existing prognostic systems. Small case numbers and heterogeneity of the underlying mechanisms might only be two of many reasons why clinical translation has not been successful. Furthermore, to substantiate hope for a cure of Hodgkin lymphoma, one would need to anticipate a virtually perfect short list of prognostic biomarkers that in aggregate define with certainty treatment outcome. Despite much work, the existing data is somewhat disappointing in this regard. Nevertheless, the increased resolution of newly developed genomics applications and the feasibility of HRS cell enrichment might at long last improve our predictive ability to an extent that the majority of patients who are destined to fail can be identified at diagnosis. Establishing favorable biomarkers and improving prediction of treatment success would likewise be of considerable benefit for patients as they might be spared from dose escalation or be candidates for dose de-escalation to decrease early and/or late therapy-related toxicities.

The published literature about genome-wide experiments, especially from gene expression profiling in Hodgkin lymphoma, provides many phenotypic features that are potential targets for novel therapeutic approaches. However, development of suitable pathway inhibitors, immunotherapeutic approaches, and preclinical/clinical testing of these treatments is a slow and laborious process. Thus, any assessment of the success of novel biomarker discovery and clinical translation will similarly take time. Moreover, with comparably effective standard therapy that is able to cure the majority of patients, changes to standard procedures are harder to justify. Therefore, the focus has to be shifted to the specific biology of treatment failure and the expected unique biology of clinical relapsed disease. Unfortunately, there is only very limited data available for these clinical scenarios. It has to be anticipated that genomics and proteomics will discover further heterogeneity within the generic group of treatment failure. Provided that effective treatment is available, only a subgroup of patients will benefit from these advances, nevertheless leading to improved overall survival and cure rates. Therefore, the hope to cure all patients with Hodgkin lymphoma may be unrealistic.

5.5 Summary

In summary, novel genomics and proteomics applications in Hodgkin lymphoma will likely substantially change our understanding of the disease, improve our current prognostic systems used to predict treatment outcome, and identify novel targets for drug intervention. Furthermore, with the help of sophisticated bioinformatics tools, we will learn more about the specific crosstalk between the malignant HRS cells and the non-neoplastic cells in the tumor microenvironment. The success of clinical translation of these experiments will depend on continued progress using genomic platforms with increasing resolution and sensitivity, the technical feasibility of these applications using enriched malignant HRS cell, and the availability of clinical and treatment outcome data. The anticipated heterogeneity of

the tumor biology linked to treatment failure will remain a major challenge for future research, but we are hopeful that the persistent efforts of interdisciplinary research and clinical teams dedicated to achieving meaningful cures and improving long-term survival in Hodgkin lymphoma will overcome this challenge.

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Part II

Diagnosis and First-Line Treatment

Clinical Evaluation

6

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Contents

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6.1 Presenting Manifestations

Hodgkin lymphoma can come to clinical attention in a variety of ways. These include symptoms caused by a growing mass and systemic symptoms that are presumably cytokine induced, and a diagnosis can be made incidentally as part of an evaluation for an unrelated problem. By far the most common presentation of Hodgkin lymphoma is the enlargement of lymph nodes that is typically painless and progressive. Although the most common place for lymph nodes to be found is in the neck and supraclavicular region, any lymph node-bearing area can be involved. Patients typically find enlarged nodes above the clavicle and seek medical attention when they do not regress, while physicians are relatively more likely to discover lymph nodes in other areas as part of a physical examination. Mediastinal lymphadenopathy is a particularly common finding in young women with Hodgkin lymphoma. This might be found incidentally on a chest X-ray or can be symptomatic. Although unusual, patients with Hodgkin lymphoma can present with superior vena cava syndrome, but chest pain and shortness of breath are more common symptoms caused by a large mediastinal mass. Lymphadenopathy found only below the diaphragm is more common in males and in elderly patients. Mesenteric lymphadenopathy is unusual in Hodgkin lymphoma. Retroperitoneal lymphadenopathy can be painful, but is more commonly asymptomatic and found on a staging

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_6, © Springer International Publishing 2015

evaluation or as part of the investigation to explain system symptoms such as fever, night sweats, or weight loss. Epitrochlear lymph node involvement is unusual in Hodgkin lymphoma.

Hodgkin lymphoma can involve essentially any organ in the body as either a site of presentation or by spread from lymphatic involvement. However, extranodal presentation of Hodgkin lymphoma is unusual. The most common sites to be involved are the spleen, liver, lungs, pleura, and bone marrow, although Hodgkin lymphoma confined to these sites is rare. Hodgkin lymphoma can rarely present in unusual extranodal sites. Primary CNS [1] and cutaneous [2] Hodgkin lymphoma are rare but well described. Perianal presentations are seen more commonly in patients with HIV infection. Gastrointestinal system, bone, genitourinary system, and other unusual sites are extremely rare but have been described. Bone involvement can be seen as an "ivory vertebrae," i.e., a densely sclerotic vertebrae [3].

By far the most common systemic symptoms that occur as the presenting manifestations of Hodgkin lymphoma are fevers, night sweats, weight loss, pruritus, and fatigue. These occur in a minority of patients but can present diagnostic challenges. Hodgkin lymphoma is one of the illnesses that can cause fever of unknown origin. Occasionally the fevers of Hodgkin lymphoma occur intermittently with several days of fevers alternating with afebrile periods. This is the Pel-Ebstein fever [4, 5] that is rare, but lymphoma typically occurs in the evening and often can be prevented with nonsteroidal anti-inflammatory drugs such as naproxen [6].

The presence of drenching night sweats (i.e., as opposed to dampness of the head and neck) and unexplained weight loss are both characteristics of Hodgkin lymphoma and, along with fever, are associated with a poor prognosis. Pruritus can be the presenting manifestation of Hodgkin lymphoma. Such patients sometimes have severely excoriated skin and sometimes have been diagnosed as having neurodermatitis. Patients who present with refractory pruritus are often grateful to find the explanation of their symptoms which usually disappear with the initiation of therapy. As with other lymphomas, fatigue can be an important, although nonspecific, symptom and also usually improves with therapy. There are many unusual, but well-described, presentations for Hodgkin lymphoma. One rare but very characteristic presentation is alcohol-induced pain [7, 8]. The pain typically begins soon after drinking alcohol and occurs primarily in areas of involvement by lymphoma. The pain can be quite severe and last for variable periods of time. Patients with the symptom have often discontinued alcohol before the diagnosis of Hodgkin lymphoma, and to elicit the symptom often requires specific questioning by the physician.

Patients can present with Hodgkin lymphoma involving the skin, but cutaneous abnormalities are more often paraneoplastic phenomenon. These can include erythema nodosum [9]; ichthyosiform atrophy [10]; acrokeratosis paraneoplastica [11]; granulomatous slack skin [12]; nonspecific urticarial, vesicular, and bullous lesions [13]; and others.

A variety of other unusual presentations of Hodgkin lymphoma have been reported. Patients can present with nephrotic syndrome [14], symptoms of hypercalcemia [15–17], and jaundice due to cholestasis without involvement of the liver by the lymphoma [18, 19].

Hodgkin lymphoma rarely presents with a primary tumor in the CNS causing the symptoms of a brain tumor characteristic of the site of involvement. Other neurological manifestations that can be present at the diagnosis of Hodgkin lymphoma include a variety of paraneoplastic syndromes. These include paraneoplastic cerebellar degeneration [20], which typically presents with ataxia, dysarthria, nystagmus, and diplopia. The symptoms may precede the diagnosis of Hodgkin lymphoma by many months. Hodgkin lymphoma can, of course, present with spinal cord compression from retroperitoneal and osseous tumors. Other rare manifestations include limbic encephalitis (i.e., which presents with memory loss and amnesia), peripheral neuropathy, and others.

6.2 Physical Findings and Laboratory Abnormalities

By far the most common physical findings in Hodgkin lymphoma are enlarged lymph nodes that might be in any lymph node-bearing area. The lymph nodes are typically firm (i.e., "rubbery") and vary from barely palpable to large masses. However, almost any aspect of the physical examination can be made abnormal by the presence of Hodgkin lymphoma. This might include icterus, involvement of Waldeyer's ring, findings of superior vena cava syndrome, a sternal or suprasternal mass from tumor growing out of the mediastinum, findings of a pleural effusion or pericardial fusion, an intra-abdominal mass, hepatomegaly or splenomegaly, skin involvement, and, rarely, cutaneous or neurological abnormalities.

Almost any laboratory test can be abnormal at the time of diagnosis of Hodgkin lymphoma, but certain tests are characteristic and should be specifically evaluated. Patients can have leukocytosis or leukopenia. Neutrophilia and lymphopenia are sometimes seen, with the latter having a poor prognosis. Eosinophilia can be found incidentally before the diagnosis of Hodgkin lymphoma, and Hodgkin lymphoma should always be included in the differential diagnosis of unexplained eosinophilia [21]. In some cases, the explanation of the eosinophilia is related to production of interleukin-5 by the tumor cells [22, 23].

The most common hematological manifestation of Hodgkin lymphoma is anemia. The most usual explanation seems to be a normocytic anemia associated with the presence of the tumor that resolves after therapy. However, patients can also have autoimmune hemolytic anemia [24] and a microangiopathic hemolytic anemia as part of the syndrome of thrombotic thrombocytopenic purpura.

Patients can present with thrombocytopenia for a variety of reasons including hypersplenism and bone marrow involvement. However, idiopathic thrombocytopenic purpura can be a presenting manifestation of the disease [25].

Other rare hematological manifestations of Hodgkin lymphoma have included autoimmune neutropenia [26], hemophagocytic syndrome [27], coagulation factor deficiencies [28], and unexplained microcytosis [29], and thrombotic thrombocytopenia purpura has been seen rarely.

Routine chemistry screening should be done in patients with Hodgkin lymphoma and might reveal renal or hepatic dysfunction, protein abnormalities, hypercalcemia, and hyperuricemia.

Elevated erythrocyte sedimentation rate and C-reactive protein are frequently seen and have been associated with a poor prognosis.

6.3 Pathologic Diagnosis: The Biopsy

The oncologist must be certain that the Hodgkin lymphoma diagnosis was based on an adequate biopsy specimen that was examined using appropriate morphologic and immunohistochemical criteria. Whole lymph node excision is preferable for pathologic examination. The pathologic diagnosis of Hodgkin lymphoma is fully discussed in Rosenwald/Küppers.

The site of biopsy must be determined with the radiologist and surgeon. The largest abnormal peripheral lymph node should be excised. However, at certain sites such as the mediastinum, the removal of a bulky lymph node (>5 cm) can lead to major surgery, with a risk of complications or sequelae. Fairly often, only a limited biopsy of the node is performed. On the other hand, too small a lymph node may only be a reactive hyperplasia. If a fluorine-18-deoxyglucose positron emission tomography (FDG-PET-CT) has been performed, the patient should be biopsied in the most avid site to avoid a partially necrotic zone.

If there are only deep node lesions, the following types of biopsy can be proposed. A thoracoscopic or laparoscopic approach under general anesthesia, with, if necessary, preoperative localization to facilitate resection is now widely used [30]. Image-guided core needle biopsy is

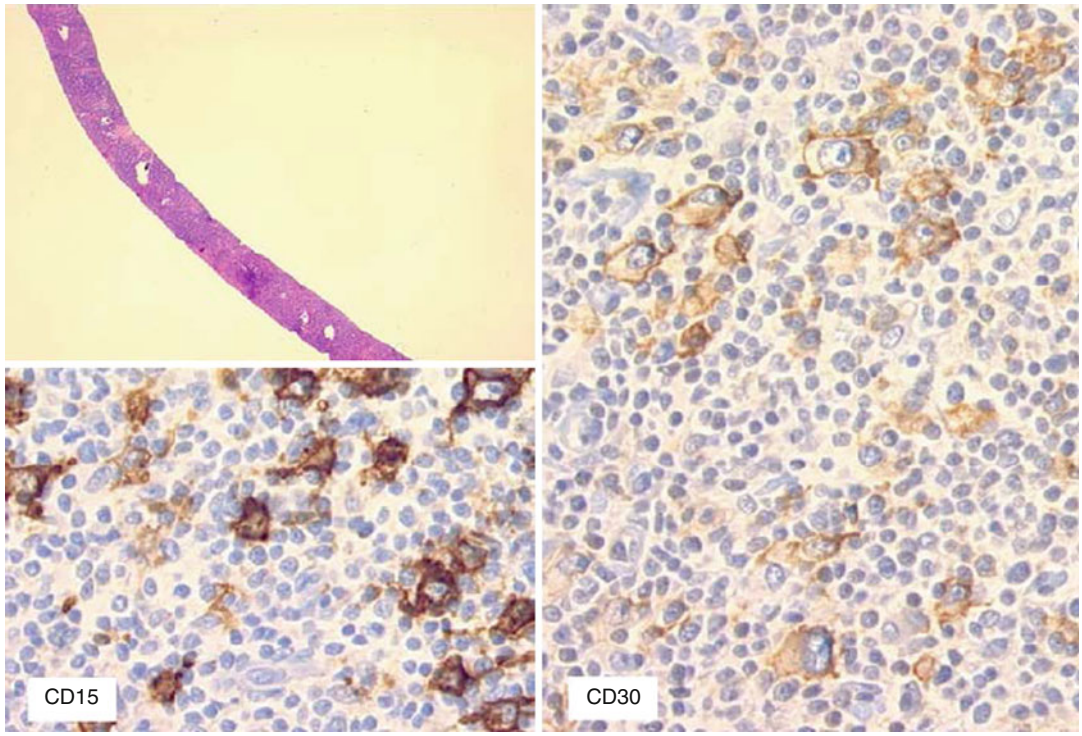

Fig. 6.1 Core needle biopsy for Hodgkin lymphoma with immunostainings for CD15 and CD30

increasingly used and has a rising success rate of more than 90 % [31–33]. However, the method has the disadvantage of only permitting relatively small biopsies, although progress has been made with automated guns and a coaxial technique. In addition, this type of biopsy is capable of sampling several core specimens with a single biopsy tract. Large-volume cutting needles, ranging from 18 gauge to 14 gauge, yield enough tissue for most immunochemistry stainings and even for RNA extraction from frozen tissue (Fig. 6.1). Moreover, this inexpensive procedure, performed under local anesthesia, can easily be done in a reference center outpatient clinic. Fine-needle aspiration cytology should *not* be used for diagnosis of Hodgkin lymphoma, but may help in a screening procedure, before biopsy [34].

Several pathologic pitfalls or differential diagnoses should be kept in mind. Drugs such as phenytoin or antibiotics may cause histologic changes within lymph nodes that may mimic Hodgkin lymphoma, particularly the mixed cellularity subtype. Other benign conditions like infectious mononucleosis, lymphoid hyperplasia, or Castleman disease may produce lymphadenopathy with histologic features similar to those of Hodgkin lymphoma. In fact, the distinction between different diseases, including certain forms of non-Hodgkin lymphoma (NHL), has been made clearer thanks to a better definition of the entities by the WHO classification. T-cell-rich large B-cell lymphoma is usually included in the differential diagnoses of both nodular lymphocyte-predominant Hodgkin lymphoma and classical Hodgkin lymphoma, while anaplastic CD30-positive NHL may display similar histology to that of classical Hodgkin lymphoma. Nevertheless, molecular studies require adequate material, including frozen tissue in difficult cases, and the role of the clinician is to make sure that the node to be analyzed is given to an experienced laboratory. If the clinical presentation of disease is not typical for the given pathologic diagnosis, then a review of the pathology by an expert hematopathologist should be considered, or even a second biopsy.

6.4 Staging Systems for Hodgkin Lymphoma

The initial clinical evaluation and staging of patients with Hodgkin lymphoma serve to confirm the Hodgkin lymphoma diagnosis, determine the extent and distribution of disease, evaluate the patient's fitness for standard treatments, and provide prognostic information (Table 6.1).

Several staging systems were developed very early and modified according to the progress made in imaging and treatment of the disease. The Ann Arbor staging was developed in the 1970s, when radiotherapy was the main curative treatment option, and was based on the tendency of Hodgkin lymphoma to spread to contiguous lymph nodes [36].

Since the Ann Arbor staging, several significant changes in the management of Hodgkin lymphoma have taken place. The Cotswolds modification of the Ann Arbor staging system was introduced in 1989 to approve the use of CT scanning for the detection of intra-abdominal disease, to formalize a definition of disease bulk, and to provide guidelines for evaluating the response to treatment (Table 6.2) [37]. This staging classification provides a basis for selecting the initial treatment and has been widely adopted by most clinical trial groups. Additional factors have been recognized (e.g., tumor bulk and the number of sites of disease) that adversely affect the prognosis of patients with a localized stage treated by radiation alone.

A prognostic factor score for advanced Hodgkin lymphoma treated by chemotherapy has

Table 6.1 Recommended studies for the initial evaluation of Hodgkin lymphoma

Mandatory for the Cotswolds classification	Histology and immunophenotyping Individual and familial history, clinical examination as per Cotswolds recommendations Blood counts and routine workup: ESR, LDH, alkaline phosphatase, albumin, liver function, β2-microglobulin, virology Chest radiograms: CT of the chest, abdomen, and pelvis; bone marrow biopsy if indicated (generally not necessary if PET-CT is done) [35]
Recommended for disease assessment	FDG-PET-CT (if this is done, a dedicated CT would generally not be necessary)
Recommended for toxicity assessment	Heart: ECG, MUGA, or echocardiogram Pulmonary: lung function tests Thyroid and gonadal functions: FSH, LH, and TSH (semen analysis and sperm storage) Psychosocial adaptation

Table 6.2 Cotswolds modifications of the Ann Arbor staging system

Stage	Definitions
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes are lateralized); the number of anatomic sites should be indicated by a suffix (e.g., II3)
III	Involvement of lymph node regions or structures on both sides of the diaphragm
III_1	With or without splenic, hilar, celiac, or portal nodes
III_2	With para-aortic, iliac, and/or mesenteric nodes
IV	Involvement of extranodal site(s) beyond that designated E

Reprinted from [37] with permission
CS clinical stage, *PS* pathologic stage
Annotation
A, no B symptoms
B, fever, drenching sweats, or weight loss
X, bulky disease, >1/3 mediastinal widening at T5–T6, or >10 cm maximum dimension of nodal mass
E, involvement of a single extranodal site, contiguous or proximal to a known nodal site

been worked out, based mostly on biological parameters, including serum albumin <4 g/dL, hemoglobin <10.5 g/dL, male sex, stage IV disease, age >45 year, white cell count >15,000/mm^3, and lymphocyte count <600/mm^3 [38].

These prognostic factors are used to define risk-adapted therapy. However, as combined modality treatment with modern chemotherapy has become the standard procedure for patients with early-stage disease, the risk of relapse is reduced, and some of these factors are no longer associated with a high risk of relapse. In addition, computed tomography (CT) and fluorine-18-deoxyglucose positron emission tomography (FDG-PET-CT) are now routinely used for the staging and evaluation of the response to treatment. PET-CT provides reliable information on treatment efficacy.

6.5 Imaging Evaluation of the Extent of Disease

Thanks to the progress and availability of imaging techniques, it has been possible to improve the accuracy of clinical staging, so that invasive pathologic procedures are no longer necessary. At present, the established radiological technique for the diagnosis of lymphoma is computed tomography [39]. Investigations should include posteroanterior and lateral chest radiography. In some clinical trials, measurements of the mediastinal mass (or the ratio of mass diameter to chest dimensions) on chest X-ray correlated with the prognosis and were used to assign treatment. A CT of the neck, thorax, abdomen, and pelvis has been standard. Intravenous contrast allows lymph nodes to be distinguished from vessels seen in cross section.

Although clinical staging based on peripheral lymph node examination is usually straightforward, staging at other sites can be problematic. Occasionally, CT imaging may reveal unclear findings in the spleen or liver. Spleen or liver enlargement does not always imply involvement. Ultrasonography may occasionally be required to rule out the presence of solid lesions, and MRI may characterize liver abnormalities better when CT findings are ambiguous.

However, the failure of CT to provide functional information can impede the identification of disease in normal-sized tissue [40]. An alternative to CT is FDG-PET, which is based on the increased glycolysis of cancer cells. This is visualized using the radioactive glucose analog FDG, which after phosphorylation is metabolically trapped within the cell. Thus, CT, FDG-PET has become an established imaging modality to stage, restage, and monitor therapy and detect recurrent lymphoma. PET and CT, which, respectively, supply metabolic and anatomic information, are complementary, and interpretation of the PET portion of the study is more accurate when the results of PET correlate with those of CT [41, 42]. Therefore, integrated PET-CT systems were developed which are now the standard care [54].

It is important that imaging results be interpreted within the framework of the known patterns of spread and other prognostic factors. A certain degree of variation in the size of mediastinal and hilar nodes is normal, but those measuring more than 10 mm on the shortest cross section can be considered abnormal. However, although clearly abnormal findings on CT scanning may be indicative of Hodgkin lymphoma, there is a risk of false positives, particularly in the abdomen, when interpreting these findings. Therefore, when lymph nodes in the 15- to 20-mm range are seen, uptake on FDG-PET-CT is indicative of involvement by lymphoma.

As previously stated [37], the 1989 Cotswolds modification to the Ann Arbor staging system explicitly indicated that involvement of extralymphatic tissue on one side of the diaphragm due to the direct extension of nodal disease should be staged according to the nodal volume, with an associated extranodal (E) designation [37]. This was determined on the basis of data indicating that patients with this presentation had a better prognosis than patients with stage IV disease, and it was implied that their prognosis was comparable to that of patients with disease confined to the lymph nodes [37]. However, treatment of this presentation should be confined to a tolerable radiation field and the delivery of radical but safe irradiation doses. Substantial variations in stage assignment have

nevertheless been demonstrated among patients with extranodal involvement, specifically as regards the distinction between stage IV and early-stage extranodal disease. Thus, even experienced oncologists vary in their stage assignment of patients with nearby but discontinuous extranodal involvement [43]. However, the involvement of two or more noncontiguous extranodal sites should typically be considered indicative of stage IV disease. The use of risk-adapted treatment with chemotherapy has reduced the importance of such factors.

The definition of bulk has varied considerably in the literature. For the mediastinum, the most widely accepted definition involved measuring the greatest transverse diameter of the mediastinal mass on a standard posteroanterior chest radiograph and dividing it by the maximal diameter of the chest wall at its pleural surfaces, usually at the level of the diaphragm or alternatively at the T5–T6 interspace (Cotswolds approach). A ratio exceeding one third (1:3) was considered bulky and a negative feature among patients treated with RT alone or chemotherapy alone. There are no widely accepted criteria for the definition of bulk using measurements obtained from CT scans: the Cotswolds Committee recommended that to constitute bulk, a nodal mass must be greater than 10 cm in diameter [37], whereas in recent and ongoing trials, bulk was defined as confluent nodal masses greater than 7 cm [44].

6.6 Clinical Evaluation During Therapy

Clinical evaluation during treatment is an important component of the individualization of treatment intensity. Re-evaluation should be made prior to each cycle of chemotherapy to monitor the resolution of lymphadenopathy and identify acute toxicities that may require changes in treatment. If palpable lymphadenopathy was not present when treatment started, images should be obtained after every two or three cycles of chemotherapy.

A rapid early response to initial therapy is increasingly recognized as a favorable prognostic factor among Hodgkin lymphoma patients and is being studied as a means to guide the overall intensity of a course of treatment. Response can be evaluated by CT, or better still, FDG-PET-CT, after two or three cycles of chemotherapy. Performing PET early during treatment has also proved to be prognostically important and has been incorporated into the response criteria. Thus, a recent meta-analysis demonstrated that for low- to intermediate-risk Hodgkin lymphoma patients, PET may be a good prognostic indicator after a few cycles of standard chemotherapy [45].

Recommendations by several authors suggest that PET should be carried out just before the next cycle of therapy and within 4 days previously [46]. Midtreatment PET has been tested in recent and ongoing randomized clinical trials to determine the duration or type of treatment, including salvage therapy in the disseminated stage. However, it is not yet quite clear whether changing the treatment favorably changes the outcome.

6.7 Definition of the Response to Treatment

Prior to 1999, response criteria for malignant lymphoma varied among study groups and cancer centers. Therefore, an international working group (IWG) comprising experts in the evaluation of NHL published a set of guidelines to standardize response criteria for NHL [47]. Although these guidelines were open to various interpretations and did not include PET evaluation as part of their assessment strategy, they were widely adopted by clinicians and regulatory bodies. However, an increase in the widespread use of FDG-PET for response assessment has prompted a need to re-evaluate and update the IWG criteria. For this purpose, an international harmonization initiative was set up to incorporate the rapid advances in FDG-PET technology that have occurred in the past 5 years into guidelines for performing and interpreting FDG-PET in malignant lymphoma including Hodgkin lymphoma, both in clinical trials and standard practice [48, 49]. For most cooperative

Table 6.3 Summary of the new Cheson guidelines for positron emission tomography/computed tomography

Response	IWG [47]	New Cheson criteria including PET [48], PET positive if uptake >mediastinum (lesions >2 cm), >local background (lesions <2 cm)
CR	Disappearance of all detectable disease LN >1.5 cm must decrease to ≤1.5 cm	CR, CRu, PR, or SD by IWG criteria and PET completely negative; BMB negative
CRu	LN >1.5 cm SPD decrease >75 % Indeterminate bone marrow	No longer exists
PR	SPD regressed >50 %	CR, CRu, PR by IWG criteria and PET positive in at least one previously affected site
SD	SPD decrease ≤50 % but no progressive disease	SD by IWG criteria and PET positive in previously affected sites
PD/relapse	New lesion SPD increase >50 % from nadir of any LN	PD by IWG criteria, and PET should be positive on the new or increased lesion if >1.5 cm

BMB bone marrow biopsy, *CR* complete response, *CRu* unconfirmed complete response, *CT* computed tomography, *IWG* international working group, *LN* lymph nodes or nodal masses, *PD* progressive disease, *PET* positron emission tomography, *PR* partial response, *SD* stable disease, *SPD* sum of the products of the greatest diameters

groups, the updated Cheson criteria have replaced the Cotswold criteria for assessing the response to therapy (Table 6.3).

One of the main criticisms of the 1999 guidelines relating to the interpretation of an unconfirmed complete response (CRu) is the definition of a residual mass. One of the advantages of PET is that it can distinguish between a viable tumor and necrosis or fibrosis in residual disease [50]. In this connection, a retrospective study carried out by Juweid et al. demonstrated that the integration of PET into the IWG criteria increased the number of confirmed complete responses (CRs), thus eliminating the need for the CRu category [51]. That is why the revised criteria state that in routinely FDG-avid lymphomas such as diffuse large B-cell lymphoma and Hodgkin lymphoma, all patients with a negative PET are classified as CR, regardless of the presence of a residual mass on CT. In cases where PET shows the presence of residual disease (i.e., in PET-positive patients), the patient is considered to exhibit a partial response, stable disease, or progressive disease on the basis of the response shown by CT, and the CRu category is eliminated (Table 6.1) [48].

In patients with advanced-stage disease who are treated by chemotherapy alone, the response should be assessed 1 month after the completion of treatment, on the basis of clinical findings and of the same imaging investigations as those that gave abnormal results at presentation (typically CT and PET). However, as false-positive PET scans may occur for up to 2–3 months after RT, repeat imaging should be done later for patients treated by combined therapies, provided they are clinically well. If there is any doubt about the response to treatment, they should be re-evaluated. Note that after the completion of treatment, regression of disease may be slow, and a residual fibrotic mass may still be visible on a chest radiograph or CT images.

6.8 Complete Remission

The patient has no clinical, radiologic, or other evidence of Hodgkin lymphoma. Changes due to the effects of previous therapy (i.e., radiation fibrosis) may, however, be present.

The category (CRu) has been eliminated from the updated response criteria and now denotes patients whose remission status is unclear, because they display no clinical evidence of Hodgkin lymphoma, but some radiologic abnormality that persists at a site of previous disease. In this respect, it is generally recognized that imaging abnormalities may persist following treatment and do not necessarily signify active disease [52].

This definition of unconfirmed or uncertain remission is still helpful in the absence of FDG-PET, when reviewing a clinical case. However, it must be borne in mind that after mediastinal RT, thymic rebound, reactive lymph node hyperplasia, or subclinical radiation pneumonitis may lead to abnormalities on FDG-PET [53]. To avoid false-positive interpretations, some authors recommend that FDG-PET re-evaluation should be delayed until 3 months after the completion of mediastinal RT, although the characteristic appearance of post-RT lung changes occurring before 3 months can usually be distinguished from lymphoma by experienced nuclear radiographers [54].

The inclusion of PET in the new response criteria and the removal of CRu have simplified the management of lymphoma patients by removing some of the limiting factors of CT, which include the size of lymph nodes that indicates involvement, the differentiation of unopacified bowel from lesions in the abdomen and pelvis, the inability to distinguish viable tumor from necrotic/fibrotic lesions after therapy, and the characterization of small lesions. However, even though PET has eliminated many of the limitations attributed to CT, it has several disadvantages, including limited resolution, inaccurate localization of the abnormalities, and physiologic variations in FDG distribution. PET and CT are therefore complementary, and consequently a combined PET-CT examination, when available, has become part of clinical practice, rather than choosing either PET or CT separately [55].

6.9 Partial Remission

Partial remission is defined as a decrease of at least 50 % in the sum of the products of the largest perpendicular diameters of all the measurable lesions. This would include patients with an abnormal but improved PET scan. Other manifestations of disease (e.g., B symptoms) should also improve. As described above, reimaging and/or re-biopsy to detect persistent active disease should be aggressively undertaken if the results can be expected to have a marked effect on treatment decisions (e.g., if the patient is a candidate for aggressive salvage therapy).

6.10 Progressive Disease

Progressive disease is defined as an increase of 25 % or more in the size of a least one measurable lesion, the appearance of a new lesion, or the recurrence of B symptoms that cannot be otherwise explained.

Most lymphoma patients will become PET negative after two to three cycles of standard chemotherapy, and response assessments based on the new Cheson criteria are proving to be robust and highly predictive of outcome [56, 57]. However, false-positive lesions occur more frequently at earlier time, particularly with intensified treatment schedules, and preliminary results indicate that the accuracy of PET differs, depending on the treatment given.

6.11 Follow-Up Management

The manner in which patients are evaluated after completing treatment may vary according to whether treatment was administered in a clinical trial or clinical practice and whether it was delivered with curative of palliative intent. In a clinical trial the requirement of uniform reassessment may lead to follow-up studies that would not be routinely done in practice.

Good clinical judgment, careful recording of history, and a thorough physical examination are the most important components of monitoring patients after treatment. A complete blood count, selected serum chemistry studies, and a sedimentation rate are frequently done with each visit. However, there is no evidence to support the need for regular surveillance CT scans. The patient or physician identifies the relapse in more than 80 % of cases without imaging studies [58]. The most important potential reason to do surveillance imaging would be the detection of early relapse that allowed early institution of salvage therapy and increased survival. However, there is no evidence to support this hypothesis. One study of 241 patients that compared patients treated at different centers who did or did not do routine surveillance imaging found a 97 % overall survival rate in patients who received routine surveillance imaging and a 96 % 5-year survival rate in patients who were only followed clinically [59]. In both groups, salvage therapy

was effective with only one patient in the routine surveillance imaging group dying of Hodgkin lymphoma. It was calculated that each relapse detected by surveillance imaging cost $629,615, with no benefit in eventual outcome. Similar results have been found in the use of surveillance imaging in pediatric Hodgkin lymphoma [60].

In addition to financial costs, surveillance imaging has other "side effects." One study found that patients undergoing surveillance imaging had increased anxiety and fear associated with the images [61]. In addition, it is known that CT scans deliver a high level of radiation and are a significant cause of cancer [62, 63].

An alternative to using CT scans would be the use of FDG-PET scans as a potential tool for detection of relapse. However, in a prospective study of 36 Hodgkin lymphoma patients, routine FDG-PET correctly identified all five relapses that followed treatment, but had a false-positive rate of 55 % [64]. A more recent study using PET-CT scans showed a positive predictive value of only 28 % for routine PET-CT scans for surveillance for relapse [65].

Conclusion

The careful and accurate clinical evaluation of patients with Hodgkin lymphoma from presentation to follow-up in remission has a significant impact on treatment outcome. The ability to perform an excellent history and physical and knowledge regarding when, where, and how to perform laboratory evaluations, images, and biopsies are necessary for excellent care.

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Functional Imaging in Hodgkin Lymphoma

7

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Contents

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7.1 Introduction

Hodgkin lymphoma (HL) has become a curable malignancy with more than 90 % of patients alive and 80 % considered cured after a minimum follow-up of 6 years [1]. These results have been obtained by a combination of factors influencing treatment outcome in different ways: (a) a high chemo- and radiosensitivity of the tumour, (b) an increasing accuracy of staging procedures, (c) treatment strategies adapted to a properly set risk-stratification of the patients. Tailored to well-defined categories of patients with a different risk of treatment failure.

Arguably, no other haematological tumour has been the object of such accurate staging definitions as HL, where a wide array of radiological, nuclear

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_7,

medicine, or even surgical procedures have been used, ranging from chest X-ray to staging laparotomy [2]. Positron emission tomography combined with computerised tomography (PET/CT) is now the cornerstone procedure for staging and response assessment. CT alone uses size criteria to distinguish between normal and malignant tissue, so it cannot detect involved nodes of normal size. Moreover, response assessment with CT uses changes in tumour size as the main criterion. But tumour shrinkage takes time, and since a residual HL mass can take years after treatment to disappear, CT does not provide an early assessment of therapy response [3]. This challenge is met by functional imaging, notably by PET, which is dependent on tumour metabolism rather than anatomy.

In HL tissues, scattered neoplastic cells (Reed-Sternberg and Hodgkin cells), account for less than 1 % of the total cell count and are surrounded by a population of seemingly non-neoplastic mononuclear bystander cells [4]. The production of chemokines by tumour cells is possibly responsible for this organisation of the neoplastic architecture. The Hodgkin and Reed-Sternberg (HRS) cells produce chemokines such as thymus and activation-regulated chemokines (TARC-CCL7) and macrophage-derived chemokines (MDC) that recruit CCR4-expressing cells including eosinophils, histiocytes, macrophages, plasma cells, and Th2 and Treg lymphocytes. There is convincing evidence that forced expression of CCR4 in these cells allows them to migrate towards a TARC gradient, so that the functionality of this receptor is not restricted to the subset of T cells in which it is physiologically expressed [5]. These cells are metabolically active and induce chemokines to recruit accessory cells and might contribute to HRS cell immortalisation. Chemotherapy is able to switch off this chemokine production, and preliminary observations suggest that serum TARC levels predict therapy response in HL patients [6].

Positron emission tomography using [18F]-fluoro-2-deoxy-D-glucose (FDG-PET) has emerged as a tool to assess chemosensitivity when performed early during standard-dose ABVD treatment in HL patients (ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine) [7]. FDG-PET detects the metabolic silencing of the neoplastic tissue induced by chemotherapy and likewise the persistence of a small chemoresistant clone with a high metabolic activity. Such early assessment of treatment response makes new therapeutic options possible, with treatment tailored to the individual patient that may potentially lead to higher cure rates with less overall toxicity. Several clinical trials exploring the role of early PET response-adapted therapy have been initiated worldwide [8].

Functional imaging includes a number of other nuclear medicine procedures as well as certain applications of magnetic resonance imaging (MRI). However, apart from relatively rare exceptions (bone scintigraphy, leukocyte scintigraphy in infected patients, lung scintigraphy), only gallium-67 scans and FDG-PET have a clearly defined role in the management of HL. New and potentially more specific PET tracers are under investigation, as discussed later in this chapter.

7.2 Gallium Scan

Since the pioneer study of Johnston published more than 40 years ago [9], gallium-67 citrate scan was used for staging [9–11], restaging [12–14], and follow-up [15, 16]. This functional imaging method made it possible to assess the significance of a CT-detected residual mass persisting after treatment. In case of viable residual disease, the radiotracer is taken up by the tumour cell in the mass, as proven by biopsy [13]. In the post-chemotherapy setting, the persistence of gallium uptake proved a strong predictor DFS and OS with a specificity 95 % and sensitivity of 60–96 %, depending on the region of persisting disease [14]. Later, Ga67 scan was proposed as a sensitive tool for prediction of treatment outcome as early as after one cycle of chemotherapy [17].

7.3 FDG-PET in Clinical Management of Lymphoma

7.3.1 Basic Principles of PET

PET is a functional imaging modality based on measurements of events related to the decay of

positron emitting radioactive nuclides. These nuclides have excess protons which transform to neutrons under the emission of positrons (β^+-decay). The positron randomly travels 2–3 mm in the tissue before it annihilates via collision with an electron and thereby emitting two photons (each 511 keV) at an angle of almost 180°. The photons are registered by the ring of scintillation detectors in the PET scanner. Two 511 keV photons registered simultaneously (or within a very narrow time frame) by two opposing detectors are considered a coincidence event originating from positron annihilation. A PET scanner holds several thousands of scintillation detectors, organised in detector rings. The detector rings are often separated by leaded ring collimators (2D mode) in order to limit sources of noise in the PET images. Data acquisition can be either static or dynamic, and the data generated provide both quantitative information and images. The spatial resolution of PET is typically around 5 mm, limited by the number of detectors and by the random travel of the positron [18]. The unstable positron emitting isotopes used in PET are produced by fusion of stable nuclei with other particles. This is possible in a cyclotron, in which the electrical repulsion between particles is overcome by accelerating particles up to 30 % of the speed of light with a beam towards the target [19]. A radiochemistry laboratory is needed to attach the isotopes to relevant tracer molecules. The most common PET isotopes molecules are ^{15}O, ^{13}N, ^{11}C, and ^{18}F [20]. PET tracers of relevance to oncology target glucose metabolism, hypoxia, blood flow, proliferation, amino acid transport, protein synthesis, DNA synthesis, apoptosis, and specific receptors.

Fusion PET/CT scanners incorporate the hardware of high-resolution CT and PET into one scanner, so that PET and CT as well as fusion images are obtained in one scanning session. PET/CT scanners have been available commercially since the late 1990s, and very few single-modality PET scanners are sold now. PET/CT has obvious advantages over PET, including better anatomical localisation as well as easier distinction between pathological findings and normal physiological uptake [21].

7.3.2 The FDG Tracer

The glucose analogue 2-[18F]fluoro-2-deoxyglucose (FDG) is the most versatile and widely used PET tracer, and it is estimated that FDG-PET accounts for 90 % of all clinical PET studies. The use of FDG in tumour imaging is based on Warburg's finding that cancer cells show accelerated glucose metabolism [22]. FDG is transported into the cell via glucose transporter molecules (GLUT 1–5), which are overexpressed in cancer cells [23–25]. In the cell, FDG is phosphorylated by hexokinase to FDG-6-phosphate, which does not cross the cell membrane. Due to the low levels of glucose-6-phosphatase in cancer cells and the inability of FDG-6-phosphate to enter glycolysis, the tracer is retained in the cancer cells [26]. Generally, the uptake of FDG is related to the number of viable tumour cells [27, 28], but dependent on a number of physiological factors including regional blood flow, blood glucose level, and tissue oxygenation [29, 30]. FDG uptake is very high in HL, but since the HRS cells only make up a small fraction of the tumour volume, the surrounding cells are probably accountable for the increased FDG metabolism. FDG is far from tumor specific biomarker and accumulates in a range of non-malignant tissues, such as brain, heart, and kidneys. Furthermore, activated inflammatory cells take up FDG, which can cause false-positive results in cancer imaging studies [31, 32]. This is obviously important since HL patients frequently experience infections, but also because chemotherapy and radiotherapy induce inflammatory responses in the tumour cells and the surrounding tissue. An increased tracer uptake in seen in response to the early phase tissue inflammation induced by chemotherapy, with very low uptake shortly after therapy [33, 34]. FDG is administered by intravenous injection.

7.3.3 Staging

Early reports on FDG-PET for lymphoma imaging were published more than 20 years ago [35]. Since most lymphomas showed FDG avidity, a number of studies have followed, investigating the properties of FDG-PET in the primary staging of both

HL and NHL. As it would be unethical and laborious to biopsy every suspected focus, the lesions were generally not validated by histopathological analysis. Discrepancies between CT and FDG-PET were later assessed at follow-up, considering all available clinical data and allowing the clinical course to eventually determine a standard of reference for analysis of diagnostic accuracy. Such a reference standard is far from optimal, but probably the best that can be achieved. Especially the early studies of FDG-PET for staging of malignant lymphomas were performed in a retrospective fashion involving mixed lymphoma populations who were scanned at different times during the course of treatment. The general impression from these investigations, regardless of technical differences in scanning protocols and experimental approach, was that FDG-PET has a very high diagnostic sensitivity [36–46]. In both HL and aggressive NHL, FDG-PET detects more disease sites, nodal as well as extranodal, than conventional imaging methods, resulting in a higher sensitivity, and leading to significant upward stage migration [36–58]. FDG-PET seems to be at least as sensitive as blind bone marrow biopsy [38, 58–60]. Later studies have focused on individual lymphoma subtypes, thus respecting the very variable nature of this heterogeneous group of diseases.

Studies focused on HL have found a very high sensitivity for nodal staging, especially for the detection of peripheral and thoracic lymph nodes. The increased sensitivity apparently does not come at the expense of a significantly decreased specificity. FDG-PET also detects extranodal disease more sensitively than conventional methods, both in the bone marrow and in other organs.

FDG-PET has a consistent, large influence on the staging in HL, with upstaging of approximately 15–25 % of patients, and downstaging in only a small minority of patients. This leads to a shift to a more advanced treatment group in approximately 10 % of patients [47–58]. The tendency towards upward stage migration is important, as HL is a disease where early and advanced stages are treated very differently. However, early-stage HL patients have an excellent prognosis and are at the same time at high risk of serious treatment-related late morbidity and mortality. With this in mind, the use of FDG-PET for HL staging should be proposed in well-designed prospective clinical trials aimed at abbreviating the course or reducing the intensity of treatment in early-stage disease.

Almost 100 % of all newly sold PET scanners are integrated PET/CT scanners and the dual-modality scanner is rapidly replacing the single-modality scanners in most centres. A few studies have looked specifically at the value of FDG-PET/CT as compared with CT and/or FDG-PET in the lymphoma staging. FDG-PET/CT is found to be more accurate for staging than both FDG-PET and CT, with an equal sensitivity and a better specificity. FDG-PET/CT has less of a tendency towards upstaging of patients than PET stand-alone; in fact FDG-PET/CT correctly downstages a number of patients compared with both CT and FDG-PET. FDG-PET/CT has fewer false-positive findings than FDG-PET alone, especially in the deep nodal regions of the abdomen and the mediastinum, a fact probably owed to the improved distinction between malignant and non-malignant FDG uptake (intestinal uptake, brown fat, muscle uptake, etc.) [56, 61].

In the PET era, the role of bone marrow trephine biopsy (BMB) for HL staging has been questioned. In a recent retrospective study, the role of routine BMB to detect bone or bone marrow (B/BM) infiltration was assessed in a cohort of 454 HL patients staged with PET/CT: none of the patients with early-stage disease had a histopathology proven B/BM infiltration, while BMB upstaged only five patients, all from stage III to IV and resulting in no treatment change for those five patients [62]. Another major issue is the definition of B/BM invasion by PET/CT: it is well known that most of patients are upstaged from stage III to stage IV in the PET era; the stage migration is due to detection of B/BMB infiltration and, to a lesser extent, lung and liver involvement [56, 62]. However, the prognostic role of B/BM attainment seems different according to the pattern and intensity of FDG uptake: (1) focal uptake with an intensity > liver uptake, (2) diffuse uptake with an intensity > liver uptake, and (3) diffuse uptake with an intensity equal or lower than liver or no FDG uptake by bone. Preliminary results from a retrospective cohort of advanced-stage, ABVD-treated HL patients, presented by Borra et al., showed that only a focal B/BM invasion could be associated with a worse prognosis, while

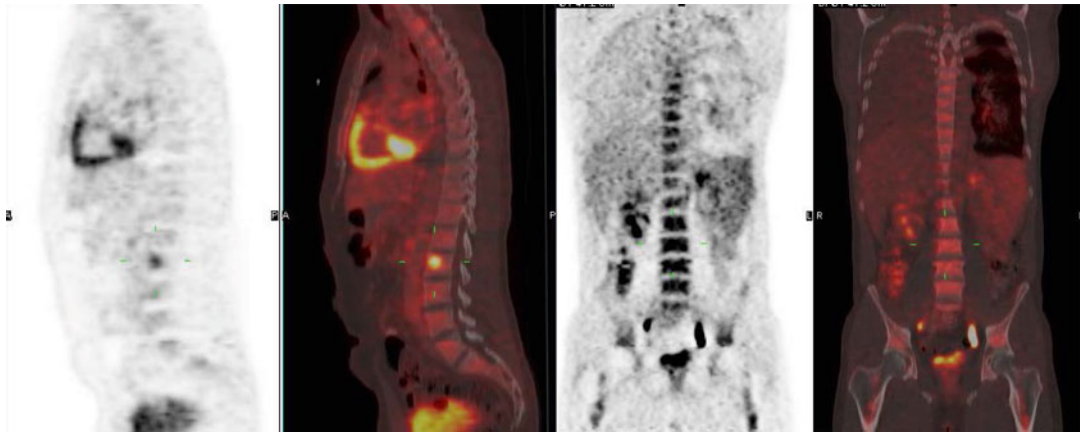

Fig. 7.1 Example of focal and diffuse FDG uptake by the bone marrow

patients with a diffuse B/BM invasion had a 3-year progression-free survival identical to those without evidence of B/BM invasion on PET/CT [63].

In conclusion, bone marrow involvement is a rare finding at disease onset in HL patients, and in HL patients staged with PET/CT, BMB should no longer be a routine procedure. This concept, along with general recommendations for the use of FDG-PET for FDG-avid lymphoma staging and restaging has been set in a dedicated workshop during the 12th International Conference on Malignant Lymphoma (ICML) of Lugano, and reported in a recently published article [64] (Fig. 7.1).

7.3.4 Metabolic Tumour Volume (MTV)

Quantitative PET assessment is being increasingly recognised as an important tool for prognosis and response monitoring in oncology [65]. Semi-quantitative analysis by means of standardised uptake value (SUV) is clinically feasible because SUV is available in every whole-body PET scan. It is a simple index for glucose matabolism and it can be obtained with good reliability, provided that FDG/PET scans are acquired in a standardised manner and adequate scanner calibration procedures have been applied. Different semi-quantitative and quantitative/kinetic analyses have been used to assess tumour metabolic response [66, 67], but the methodology for determining total lesion glycolysis is still evolving. Metabolic tumour volume (MTV), defined as the volume of tumour tissue with increased FDG uptake, measures the neoplastic volume on the basis of the distribution of metabolic activity instead of the traditional X-ray or CT densities. Total glycolytic activity (TGA) goes a step further and effectively weighs this volume by its mean metabolic activity. Hence, a large TGA may reflect a small volume with high metabolic activity (high SUVmean) or a large volume with a lower metabolic activity. Both MTV and TGA could be better surrogate imaging markers for tumour biology than SUVmax or tumour diameter [68]. A large number of approaches have been proposed to segment tumours in PET images and the relative advantages or drawbacks discussed [69]. To date, there is no consensus on which method should be preferred for tumour segmentation, because of the difficulty in assessing tumour volumes in vivo [70]. Two main approaches in MTV calculation are currently being used: one (threshold method) consisting in measurement of all the voxel contained in an area corresponding to the tumour and with an intensity superior to a fixed absolute or relative threshold of SUV value, and another (gradient method), relying on the identification of tumour based on a change in count level at the tumour border [71–74]. The identification and contouring of the neoplastic lesions is performed manually or as an automated procedure using software to detect the tumour lesions according to the high ratio of tumour to background uptake (T/B) at the border of tumour.

Tumour burden, calculated on the CT scan as the sum of the product of the two perpendicular

diameters of all the nodal and extranodal lesions in HL, is a well-known prognostic parameter [75]. However, third parameter is too laborious for practical use, and therefore, it was suggested that the relative tumour burden (rTB), the tumour burden normalised to body surface area, could be calculated with the best approximation starting from a set of very simple clinical variables such as the number of involved sites, bulky mass, and the IPI score [76]. MTV at baseline turned out an important prognostic factor in preliminary reports both in early-stage [77] and advanced-stage HL. In a retrospective study of 59 advanced-stage HL patients enrolled in GELA trials, Casanovas et al. reported that patients showing a MTV at baseline higher than 225 cc had a 3-year progression-free survival of 42 % as compared to 85 % in patients with a MTV lower than this value [78].

7.3.5 Early Assessment of Chemosensitivity

Seventy to eighty percent of HL patients show normalisation of their FDG-PET scan after two courses of ABVD [3, 79]. However, very similar findings have been reported after one single cycle [80] or even 7 days after the very first chemotherapy administration [81]. Non-neoplastic cells in HL tissue show an impressive FDG avidity, resulting in a baseline scan positivity in 100 % of HL cases. However, their metabolic activity and chemokine production are apparently shut down after two courses of chemotherapy. This phenomenon occurs in normal-size but also bulky nodes, in spite of a persisting mass, as tumour shrinkage takes time and depends on several factors in the host. The paradoxical phenomenon of a persisting mass without evidence of a viable neoplastic tissue has been called "metabolic complete remission" [82, 83] and accounts for the high overall accuracy of interim PET scan in predicting treatment outcome in HL patients. Non-neoplastic microenvironmental cells are metabolically active at baseline. They are shut down in chemotherapy-responsive patients, but they are responsible for the persisting FDG uptake in chemoresistant refractory disease [84]. This situation is quite different in diffuse large B cell non-Hodgkin lymphoma (DLBCL). In DLBCL neoplastic cells make up 85–99 % of the nucleate cells. Their proliferative fraction is very high, sometimes up to 90 %. The persisting FGD uptake could be the balance between cell kill by chemotherapy and cell regrowth [85].

Interim FDG-PET scan performed very early during treatment has shown a high overall accuracy as it predicts treatment outcome in more than 90 % of the patients. In a retrospective analysis of 88 patients scanned after 2 or 3 cycles of ABVD-like chemotherapy for HL, Hutchings et al. found a 5-year PFS of 39 % in the PET-positive group compared with 92 % in the PET-negative group [86]. These results were later confirmed in prospective studies by Hutchings [3], Zinzani [87], and Gallamini [79], the latter study focusing on advanced HL patients alone. In all three studies, almost all (94–100 %) of the patients who were PET positive after two cycles of ABVD had refractory disease or relapsed within 2 years, while all the early PET-negative patients entered a good remission and very few later relapsed (~6 %). More recently, Terasawa et al. systematically reviewed all the studies published so far on this issue and reported a sensitivity for HL patients ranging between 43 and 100 % and a specificity ranging between 67 and 100 % [7]. In all reviewed studies, the authors confirmed the prognostic role of early FDG-PET in predicting treatment outcome and concluded that it is useful and reliable for assessment of the treatment response. In a joint Italian and Danish study, the 2-year progression-free survival for early PET-negative and PET-positive patients was 95 and 12 %, respectively. Early interim FDG-PET emerged as the only independent factor able to predict treatment outcome, thus overruling the pre-therapeutic risk index, IPS (International Prognostic Score) [88] (Fig. 7.2).

Recent studies have raised concerns that the positive predictive value of early FDG-PET may be lower in patients treated with the more dose-intensive BEACOPPesc regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) than in patients treated with ABVD [89–91].

Eight to ten percent of the patients who undergo early interim FDG-PET show a persisting, faint

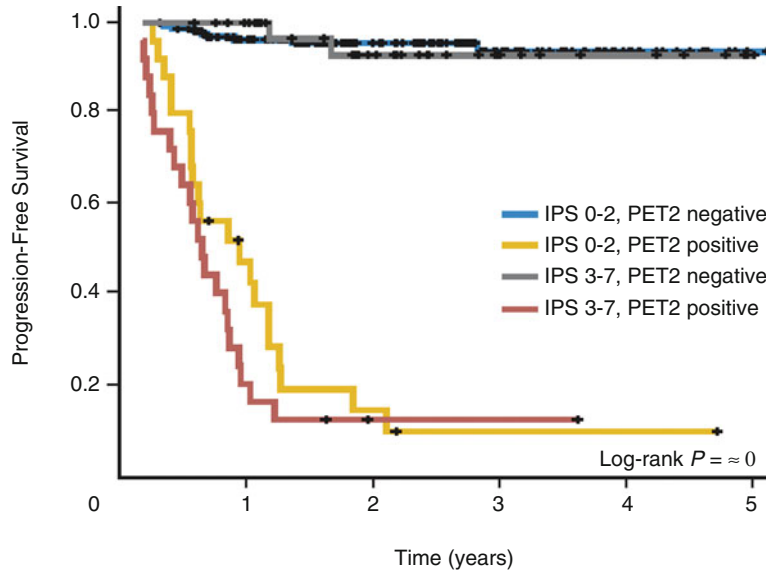

Fig. 7.2 Kaplan-Meier plot showing the progression-free survival according to the International Prognostic Score (IPS) group and positron emission tomography results after two cycles of ABVD (From Gallamini 2007, by permission) [89]

FDG uptake, most often in a site where a bulky tumour was recorded at baseline. This area of persisting FDG uptake was first described as minimal residual uptake (MRU), defined as low-grade uptake of FDG (just above background) in a focus within an area of previously noted disease reported by the nuclear medicine physicians as not likely to represent malignancy [86]. The significance of this finding is unknown and probably is a consequence of the inflammatory tissue reaction to the cytolytic effect of the chemotherapy, with an unspecific FDG uptake by inflammatory cells infiltrating the neoplastic lesion as a consequence of the chemotherapy [34]. The prognosis of MRU + patients is quite similar to the one observed in patients with an early negative scan, and for these reasons, it has been proposed that MRU + patients should be considered as early PET negative.

Two questions concerning the ideal time for interim FDG-PET scanning are still unsettled: (1) What is he ideal time lag between the last chemotherapy cycle administration and PET scan? (2) What is the best number of chemotherapy cycles before the early interim FDG-PET scan? As far the point (1) is concerned, in mice undergoing FDG scan, the FDG uptake by neoplastic cells and reactive inflammatory macrophages was minimal 14 days after chemotherapy administration [34]. In a review of the published experience of interim FDG-PET early during treatment, Kasamon concluded that the optimal time for performing interim PET during chemotherapy ranged between 7 and 14 days after chemotherapy [92]. The answer to point (2) could depend on the aggressiveness of the tumour and the efficacy of the chemotherapy. In HL, there is most evidence for the use of FDG-PET after two courses of chemotherapy, but promising preliminary reports have indicated an equally high predictive value already after one cycle of therapy [80]. In a recently published prospective study of 126 HL patients, Hutchings et al. found a very high prognostic value of PET after one cycle of chemotherapy, and a higher negative predictive value after one cycle than after two cycles of chemotherapy. The authors concluded that PET after one cycle should be the preferred method for PET-response adapted strategies designed to select patients candidate to a less intensive or a de-escalated treatment [93] (Fig. 7.3).

7.3.6 Treatment Response Assessment

Between 1999 and 2001, several reports in the literature demonstrated a high sensitivity and specificity of FDG-PET in tumour response assessment. In a meta-analysis of 13 studies on 408 HL patients and after exclusion of studies not fulfilling the minimal requirements for review

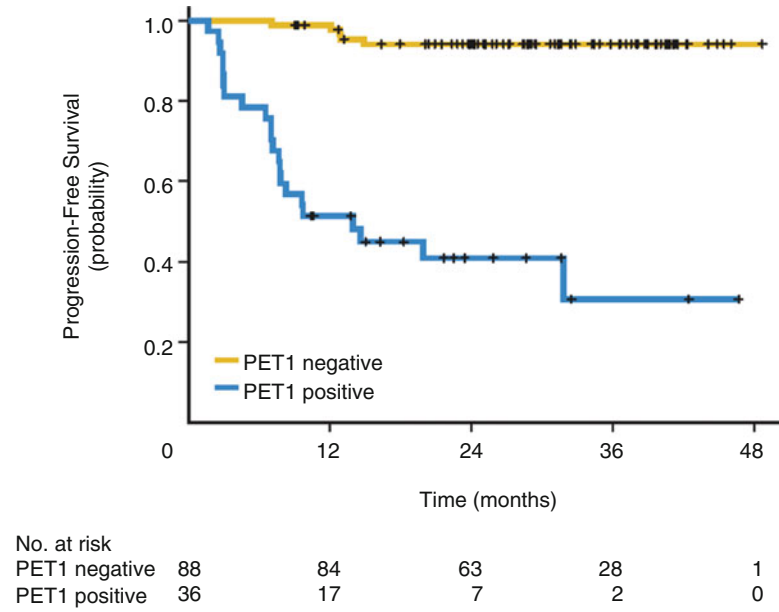

Fig. 7.3 Progression-free survival according to PET1 results. *Yellow curve* = PET1 negative, *blue curve* = PET1 positive (Hutchings 2014, by permission) [93]

(full ring of CT-PET, adequate follow-up, definition of the reference test), Zijlstra and colleagues were able to demonstrate a pooled sensitivity and specificity of PET in defining treatment outcomes of 84 % and 90 %, respectively [94] (Fig. 7.4).

As a consequence, FDG-PET was proposed in 2007 as a mainstay for the defining the treatment response by the International Harmonization Project (IHP) criteria for treatment response evaluation in lymphoma [95]. Later on, a few prospective clinical studies reported the clinical consequences of this new criteria to assess the treatment response. The concept of CRu has been abandoned, and patients defined in CR or CRu at the end of treatment had an identical outcome; patients in PR had a progression-free survival similar to the ones in stable or progressive disease [96]. Therefore, the number of false-negative results obtained with the new response criteria was much smaller than the number of false-positive results obtained with the old ones, thus sparing a significant number of patients from unnecessary treatment.

Despite the good response to therapy, treatment of HL results in residual mass in up to 64–80 % of the patients, as shown by conventional restaging modalities [12, 97]. Since the study by Jerusalem et al. [98], many reports focused on the role of FDG-PET for post-treatment evaluation of a residual mass in lymphoma. Later on, Terasawa systematically reviewed all the studies published so far on this issue and reported a sensitivity for HL patients ranging between 43 and 100 % and a specificity ranging between 67 and 100 % [99]. FDG-PET has been proposed as determinant for the decision to deliver consolidation radiotherapy in cases of single residual mass persisting at the end of treatment, and its role has been proven essential [100, 101]. The prognostic meaning of a residual mass at the end of chemotherapy and the role of consolidation radiotherapy for FDG-avid residual mass in the PET era have been further explored recently. As mentioned above, the NPV of PET scan for a residual mass in this setting is very high but depends on the efficacy of the administered chemotherapy, with values as high as 94 % after an aggressive regimen, such as BEACOPP escalated in advanced-stage HL or as low as 75 % after the low-intensity regimen VEBEP [102–104]. In a large, prospective trial with more than 2,100 patients comparing the efficacy of three different BEACOPP regimens in advanced-stage HL, consolidation radiotherapy was selectively administered to patients showing a FDG-avid residual mass of more than 2.5 cm at the end of chemotherapy [102]. One third of the patients showed a residual mass, and in one quarter of this third, the residual mass proved FDG-avid. The 4-year PFS of irradiated versus non-irradiated patients was

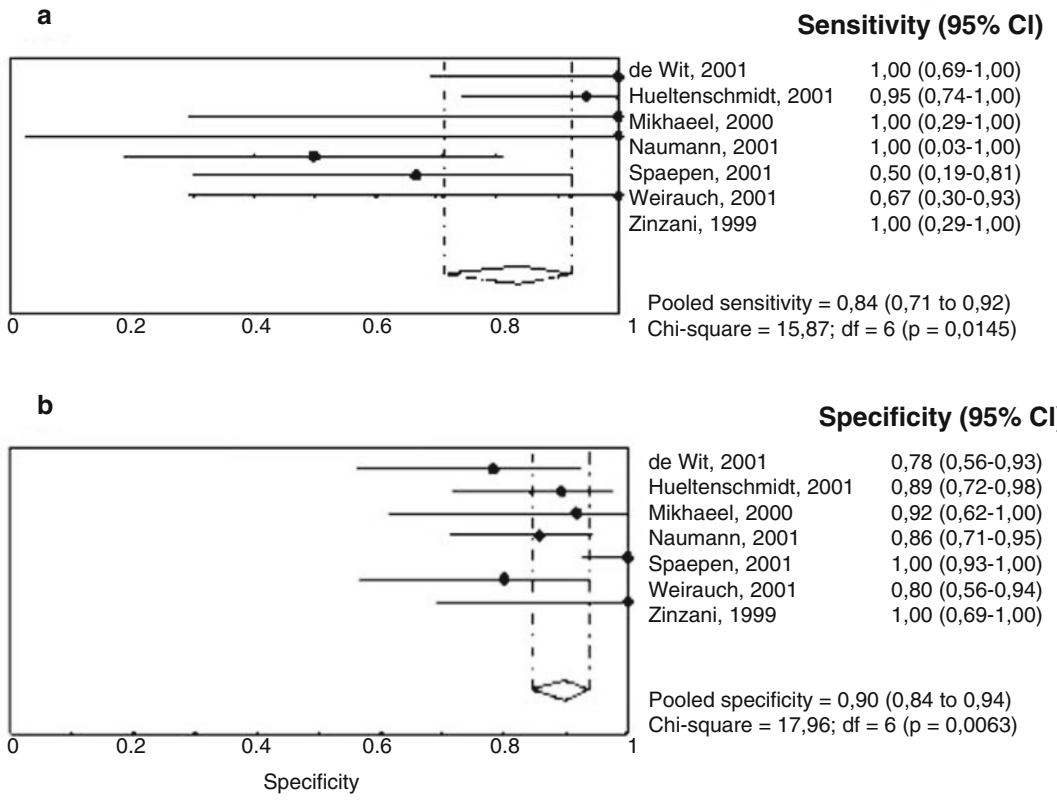

Fig. 7.4 (**a**) Sensitivities and 95 % confidence intervals for studies assessing the diagnostic accuracy of FDG-PET in patients with HD. (**b**) Specificity and 95 % confidence intervals for studies assessing the diagnostic accuracy of FDG-PET in patients with HD. *The diamond represents the 95 % CI of the pooled estimate (From Zijlstra 2006, by permission) [94].

86.2 and 92.6 %, respectively ($p=0.022$), while the treatment outcome in patients with a PET-negative mass was identical to those not showing any residual mass on CT scan. Overall, the NPV of end-therapy PET was 94 %. The authors concluded that this procedure allowed reducing radiotherapy to only 12 % of the patients. Savage et al. reported similar results, in a retrospective analysis of 163 advanced-stage HL patients undergoing consolidation radiotherapy only in case of a residual, FDG-avid mass of 2 cm or more at the end of ABVD chemotherapy. Biopsy was performed in several cases to prove the presence of residual active disease in PET-positive patients. Patients with a PET-negative scan ($n=130$, 80 %) had a 3-year time to progression superior to that of patients with a PET-positive scan (89 % vs. 55 %, $p=0.00001$). There was no difference between those with bulky versus non-bulky disease. The NPV for end-treatment PET was 92 % [104].

7.3.7 PET in Radiotherapy Planning

In the treatment of HL, radiotherapy is mainly used in a combined-modality setting. The extended field technique developed for single-modality treatment was replaced by more and more conformal fields designed for combined-modality treatment, encompassing the initially macroscopically involved tissue volumes in early-stage disease and bulky masses and/or residual masses after chemotherapy in advanced disease [105–108]. These changes have led to dramatic reductions in the volume of normal tissue being irradiated and to a comparable reduction in the risk of serious late effects of radiotherapy. But such modern therapy also demands a higher accuracy of the imaging procedures used for treatment planning. As FDG-PET has been shown to be more accurate for staging of HL, it is also more precise in defining the initially involved regions that are to be irradiated

in patients with early-stage disease. No diagnostic modality has 100 % sensitivity and specificity, and the delineation of the lymphoma volume must be based on all the diagnostic information available of both anatomy and physiology of the disease [109, 110]. Therefore, treatment planning using a combined FDG-PET/CT scan is preferable [111].

In the primary treatment of early-stage HL, chemotherapy is most often the initial treatment followed by radiotherapy. In this situation, the initial lymphoma volume seen on the pre-chemotherapy FDG-PET/CT scan must be contoured on a planning CT scan done after chemotherapy. Image fusion may then be employed later to allow pre-chemotherapy images to be combined with the post-chemotherapy planning CT, thus aiding the accurate delineation of the initially involved volume on the planning CT. If PET is to be used to its full potential, pre-chemotherapy PET/CT should be acquired with the patient in the same position that will later be used for radiotherapy. In advanced disease, radiotherapy is used less frequently and usually only to residual disease. Here FDG-PET/CT may help in discriminating between a residual mass with viable lymphoma cells and a residual mass consisting only of fibrotic tissue. However, FDG-PET cannot detect microscopic disease, and it is not clear whether the target volume for irradiation in this situation should be only PET-positive lesions or whether it should also include CT-positive but PET-negative areas.

Relatively limited clinical data are available on the role of FDG-PET in target definition for the planning of radiotherapy for HL [112, 113]. If extended field irradiation is still used, the impact of FDG-PET is not expected to be very large since additional involvement found on FDG-PET will often be included in the large treatment fields anyway [114, 115]. But if modern, more conformal radiotherapy is planned, changes due to FDG-PET have been shown to be significant [116–118]. This technique makes mediastinal masses appear smaller and better defined. When radiotherapy is delivered with a similar respiratory gated technique, the technique can be used to refine and reduce radiotherapy fields and margins and to minimise the damage to the lungs.

7.3.8 PET for Response Prediction During Salvage Treatment

Standard or high-dose second-line chemotherapy followed by autologous stem-cell transplantation (ASCT) is considered the standard treatment for relapsing or primary resistant HL [119, 120]. The only significant prognostic factors were the duration of response to first-line chemotherapy and the status of the disease at transplant or, in other words, the chemosensitivity before ASCT. A review of the published literature points towards a high predictive value of pre-transplant FDG-PET [121]. Some reports include a mixture of NHL and HL patients, while others focus exclusively on HL. In general, the predictive value is higher in HL than in NHL and the positive predictive value (PPV) is higher than the negative predictive value (NPV) [122–127] (Table 7.1).

In particular the PPV ranges between 91 and 43 %, while the PNV between 90 and 46 %. These wide-range fluctuations are mainly due to the presence of a wide array of NHL subtypes that, as already known, display different FDG avidity [128, 129].

As a consequence, a new paradigm for transplantation eligibility in relapsing/refractory HL patients has then been proposed, relying on a pre-ASCT PET-based strategy. Patients with a negative PET scan had the best outcome, while patients with a positive PET scan and extranodal disease before ASCT had the worst prognosis. According to results from Memorial Sloan Kettering Cancer Center, patients who respond poorly to one induction regimen but became PET negative after a second induction regimen and then proceed with ASCT have as good outcomes as those patients who become PET negative after the first induction regimen [130]. More recently, the same group presented preliminary results of a phase II trial combining brentuximab vedotin (BV) and augmented ICE (ifosfamide, carboplatin, and etoposide), with the aim of obtaining the higher percentage of negative PET scan before ASCT [131]. In a cohort of 24 refractory/relapsed HL patients, two doses of BV at the dose of 1.8 mg./kg were given, and a PET scan performed afterwards. Eight showed a negative scan and went straight to ASCT, while 16 with a positive scan were treated with two cycles

Table 7.1 Proposed Lugano criteria

Response assessment at interim	PET-CT findings at interim	Remission assessment at end of treatment	PET-CT findings at end of treatment
Complete metabolic response (CMR)	Score 1, 2	Complete metabolic response (CMR)	Residual mass of any size and score 1, 2
	Score 3 also likely represents a good response at interim, but an end-of-treatment scan is recommended for further evaluation		Score 3 should be interpreted according to the clinical context and pretreatment prognosis but in many patients indicates a good prognosis/CMR with *standard treatment*. For trials where de-escalation strategies are being investigated, it may be preferable to consider score 3 as inadequate response to avoid undertreatment
Partial metabolic response (PMR)	Score 4 or 5 and reduced uptake from baseline	Residual metabolic disease (RMD)	Score 4 or 5, with reduced uptake from baseline and residual mass of any size (but no new lesions)
No metabolic response or progressive metabolic disease (NMR/PMD)	Score 5 and no significant decrease in uptake or new FDG-avid foci consistent with lymphoma	No metabolic response or progressive metabolic disease (NMR/PMD)	Score 4 or 5 and no significant change in uptake from baseline or new FDG-avid foci consistent with lymphoma or increase in uptake in previous disease foci

of augmented ICE. A new PET scan was then performed showing a negative result in 14/16 (87 %) patients. The latter proceeded successfully to ASCT. In conclusion, 22/24 patients were able to undergo ASCT with a negative pre-transplant scan, but the follow-up was too short for any firm conclusions to be made.

Interim PET scan might also be useful to predict the final outcome or therapy during BV single-agent rescue treatment for refractory, relapsed HL. Younes et al. reported the predictive role of interim PET performed after administration of four BV doses in a phase II prospective trial in relapsed/refractory HL: patients with a negative or positive PET scan had patients with a negative or positive interim PET scan had a 2-year overall survival of 86 and 58 %, respectively [132].

Several other experiences in the so-called national named patient programme for BV single-agent treatment in relapsed refractory HL confirmed the predictive value of interim PET after two to four BV administrations [133–135].

7.3.9 PET for Patient Follow-Up

The value of surveillance procedures during follow-up of lymphoma patients in CR after treatment is still a matter of debate. In general, the probability of detecting an impending relapse with a given test during patient monitoring for disease recurrence depends on the intrinsic probability of relapse of the disease itself in the population being tested, as well as the sensitivity, specificity and the frequency of the test [136]. The prevalence of relapse in a patient with HL in complete remission at the end of treatment is rare, corresponding to one relapse per 68 visits in HL [137]. Moreover, the risk of relapse depends on a number of clinical parameters such as (1) the presence of clinical symptoms, (2) poor chemosensitivity at interim evaluation, (3) the preferred anatomical pattern of recurrence of a given lymphoma subtype, and (4) persistence of a residual mass at the end of treatment [138]. Up to 80 % of relapses in HL are associated with symptoms [137, 139] and PET might become an important marker also in the relapse setting [140]. HL tends to recur in sites involved by disease at baseline, with a preference for sites with bulky tumour [141]. By contrast, aggressive B-cell lymphomas tend to recur both in sites attained at baseline and in new sites [15]. Overall, HL relapse is more likely in those with a PET-positive finding, associated with a concomitant positive result on CT [139, 140, 142]. In a group of 192 HL patients, the

factors that were found to significantly improve the PPV in detecting recurrent HL included PET and CT concordance, involvement of a prior site of disease, and the occurrence of a radiographic abnormality within 12 months [143]. Finally, as previously mentioned, a residual mass can be demonstrated by radiological means in up to 80 % of HL and up to 40 % of non-Hodgkin lymphoma (NHL) patients after completion of treatment [12, 97, 144], even if only less than half of these masses will harbour residual disease [4].

Dittmann et al. retrospectively studied 21 HL patients and found that FDG-PET and CT were equally sensitive in detecting relapses before the occurrence of symptoms [145]. Jerusalem et al. performed FDG-PET every 4–6 months for 3 years in 36 HL patients in CR after ABVD. Six false-positive and no false-negative cases were detected in 119 scans. In five positive cases, FDG-PET preceded the relapse by a median of 3.5 (1–9) months [146]. Zinzani investigated the role of surveillance FDG-PET performed every 6 months for 4 years a cohort of 160 HL patients in CR. Overall, 778 scans were evaluated in HL. In 11/778 scans (1.4 %), PET results were classified as inconclusive/positive, mostly in the first 18 months after CR. All these patients underwent a confirmatory biopsy, and 6/11 were proven true positive [140]. El-Galaly et al. recently reported a large study of 258 patients with aggressive lymphoma in the first relapse. The authors surprisingly found a significant survival advantage for patients with a relapsed detected by routine imaging only: however, since almost 200 routine scans were needed to detect one relapse that would not otherwise have been detected at the same time due to clinical symptoms or signs, the cost/benefit ratio seems poor. During the studied period, 806 HL patients in CR/CRu after first-line treatment were followed and typically routine scanned twice yearly for 2 years. Of 43 HL relapses, 16 were imaging-detected (37 % of all relapsing patients, 2 % of all patients). Those 16 patients had an overall survival benefit (HR 0.47) compared to patients with clinical symptoms or abnormal clinical or lab findings at the time of relapse. But the detection of one single imaging-detected HL relapse took 255 routine scans [147].

At the moment, surveillance FDG-PET cannot be recommended as a routine follow-up procedure for HL patients. Early FDG-PET detection will allow a small number of patients to enter salvage therapy with minimal disease rather than overt relapse, but the survival benefit is uncertain (the demonstrated advantage could in part be explained by length-time bias) and it can hardly justify the large number of routine scans needed per relapse. A possible exception could be the follow-up of high-risk patients, e.g. those with positive interim PET during first-line treatment; however, further studies are warranted to investigate the cost-effectiveness of such procedures.

7.3.10 PET-Response-Adapted Therapy in Clinical Trials

While early FDG-PET quite precisely identifies responders and non-responders, there is yet no evidence that HL patients benefit from having treatment adapted according to the results of early FDG-PET. Seeing that a large fraction of early-stage HL patients are subject to some amount of overtreatment, there is potential benefit in identifying good-risk early-stage patients eligible for less intensive treatment. A number of trials investigate PET-response-adapted therapy in early-stage HL (Table 7.2).

In the EORTC/GELA/IIL H10 protocol launched in October 2006, the primary endpoint was progression-free survival (PFS). HL patients were included and the treatment was adapted on early PET scan results and compared to a standard arm, where patients were treated with chemoradiation (ABVD x 3–4 courses followed by involved-node radiotherapy) [148]. In the experimental arm, PET-negative patients were assigned to chemotherapy alone with four or six ABVD courses; interim PET-positive patients switched to escalated BEACOPP (two courses) followed by INRT. This trial tested the safety and efficacy of treatment de-intensification or escalation in PET-2-negative or PET-2-positive patients, respectively. As a consequence of an interim futility analysis, the de-escalation arm of the experimental therapy was prematurely closed due to an exceedingly high number of events both in the favourable and in unfavourable strata as compared to the standard arm: 9 versus 1 and 16 versus 7, respectively. The RAPID trial, conducted

Table 7.2 PET-response-adapted therapy in early-stage HL

Trial	Stage	Treatment	Number
Israeli H2 [148] protocol	I-II A B	ABVD×2→PET; favorable: PET−INRT; PET+ABVD×2+INRT; unfavorable: PET−ABVD×2+INRT; PET+ABVD×4+INRT	350
CALGB 50604 (NCT 1132807)	I-II A B non-bulky	ABVD×2→PET; PET−ABVD×2; PET+BEACOPP×2+IFRT	160
CALGB 50801 (NCT 1118026)	I-II A B bulky	ABVD×2→PET; PET−ABVD×4; PET+BEACOPP×4+IFRT	123
EORTC/LYSA/FIL H10 F [149]	I-II favorable	ABVD×2→PET; Stand. arm: ABVD×1+INRT; Exp. arm: PET−ABVD×1+INRT; PET+BEACOPP×2+INRT	761
EORTC/LYSA/FIL H10 UF [149]	I-II unfavorable	ABVD×2→PET; Stand. arm: ABVD×2+INRT; Exp. arm: PET−ABVD×2+INRT; PET+BEACOPP×2+INRT	1,191
UK NCRI RAPID [150]	I-II A non-bulky	ABVD×3→PET; PET−rand. vs. no further treatment or IFRT; PET+ABVD×1+IFRT	602
GHSG HD 16 (NCT 01356680)	I-II A favorable	ABVD×2→PET; Stand. arm: ABVD×2+INRT; Exp. arm: PET-2: ABVD×2; PET+ABVD×2+IFRT	1,100
GHSG HD 17 (NCT 00736320)	I-II unfavorable	BEACOPP×2+ABVD×2→PET; PET−No RxT; PET+Random: 20 Gy INRT vs. IFRT	1,100

CALGB Cancer and Leukemia Group–B, *EORTC* European Organization for Radiotherapy and Treatment of Cancer, *LYSA* Lymphoma Study Group of Adult, *FIL* Italian Foundation for Lymphoma Study, *NCRI* National Cancer Research Institute, *GHSG* German Hodgkin Lymphoma Study Group

by the UK National Cancer Research Institute, was aimed at assessing the efficacy of omitting radiotherapy in stage I–IIA non-bulky HL [149]. Patients with a negative interim PET after three courses of ABVD were randomised to INRT or no further treatment, while patients with a positive PET received a further ABVD course for a total of four cycles, followed by IF radiotherapy. The trial was powered to demonstrate a 7 % or less inferiority in terms of 3-year PFS in the non-irradiated cohort compared to the irradiated one. In the most recent update, 74.6 % of patients had negative results after three courses of ABVD and were randomised to receive IF radiotherapy or no further treatment. After a mean follow-up of more than 44 months, the 3-year PFS of irradiated and non-irradiated patients was 94.5 and 90.8 %, respectively, thus meeting the principal end point of the study. In conclusion, in early-stage HL, a PET response–adapted strategy could be a possible approach to omit consolidative radiotherapy in a large majority of patients, while accepting a slightly reduced long-term disease control.

In advanced-stage HL, patients who fail to reach remission or relapse early after first-line therapy have a much worse prognosis and need to be identified as early as possible to lower their risk of treatment failure, avoid unnecessary toxicity, and increase the chance of long-term survival [150]. Around 70 % of patients are cured with a prolonged course of ABVD with or without consolidation radiotherapy, which is the standard-care first-line therapy in most centres. The more intensive BEACOPP escalated (BEACOPP esc.,) regimen cures 85–90 % of patients if given, but is associated with more acute toxicity [151]. A number of trials investigating PET response–adapted HL therapy have been launched to prospectively assess the role of PET response-adapted strategy in advanced-stage disease. Most trials use early treatment intensification with BEACOPPesc (Italian GITIL trial*, the European RATHL trial and the American intergroup trial SWOG-CALG-B **) [152, 153] or even ASCT (Italian IIL trial) [154] in patients who are still PET positive after two cycles of ABVD. More recently, preliminary interim analyses of these trials have been presented in a fraction of patients showing an adequate follow-up. In three of these trials, the Deauville five-point scale was used for interim PT interpretation; surprisingly, the percentage of PET positive and negative were reproduced across those trials. (Positive and negative scans in 16–20 % and 80–84 % of the patients, respectively). Patients switching to BEACOPP escalated showed a 2-year PFS of 60–70 %, while those with a negative interim scan keeping straight on with ABVD had a probability or remaining in

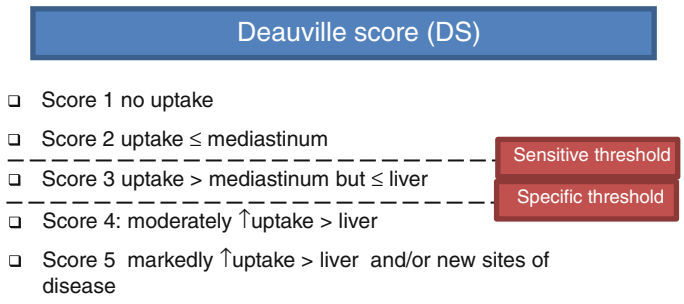

Fig. 7.5 The Deauville five-point scale

Barrington S: Eur J. Nucl Med Mol Imaging 2010;37:1824-1833
Meignan M. Leukemia & Lymphoma 2009;50(8):1257–1260

continuous complete remission ranging between 80 and 90 % [155–158]. A different approach was adopted in the GHSG HD 18 trial in which interim PET scan is performed after two cycles of BEACOPP escalated. In the experimental arm, patients with a negative and positive scan are treated either with an abbreviated BEACOPP escalated programme or with BEACOPP escalated supplemented by rituximab with a standard number of cycles, respectively [159].

7.4 Interpretation Criteria for PET Scan

7.4.1 Interim PET Scan

Early studies on interim PET scan demonstrated that not all interim scans are either positive or negative; some patients had "equivocal" or "inconclusive" results: they showed some residual FDG uptake defined as minimal residual uptake (MRU). The MRU definition evolved over time to encompass a residual unspecific FDG uptake with intensity equal or slightly superior to the mediastinum [88] or equal to the liver [160]. This was proposed with the aim to increase the specificity and reduce the false-positive results of interim PET scan in predicting treatment outcome [84]. Later, during a series of international workshops, a five-point scale for interpretation and reporting of interim PET in lymphoma, the Deauville criteria, has been developed. These criteria are now generally accepted by imaging specialists and clinicians as a useful tool for visual interim PET assessment in lymphoma [64, 74] (Fig. 7.5).

The Deauville five-point scale (5-PS) has been retrospectively validated in two different international studies in HL [161, 162] and DLBCL [163]. In HL, the 5-PS was used as interpretation key to confirm the prognostic role of interim PET scan in a cohort of 260 advanced-stage, ABVD-treated, HL patients enrolled in 17 different haematological Institution all over the world. A panel of six experts reviewed the scans by blinded independent central review. Interim PET scans with scores of 1–3 were considered negative: scores of 4 and 5 were considered positive, respectively. The sensitivity, specificity, and the negative and positive predictive values of interim PET in predicting treatment outcome were 0.73, 0.94, 0.94, and 0.73, respectively. Binary concordance amongst reviewers was good (Cohen's kappa 0.69–0.84). The 3-year progression-free survival was 83 % for the study population, 28 % for patients with interim positive scans, and 95 % for patients with interim negative PET scans, respectively ($p < 0.0001$) [161, 162].

7.4.2 End-of-Treatment PET Scan

In two large meta-analyses, the FDG-PET scan performed at the end of therapy (EoT-PET) was shown to have a very high negative predictive value and a suboptimal positive predictive value, especially in HL [94, 99]. In the latter, the presence of a FDG-avid residual mass at the end of treatment, very often in the site where a bulky mass was detected at baseline, represents a true diagnostic dilemma. As mentioned above, only half of the residual masses at the end of treatment in HL have been considered as a harbinger of persisting disease [4]. Moreover, false-positive results, particularly in follow-up studies, but also at the end of therapy, could be found in FDG-PET

scan, reflecting inflammatory response to therapy or even tissue sarcoid-like reaction [164–166]. For the above reason, in 2013 an expert committee of nuclear medicine physicians, radiologists, and oncologists met during the XII° International Congress on Malignant Lymphoma (ICML) in Lugano and proposed new criteria for EoT-PET scan assessment; those criteria have been recently submitted for publication [167]. Briefly, for most FDG-avid lymphoma subtypes, both contrast-enhanced CT and PET/CT are the required imaging techniques: for the latter, a PET scan qualitative assessment using the five-point Deauville scale was proposed as interpretation key, while for the few FDG non-avid lymphoma (small lymphocytic lymphoma, cutaneous lymphoma, MALT extranodal lymphoma), only CT scan is required, using the RECIST 1.1 criteria. Only four categories of treatment response are proposed: complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD), and progressive metabolic disease (PMD). No definite cut-off for a negative versus positive scan along the 5-PS was proposed; however, the following recommendations were issued: score 1 or 2 by the 5-point scale is considered complete metabolic response (CMR); patients with score 3 may have differing outcomes depending on clinical context and treatment regimen. Therefore, in response-adapted trials exploring treatment de-escalation, score 3 may be regarded as inadequate response to avoid undertreatment, whereas in trials of dose escalation, score 3 may be regarded as satisfactory response to avoid overtreatment [167].

7.5 Future Perspectives

7.5.1 Other PET Tracers

FDG is a glucose analogue and FDG uptake reflects the level of glucose metabolism in the tissue. However, like other cancers, lymphoma is characterised by deregulated cell cycle progression, and most anticancer drugs are designed to inhibit cell proliferation. Thus, a tracer enabling imaging of cell proliferation could be useful for both initial characterisation and treatment monitoring of the disease. FDG uptake is somewhat correlated with cell proliferation, but this correlation is weakened by a number of factors, including FDG uptake in non-malignant lesions [168–170]. The nucleoside [^{11}C]thymidine was the first PET tracer to specifically address cell proliferation. Early studies showed that [^{11}C]thymidine could determine both disease extent and early response to chemotherapy in aggressive NHL patients [171, 172]. However, the short 20 min half-life of ^{11}C along with rapid in vivo metabolism has limited the clinical application of [^{11}C] thymidine. The thymidine analogue 3′-deoxy-3′-[^{18}F]fluorothymidine (FLT) offers a more suitable half-life of 110 min and is stable in vivo [173]. More recent studies have shown that FLT-PET can sensitively identify lymphoma sites [174]. FLT uptake is highly correlated with proliferation rate and may thus be able to distinguish between high- and low-grade lymphomas [175, 176]. Furthermore, recent studies suggested a potential of FLT for imaging early response to treatment in lymphoma [177, 178]. Amino acid metabolism of cancer cells is influenced by catabolic processes favouring tumour growth [179]. It has been shown that increased uptake of amino acids reflects the increased transport and protein synthesis of malignant tissue [180, 181]. This is the background for PET imaging of amino acid metabolism with the labelled amino acids L-[methyl-^{11}C]methionine (MET) and O-2-[^{18}F]fluoroethyl-L-tyrosine (FET). Nuutinen et al. studied 32 lymphoma patients and found MET-PET highly sensitive for the detection of disease sites although there was no correlation between MET uptake and patient outcome. While these results are encouraging, it should be noted that no studies have shown the usefulness or cost-effectiveness of amino acid or nucleoside tracers in large patient cohorts. Furthermore, high physiological tracer uptake in the abdomen limits the usefulness of these tracers for imaging of abdominal and pelvic lymphomas [182].

7.5.2 PET/NMR

There are currently no data from studies specifically comparing the performance of PET/NMR and PET/CT in lymphoma. Recently both modalities have been the object of a head-to-head comparison for tumour staging in a cohort of 50 patients affected by miscellaneous cancers

undergoing first PET/CT with an unenhanced low-dose CT for attenuation correction at 120 KeV with 10 mA, followed 20 (10–45) min later by PET/NMR [183]. All patients underwent whole-body PET/CT from the vertex to the mid-thigh after a single intravenous injection of PET tracers 18F-FDG, 68Ga-DOTATATE, or 18F-fluoroethyl-choline (18FFECH), according to a standard clinical protocol performed on an integrated 64-slice PET/CT scanner (Discovery VCT; GE Healthcare). PET/MR imaging was performed using a Siemens 3T Biograph mMR system with an integrated PET system within the MR gantry, which allows simultaneous PET and MR acquisitions without having to reposition the patient. The PET/MR imaging scan was started 135 ± 36 min after injection. Two hundred twenty-seven FDG-avid lesions were found: 225 were detected on PET/CT and all the 227 on PET/NMR. The two lesions thought to be bladder diverticula on PET/CT were anatomically localised to the bladder dome due to deposits from vaginal paraganglioma. In 45 of 50 patients, there was concordance between PET/CT and PET/MR imaging findings. In five patients (10 %), there was change in T staging of the disease based on the MR imaging component of PET/MR imaging. One patients was upstaged and two downstaged by PET/NMR. In one of the five patients, two additional lesions were identified over the dome of the bladder on PET/MR imaging, which was within the surgical field, that were missed on PET/CT, thought to be urinary bladder diverticula. In one lung cancer patient with mediastinal nodal disease, PET/CT proved to be better than PET/MR imaging in T and N staging. Overall, anatomic localisation was superior in 5.1 % of the cases in PET/MR modality compared with PET/CT; this was attributed to the established superior soft-tissue contrast seen in head and neck, pelvis, and colorectal cancer patients. The image quality was slightly better for PET/CT, while alignment was better for PET/MR because in the latter modality, images were acquired simultaneously for each bed position. In conclusion, while PET/MR proved superior for soft-tissue resolution over PET/CT in cancers of the head and neck, pelvis, and colon or rectum, PET/CT remains the preferred imaging modality in lymphoma, where mediastinal nodal disease is relatively frequent.

7.5.3 Future Perspectives

Ongoing and upcoming clinical trials will hopefully identify patients who can benefit from treatment adaptation based on early FDG-PET response. However, this approach is still response adapted and not risk adapted. Further insight into the natural history of lymphomas on a molecular level might result in more precise pretreatment prognostic and predictive markers. Hopefully, such markers will help us to offer more refined therapy upfront, tailored to the individual patient's risk profile and responsiveness and thus reduce the importance of treatment monitoring. New imaging techniques such as diffusion NMR have been developed, aimed to assess the microscopic mobility of water within the neoplastic tissue at diagnosis and after treatment. They have shown, in preliminary studies, high accuracy in lymphoma staging [184] and treatment response [177]. More recently, ultrasonography with tissue harmonic compound technology and intravenous microsphere-based microvasculature studies (named angiosonography) improves ultrasound accuracy [185–187]. Angiosonography scan has been recently reported to be more sensitive than CT or FDG-PET to detecting nodular infiltration in the spleen of patients with newly diagnosed Hodgkin lymphoma [188]. Modern radiotherapy is evolving rapidly, and PET/CT plays an increasingly important role in both the selection of patients and in the radiotherapy planning. Other PET tracers are likely to emerge, including radiosensitivity tracers and perhaps tracers directly targeting HL-specific cell surface molecules. The most predictable evolution is the ongoing technical development, involving image acquisition and image processing/reconstruction, brought about by advances in hardware development and increased computing power. Integrated PET/MRI systems are being introduced into clinical practice and are likely to prove useful for evaluation of bone marrow involvement and other forms of extranodal disease.

7.5.4 General Recommendations

The value of adding FDG-PET/CT to the conventional HL staging procedures is well established.

Although no studies show better outcomes in cohorts staged with FDG-PET/CT, the method is recommended as a standard procedure. FDG-PET/CT has a general tendency to upstage the patients, so the method should be accompanied by steps to reduce the overall amount of treatment. FDG-PET/CT is operational in the revised response criteria for post-treatment evaluation of aggressive lymphomas. The benefit for the patients of FDG-PET/CT in this setting remains to be clearly shown, but a number of ongoing trials address the issue. There is insufficient evidence for routine use of FDG-PET/CT in the follow-up setting. While the prognostic value of early interim FDG-PET/CT is well established in HL, there is still no evidence that it improves the patient outcomes. With the abundance of early PET response–adapted clinical trials, the new and evidence-based interpretation criteria and reporting guidelines for early interim FDG-PET/CT are an important step forward. A number of PET tracers other than FDG are promising, but their use is still on an experimental level.

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Prognostic Factors

8

Lena Specht and Dirk Hasenclever

Contents

Abbreviations

ABVD	Adriamycin, bleomycin, vinblastine, dacarbazine
BEACOPPesc	Bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, prednisolone, escalated
BNLI	British National Lymphoma Investigation
CALGB	Cancer and Leukemia Group B
ECOG	Eastern Cooperative Oncology Group
ESR	Erythrocyte sedimentation rate
EORTC	European Organization for Research and Treatment of Cancer
FDG	2-[18F]fluoro-2-deoxy-D-glucose
GELA	Groupe d'Etudes des Lymphomes de l'Adulte
GHSG	German Hodgkin Lymphoma Study Group
IPS	International Prognostic Score

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_8,

LDH	Lactic dehydrogenase
MOPP	Mechlorethamine, vincristine, procarbazine, prednisolone
NCI-C	National Cancer Institute of Canada
NCI-US	National Cancer Institute of the United States
PET	Positron emission tomography
SWOG	Southwest Oncology Group

8.1 Historical Perspective

The concept that Hodgkin lymphoma (then called Hodgkin's disease) passes through successive clinical stages with increasing spread of the disease and progressive worsening of prognosis was developed early on [1]. Different staging classifications were proposed based on the anatomic extent of disease [2–8]. A consensus was reached at the Workshop on the Staging of Hodgkin's Disease at Ann Arbor in 1971 [9], and the Ann Arbor staging classification was universally adopted. It remains the basis for the evaluation of patients with Hodgkin lymphoma, and its prognostic significance has been documented in numerous studies of patients treated with different treatment modalities [10–17]. Survival curves according to Ann Arbor stage for more than 8,000 patients from the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) programme are shown in Fig. 8.1 [18].

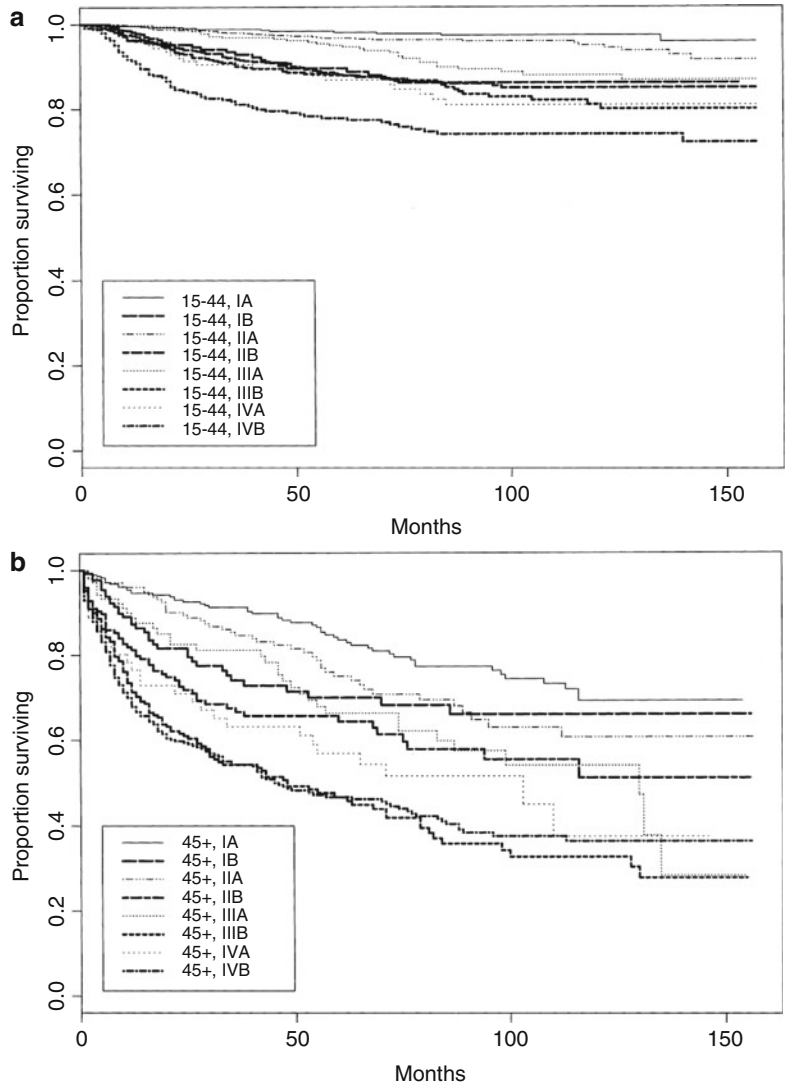

Fig. 8.1 Disease-specific survival according to Ann Arbor stage for 8,054 patients in the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (*SEER*) programme treated in the period 1983–1995, (**a**) young adults [15–44] and (**b**) older adults (45 +) (Reprinted with permission from Clarke et al. [18])

However, the extent of disease varies within the Ann Arbor stages leading to variations in prognosis. A modification of the Ann Arbor classification was proposed at the Cotswold meeting, incorporating a designation for number of sites and bulk [19]. This modification has not been universally adopted. Numerous other prognostic factors for different Ann Arbor stages, disease presentations, treatments, and outcomes have been introduced, and varying combinations of these factors are being used by different centres and groups.

8.2 Prognostic Factors

8.2.1 Definition and Use

Prognostic factors are variables measured in individual patients that offer a partial explanation of the heterogeneity in the outcome of a given disease [20]. They are important in clinical practice for allocating patients into different risk groups, for selection of treatment strategy, and as an aid in patient counselling [21]. However, it is important to realise that prediction is very uncertain for the individual patient. Statements of probability can be made, but even these will be more accurate for groups of patients than for individuals [22]. Prognostic factors can also be used in the design of clinical trials to define eligibility criteria and strata to ensure comparability of treatment groups [20–23]. However, prognostic factors are rarely sufficiently explanatory to justify the comparison of treatments by use of non-randomised data [24, 25].

8.2.2 Types of Prognostic Factors

Prognostic factors are divided into tumour-related factors, host-related factors, and environment-related factors [21]. Tumour-related factors include those directly related to the presence of the tumour or its effect on the host, reflecting tumour pathology, anatomic extent, or tumour biology. Host-related factors include factors that are not directly related to the tumour but which may significantly influence outcome, such as demographic characteristics and co-morbidity. Environment-related factors include factors outside the patient, such as socioeconomic status and access to and quality of health care.

The values of prognostic factors are generally assumed to be known from the outset, before start of treatment, so-called fixed covariates. However, other important prognostic variables may only be known later, such as time to response, toxicity of treatment, and the value of presumed markers. These are time-dependent covariates. They may be important for answering biological questions, but they should not be applied for adjustment for treatment comparison, as they are themselves affected by treatment [20–22].

8.2.3 Different Endpoints

Different outcomes may be of interest in analyses of prognostic factors. Overall survival and progression-free survival are usually analysed, but others may be relevant, e.g. disease-free survival for early-stage patients as virtually all patients achieve remission. For each endpoint there must be clear information on the point in time from which it is measured, and the clinical characteristics of events and censoring. International guidelines have been published [26].

8.2.4 Types and Analyses of Prognostic Studies

Three different study phases of prognostic factors have been proposed, beginning with phase I early exploratory analyses to identify potential markers and generate hypotheses for further investigation. Phase II studies are exploratory studies attempting to use values of a proposed prognostic factor to discriminate between high- and low-risk patients. Phase III studies are large, confirmatory studies based on prespecified hypotheses involving one or a few new factors, and the purpose of these studies is to determine how much the new factor adds to the predictive power of already accepted factors [23, 27].

A useful prognostic factor must be significant, independent, and clinically important [28]. Many variables may be prognostic in univariate analysis. However, different variables are likely to be interrelated. The important question is whether a particular variable adds useful information to what is already known. Multiple regression analysis is commonly employed to determine whether a variable has independent significance when other known variables are taken into account. This kind of analysis may form the basis for the development of a prognostic model and a risk score or risk groups [27]. The Cox proportional hazards regression model is most commonly used when time-to-event outcomes are of interest [29]. The selection of variables for the final model is usually done by stepwise selection. By play of chance different factors may be selected in different studies. An important additional analysis for a new marker is therefore to determine its prognostic ability in a model including all previously defined prognostic factors [27, 30]. Differences may also be due to small sample size, different assay techniques, different cut points for variables, inclusion of different subsets of patients, and different study endpoints.

8.3 Prognostic Factors in Early-Stage Disease

In the past when patients were still treated with radiotherapy alone, patients with stage I or II disease were staged with laparotomy and splenectomy to select patients suited for radiotherapy alone [31, 32]. In these patients the information on the extent and anatomic distribution of disease was very accurate, and numerous studies of prognostic factors showed that the anatomic extent of disease, measured as the number of involved lymph node regions, and the volume of disease in individual regions, in particular the mediastinum, were prognostically important [33–37]. An estimate of the total tumour burden, based on a combination of the number of involved regions and the volume of disease in individual regions, was shown to be by far the most important prognostic factor of all [38–40]. Prognosis seemed to be determined by the bulk of disease rather than the precise localisation in the body [41–44]. The prognostic significance of E lesions, localised extralymphatic lesions, is controversial, partly because of disagreement regarding the distinction between E lesions and stage IV disease [45]. Today, patients are no longer staged with laparotomy. Consequently, information on extent and distribution of the disease is less accurate in the individual patient. Therefore, additional factors become important, usually factors providing an indirect measure of the total tumour burden and possibly also the growth characteristics of the tumour.

Today, very few patients are treated with radiotherapy alone, except for patients with lymphocyte predominant histology. From early studies it is evident that the number of involved regions and size of mediastinal disease, B symptoms, histological subtype, age, gender, ESR, haemoglobin, and serum albumin are prognostically significant [14, 43, 46–50].

Most patients with early-stage disease are currently treated with a combination of chemotherapy and radiotherapy. A meta-analysis showed that combined modality therapy improves progression-free survival compared with radiotherapy alone but that it does not improve the chance of being cured of Hodgkin lymphoma (although with very long follow-up survival is superior with combined modality treatment due to an excess mortality from long-term complications in patients who relapse) [51–53]. In the meta-analysis the size of the reduction in the risk of failure in patients separated by stage, B symptoms, gender, and age was remarkably similar. Therefore, prognostic factors in patients treated with combined modality therapy do not seem to differ from the factors in patients treated with radiotherapy alone. Treatment of early-stage patients is now often tailored according to prognostic subgroups. Hence, in many publications patients are selected, making the detection of prognostic factors difficult. However, a number of studies have confirmed the significance of the prognostic factors mentioned above also for patients treated with combined modality [54–57].

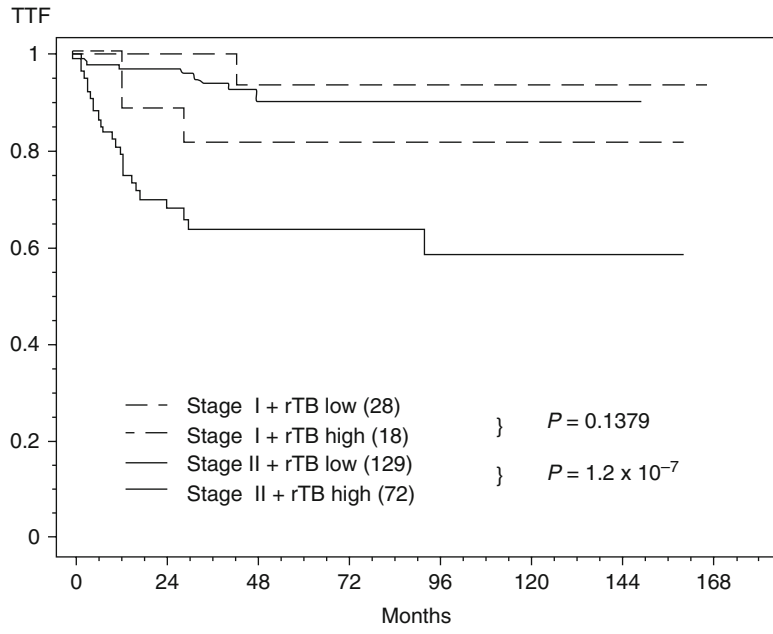

Fig. 8.2 Time to treatment failure curves for 46 patients with stage I and 201 patients with stage II disease divided according to whether their mean tumour burden normalised to body surface area (rTB) was below or above the mean value for each stage (Reprinted with permission from Gobbi et al. [59])

Most of the important prognostic factors are correlated with and provide indirect measures of the patient's total tumour burden [39, 40, 43]. Modern imaging with CT scans and FDG-PET scans makes it possible to directly quantitate the total tumour volume in each individual patient. Studies using these techniques have confirmed the pivotal prognostic role of the total tumour burden [58–65]. Figure 8.2 shows time to treatment failure for patients with stage I and II disease according to whether their mean tumour burden normalised to body surface area was below or above the mean value for each stage [59].

Functional imaging with FDG-PET is now an important part of staging and treatment evaluation of lymphomas. An early interim FDG-PET scan after one or two cycles of chemotherapy has been shown to be highly predictive of outcome after combined modality treatment [66–70]. However, in early-stage disease there are many false positives, the predictive value depends on the chemotherapy regimen used, and the majority of the patients with interim PET positivity were cured with combined modality therapy, yielding a positive predictive value of only 15 % [71]. The negative predictive value is very high in early-stage disease, as would be expected in a disease with a very good prognosis. The early interim FDG-PET scan may be regarded as an in vivo test of the chemosensitivity of the disease. As the result of the scan is not known at the outset, there is a methodological problem with this test. Strictly speaking, outcome according to the result of an early interim FDG-PET scan should only be measured from the time when it is available, and it should be regarded more as a predictive factor indicating the sensitivity to a particular treatment rather than as a usual prognostic factor.

From a clinical point of view, it would be better to be able to predict the outcome with a given regimen up front rather than having to initially administer possibly ineffective treatment. Recent research into molecular abnormalities in either tumour cells or non-malignant background cells has demonstrated important biomarkers that will hopefully in the future enable us to individualise treatment up front [72–78].

Table 8.1 lists the established prognostic factors in early-stage Hodgkin lymphoma. Today, early-stage patients are commonly divided into favourable and unfavourable groups, depending on various combinations of these factors; see below in Sect. 8.6.

Table 8.1 Prognostic factors in early-stage Hodgkin lymphoma

Number of involved lymph node regions
Large tumour mass, particularly mediastinal
Tumour burden
B symptoms
Histological subtype
Age
Gender
Erythrocyte sedimentation rate (ESR)
Haemoglobin
Serum Albumin
(Early interim FDG-PET scan)

Recently, chemotherapy alone has been used in early-stage patients. Relapse-free survival is poorer than with combined modality therapy, and a recent meta-analysis has shown that overall survival is also poorer for patients treated with chemotherapy alone [79]. Prognostic factors in this group of patients have not been analysed as large cohorts of patients with reasonable follow-up are not yet available.

8.4 Prognostic Factors in Advanced Disease

Advanced-stage patients are those requiring full systemic treatment. The term is not sharply defined. Stages IIIB and IV certainly form the core group. Most study groups also include all or selected stage IIIA and possibly selected stage I or II patients with multiple adverse prognostic factors.

The role of radiotherapy added to full systemic treatment in advanced stages is limited [80]. Thus, these treatment variants can be considered together in prognostic factor analyses.

Large data sets are important to reliably assess the independent contributions of single routinely documented prognostic factors which tend to be small to moderate (5–10 % in tumour control) [81]. Two very large data sets resulted from international cooperation: The International Database on Hodgkin's disease was set up in 1989, combining more than 14,000 individual patient data in all stages from 20 study groups in the MOPP era [14]. In 1995 the International Prognostic Factors Project on advanced Hodgkin's disease combined data of 5,141 advanced-stage patients mainly treated with doxorubicin-containing regimen [81].

8.4.1 Patients Treated with Conventional Chemotherapy with or Without Additional Radiotherapy

The most important patient-related prognostic factor for overall survival in advanced-stage Hodgkin lymphoma is age [82–90]. Elderly patients (>60–65 years) are often excluded from clinical trials study populations and treated in separate studies [91]. Prevalence of co-morbidity increases with age and risk of treatment-related mortality and toxicity-associated treatment reductions are increased [92, 93]. In patients up to 65 years of age, age (e.g. >45 years) is an independent prognostic factor for freedom from progression. This may be related to tumour biology as unfavourable histological subtypes are more frequent in the elderly [14]. The impact of age is amplified in overall survival as compared to progression-free survival due to compromised results of salvage treatment in elderly relapsed patients (e.g. [94]).

About two thirds of advanced-stage patients are men [14, 81]. Male gender is an independent, although quantitatively moderate, adverse prognostic factor within advanced stages [14, 81, 88, 95, 96].

The histological subtype plays a minor role among the tumour-related prognostic factors. Some studies report mixed cellularity or lymphocyte depletion subtypes as unfavourable prognostic factors [12, 97–99], several other studies do not confirm these findings [81, 82, 88, 89, 100]. Unfavourable subtypes are correlated with male gender, age, lack of mediastinal involvement, stage, systemic symptoms, and related abnormal blood parameters [14, 50]. Histology subtyping does not lend itself to prognostication, at least in multicentre settings, because of a relatively high reclassification rate under expert pathological review [101, 102].

Tumour burden is a main determinant of prognosis [59, 88, 89]. Tumour burden can be quantified directly from imaging [58, 103, 104].

Unfortunately this is rarely done routinely. A variety of clinical patterns of involvement can be seen as surrogates for tumour burden [103]: Information on the number of involved areas [89, 100], the amount of tumour in the spleen [105–108], the subdivision of stage III [105, 106, 109–111], and inguinal involvement (as marker for maximal nodal spread) [90] were reported as independently prognostic with older types of treatment.

Very large mediastinal bulk (e.g. >0.45 of the thoracic aperture) is relatively rare (<10 % of advanced disease) but has been reported as an adverse prognostic factor in some studies [90, 112], but not in others [113]. Large, but not very large (e.g. 0.33–0.45 of the thoracic aperture), mediastinal mass is not related to prognosis in advanced Hodgkin lymphoma treated with modern chemotherapy [81].

Several haematological and biochemical laboratory parameters form a cluster of interrelated prognostic indicators that mirror both tumour burden as well as inflammatory processes [47]. Decreased serum albumin [81, 84, 114, 115] and haemoglobin levels [14, 81, 83, 86] (or haematocrit [90]) as well as an elevated ESR [50, 116] or alkaline phosphatase [116, 117] are correlated [14, 50, 81, 118] with one another as well as with the presence of B symptoms [14, 119] and tumour burden [59]. Serum albumin [81, 114] (see Fig. 8.3) and haemoglobin level [81] (see Fig. 8.4) show a remarkably monotone relation to prognosis over their full range of variation. This

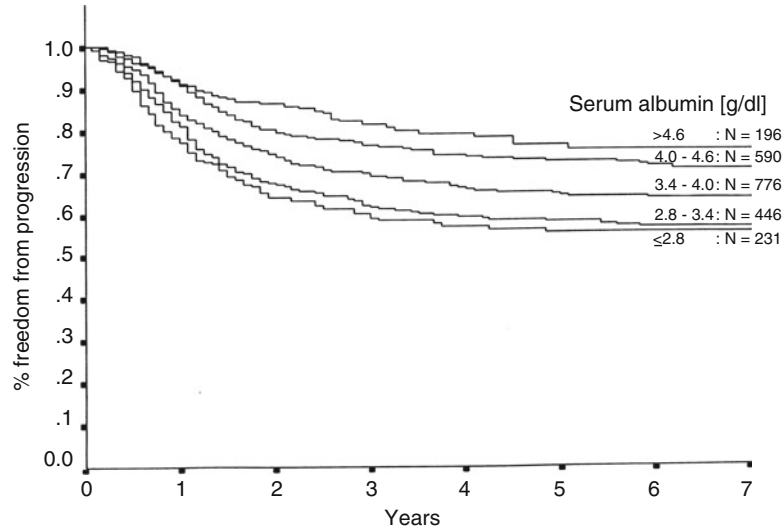

Fig. 8.3 Freedom from progression according to albumin levels for 2,239 patients with advanced disease in the International Prognostic Factors Project (Reprinted with permission from Hasenclever and Diehl [81])

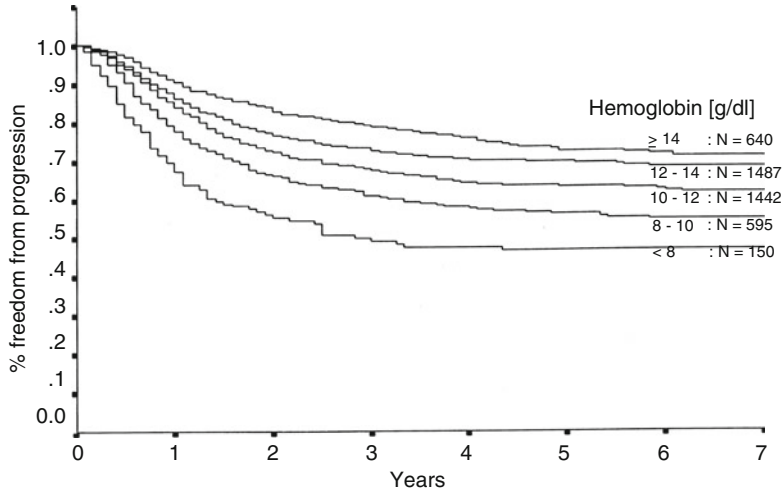

Fig. 8.4 Freedom from progression according to haemoglobin levels for 4,314 patients with advanced disease in the International Prognostic Factors Project (Reprinted with permission from Hasenclever and Diehl [81])

singles them out as the most informative prognostic factors in advanced-stage Hodgkin lymphoma. Given haemoglobin and serum albumin, the other members of this cluster, in particular B symptoms, lose their independent prognostic impact [81].

Stage IV marks dissemination of the disease to extranodal sites and is independently prognostic within advanced disease [14, 81, 99]. It remains controversial whether a specific organ involvement site carries a particularly bad prognosis within stage IV. Bone marrow involvement was an adverse factor in some studies [88, 90, 120], but not in others [121, 122]. Pleura, lung, or liver involvement have been reported as prognostically unfavourable [120, 121, 123, 124], but not in other studies [88, 90, 125]. The number of involved extranodal sites has been reported to be independently prognostic [83, 126, 127], but this could not be confirmed in the International Prognostic Factors Project [81].

Leukocyte and lymphocyte counts form a second correlation cluster of laboratory parameters. Analysing the joint distribution of leukocyte and lymphocyte counts in advanced Hodgkin lymphoma, there is a simultaneous shift away from the normal pattern towards both leukocytosis [81] and lymphocytopenia [83, 84, 86, 88] that carries independent prognostic impact [81]. These relatively unspecific measurements may indirectly capture dysregulation of haematopoiesis due to cytokine release by Hodgkin lymphoma cells.

Serum LDH plays a lesser role in Hodgkin lymphoma than in aggressive non-Hodgkin's lymphoma. Elevated serum LDH was found by some groups [83, 90], but was not confirmed in large data sets [14, 81]. The relevance of elevated β_2-microglobulin is controversial [128, 129]. Table 8.2 summarises the prognostic factors in advanced disease.

A plethora of biological parameters – levels of cytokines released by Hodgkin and Reed-Sternberg cells, soluble forms of membrane-derived antigens, and molecular markers – have been investigated for prognostic value. Many of these studies have been done in rather small data sets (N from 40 to 300). The soluble form of the CD30 molecule is released by Hodgkin and Reed-Sternberg cells and is detectable in the serum of virtually all untreated patients [130–133]. It maintains independent prognostic significance in multivariate analysis in moderately sized data sets [132, 134–136]. The relevance of cytokine levels requires further investigation [135].

Table 8.2 Prognostic factors in advanced Hodgkin lymphoma

Age
Gender
Histology
Stage IV disease
Tumour burden
Inguinal involvement
Very large mediastinal mass
B symptoms
Anaemia
Low serum albumin
High erythrocyte sedimentation rate (ESR)
High serum alkaline phosphatase
Leukocytosis
Lymphocytopenia
High serum lactic dehydrogenase (LDH)
High serum β2-microglobulin
(Early interim FDG-PET scan)

Most recent research focuses on the contexture of the HRS cells [78] characterising the composition of the so-called bystander cells in biopsy specimen. Proportions of various types of immune cells show strong variation. High density of CD68+ macrophages has been shown to be adversely prognostic with ABVD treatment [78, 137]. Tumour-associated macrophages (TAM), together with cells involved in a th1 immune response, possibly create an inflammatory environment favouring rapid lymphoma proliferation. In order to obtain a method usable in practice, a respective 23 gene expression signature measured from paraffin-embedded biopsies was shown to be predictive in advanced-stage ABVD-treated patients [77]. Further validation in large clinical trials is required.

An early interim FDG-PET scan after one or two cycles of chemotherapy has been shown to be highly predictive of outcome in advanced-stage Hodgkin lymphoma [68, 138–140]. In

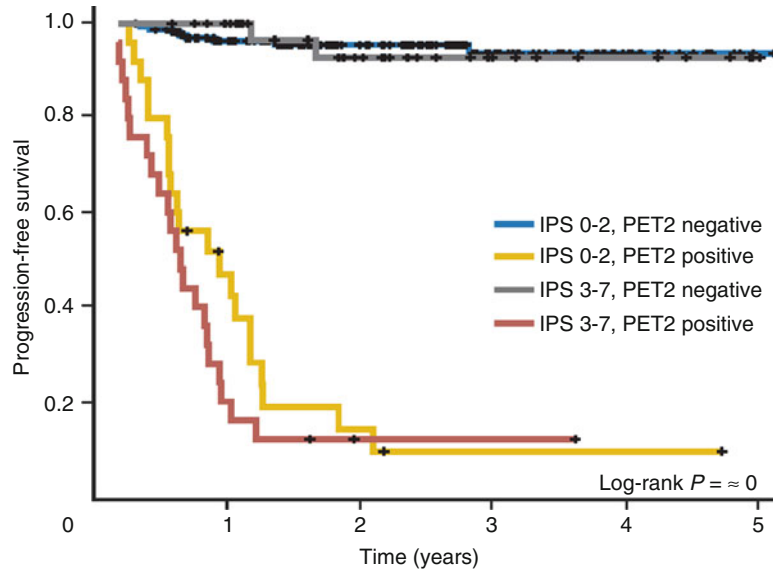

Fig. 8.5 Progression-free survival in 260 patients with advanced disease according to International Prognostic Score (*IPS*) and PET results after two cycles of ABVD (Reprinted with permission from Gallamini [141])

a large study of patients treated with ABVD, the prognostic value of an early PET scan completely overshadowed the role of the International Prognostic Score (see below) [141]. Figure 8.5 shows progression-free survival according to International Prognostic Score and the result of an early PET scan. However, an early FDG-PET scan is a marker for chemosensitivity, and it is therefore dependent on the specific given treatment. Concerns have been raised that the positive predictive value may be much lower in patients treated with more aggressive regimens such as BEACOPPesc [142].

8.4.2 Prognostic Indices or Scores in Advanced-Stage Hodgkin Lymphoma

Prognostic indices or scores for advanced Hodgkin lymphoma are clinically important to tailor treatment to patients: to select patients who may be overtreated and in whom treatment reduction may be considered or to select patients in whom standard treatment is likely to fail to eliminate the disease and in whom experimental approaches may be indicated.

Several groups developed prognostic indices or scores based on a few hundred cases and defined high-risk groups. Wagstaff et al. defined risk groups based on age >45, male gender, absolute lymphocyte count $<0.75 \times 10^9$/l and stage IV [117, 143]. Straus et al. proposed a five-factor score including age >45, elevated serum LDH, low haematocrit, inguinal involvement, and mediastinal mass >0.45 of the thoracic aperture [90]. Proctor et al. developed a numerical index to predict overall survival based on age, stage, haemoglobin level, absolute lymphocyte count, and bulky disease (>10 cm) [86, 112]. Gobbi et al. also set up a predictive equation based on age, sex, stage, histology, B symptoms, mediastinal mass, ESR, haemoglobin, and serum albumin [12, 144]. Low et al. defined a score based on age ≥45, serum albumin <35 g/l, and lymphocyte count <1.5 G/l and validated the score in a large historic BNLI data set [84, 145]. However, none of these indices have received general acceptance.

Gobbi et al. developed a parametrical model to derive numerical estimates of expected survival in all stages [95]. Seven factors were incorporated: stage, age, histology, B symptoms, serum albumin, sex, and involved area distribution (infradiaphragmatic disease or more than three supradiaphragmatic areas). This work was based on 5,023 patients in both early and advanced stages from the International Database

on Hodgkin's Disease [14]. Patients were treated rather heterogeneously with radiotherapy alone or mainly MOPP-type chemotherapy with or without radiotherapy. All these models used overall survival as main endpoint.

The International Prognostic Factors Project on advanced-stage Hodgkin lymphoma focused on freedom from progression [81]. Individual patient data were collected from 23 centres or study groups on 5,141 patients diagnosed as having advanced-stage Hodgkin lymphoma and treated with (mainly) doxorubicin-containing chemotherapy with and without radiotherapy according to a defined protocol. A prognostic score was developed from this data set in patients up to 65 years of age. The score is the simple count of how many of seven binary adverse prognostic factors (summarised in Table 8.3) of approximately similar prognostic impact are present: age ≥45, male gender, stage IV, albumin <4.0 g/dl, haemoglobin <10.5 g/dl, leukocytosis $>15\times10^9$/l, and lymphocytopenia (lymphocyte count $<0.6\times10^9$/l, or <8 % of leukocytes, or both).

Table 8.3 Adverse prognostic factors incorporated in the International Prognostic Factors Project score for freedom from progression in advanced Hodgkin's disease

Age ≥45 years
Male gender
Stage IV disease
Haemoglobin <10.5 g/dl
Serum albumin <4.0 g/dl
Leukocytosis $\geq15\times10^9$/l
Lymphocytopenia $<0.6\times10^9$/l or <8 % of white blood cell count

The International Prognostic Score (IPS) predicts 5-year tumour control rates in the range of 45–80 %. Each additional factor reduces the prognosis by about 8 %. Figure 8.6 shows freedom from progression according to the number of adverse prognostic factors for 1,618 patients in the International Prognostic Factors Project on advanced Hodgkin lymphoma.

Since its publication, the IPS has performed reasonably well in independent data sets [146–151]. With intensified BEACOPP chemotherapy, outcome uniformly improved in all IPS groups [146, 151]. Differences persisted but were quantitatively reduced.

Two publications compared several prognostic models [83, 148]. None of the models including the IPS is able to select either a very low-risk group (e.g. <10 % failure rate) nor a substantial very high-risk group (>50 %). The prognostic models only discriminate between relatively low-risk and relatively high-risk patients (e.g. IPS ≤2 versus IPS >2). Until new powerful, biologically more specific prognostic markers emerge, the IPS remains a workable method of

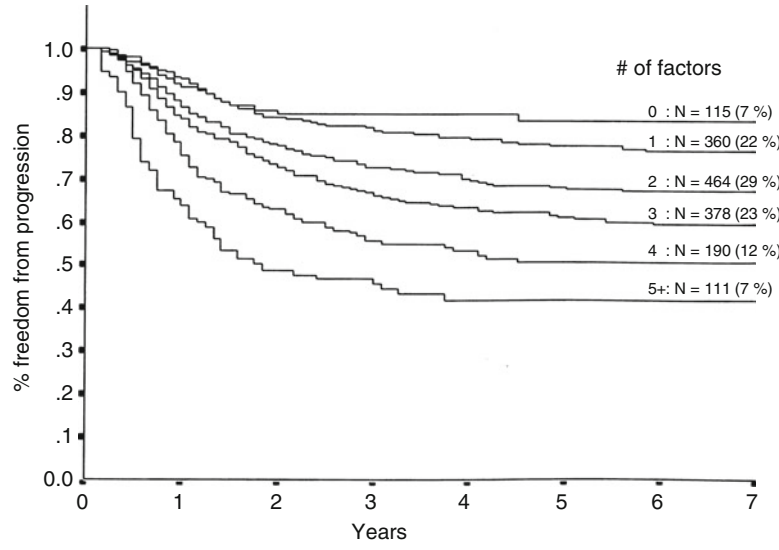

Fig. 8.6 Freedom from progression according to the number of adverse prognostic factors (see Table 8.3) for 1,618 patients with advanced disease in the International Prognostic Factors Project (Reprinted with permission from Hasenclever and Diehl [81])

choice. It is currently used in intergroup trials to select higher-risk advanced-stage patients for treatment intensification.

Several authors tried to extend the IPS beyond advanced stages. The IPS works nicely to predict outcome after autologous haematopoietic stem cell transplantation [152]. It appears to be moderately predictive in early and intermediate stages, extending the factor stage IV to include any extranodal disease [46, 153].

8.5 Prognostic Factors for Outcome After Relapse

Relapses of Hodgkin lymphoma after radiotherapy alone are qualitatively different from relapses after chemotherapy alone or combined modality therapy. Both freedom from second relapse and overall survival are considerably better for patients relapsing after radiotherapy alone than for the others [52, 154, 155]. However, today patients are rarely treated with radiotherapy alone except for patients with lymphocyte predominance subtype. Hence, it is now very rare for patients to relapse after radiotherapy alone.

8.5.1 Patients Treated for Relapse with Conventional Treatment

Patients relapsing after initial treatment with chemotherapy or combined modality therapy, whether for early-stage or advanced disease, have a poor prognosis with conventional chemotherapy. Durable remissions are obtained in only 10–30 % of cases [156–161]. The extent and duration of the initial remission is the most important prognostic factor for outcome after relapse. Patients who never achieve a complete remission have an extremely poor prognosis, patients who relapse within 12 months of complete remission have an intermediate prognosis, and patients who relapse more than 12 months after achieving complete remission have the best prognosis [156–159, 161, 162]. But even for the latter, long-term outlook is poor with conventional chemotherapy. Figure 8.7 shows survival curves

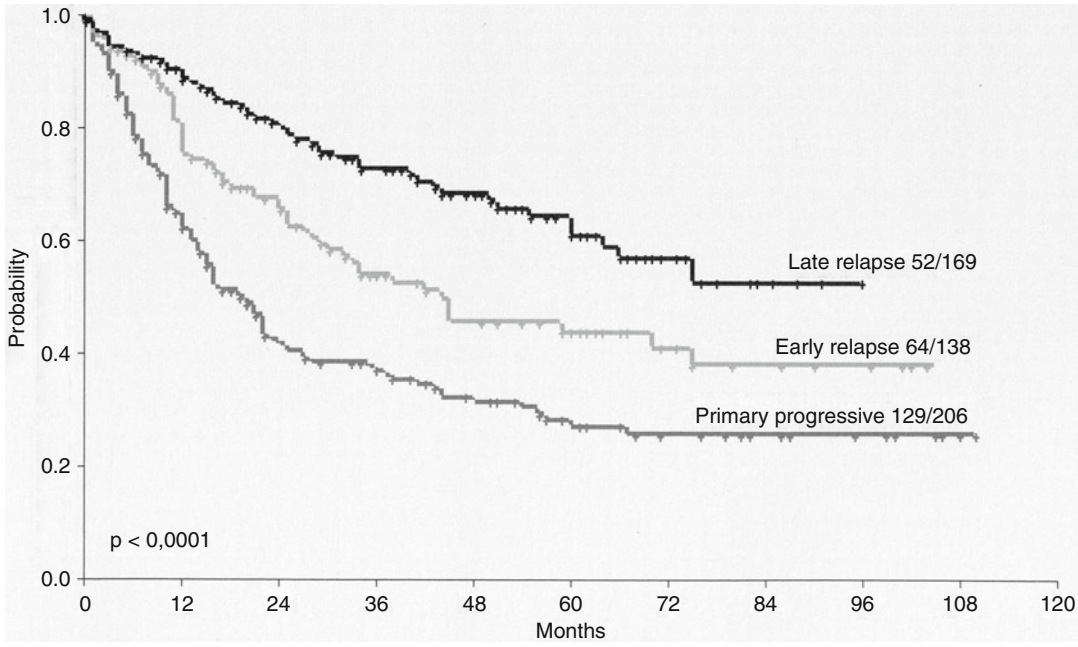

Fig. 8.7 Overall survival of patients with primary progressive, early relapse or late relapse of Hodgkin lymphoma, treated in the German Hodgkin Study Group from 1988 to 1999, primarily with conventional salvage (Reprinted with permission from Josting and Schmitz [163])

Table 8.4 Prognostic factors for outcome after relapse treated with conventional salvage treatment

Extent and durability of first remission
Extent of disease at relapse (relapse stage, extranodal relapse, ≥3 sites of relapse)
B symptoms at relapse
Haemoglobin at relapse
Histology
Age
Performance status

for patients relapsing after initial chemotherapy divided into these three prognostic groups [163]. Patients in second or higher relapse have a dismal prognosis [164–166].

The extent of disease at relapse is also independently significant for prognosis. Advanced stage, extranodal disease, and more than three involved sites at relapse are adverse prognostic factors [94, 156, 157, 161, 167]. Age, performance status, histology other than nodular sclerosis, B symptoms at relapse, and a low haemoglobin have also been shown to be significant [94, 156, 158, 159, 161, 162, 167]. Prognostic factors which have been shown to be independently significant for outcome after relapse after primary chemotherapy or combined modality therapy are summarised in Table 8.4.

A subgroup of patients relapsing after chemotherapy have anatomically limited relapse in nodal sites alone. For selected patients in this subgroup, radiotherapy with or without additional chemotherapy offers some chance of durable remission [159, 168–173]. Prognostic factor analyses indicate that patients suitable for this kind of relapse treatment are those relapsing exclusively in supradiaphragmatic nodal sites, with no B symptoms at relapse, with favourable histology (lymphocyte predominance or nodular sclerosis), and after a disease-free interval of 12 months or more [168, 169, 172, 174]. In patients with these favourable characteristics, durable remission with radiotherapy may be achieved in up to 50 % of cases.

8.5.2 Patients Treated for Relapse with High-Dose Chemotherapy and Stem Cell Transplantation

High-dose chemotherapy with stem cell transplantation is superior to conventional chemotherapy in patients relapsing after chemotherapy or combined modality treatment [175, 176]. It is the preferred treatment in patients able to tolerate intensive treatment. A number of prognostic factors are independently significant for outcome in this situation. The chemosensitivity of the disease is extremely important. Hence, the response to initial or salvage therapy, the duration of initial remission, and the number of prior failed regimens have been shown to be important for outcome [177–189]. Evaluation of response to salvage treatment before transplant by PET/CT can predict which patients are likely to achieve long-term remission [190–194].

The disease burden before transplantation is another important prognostic factor, and measures reflecting tumour burden such as stage of disease and bulky or extranodal disease at salvage have been shown to be independently significant [163, 177, 178, 186, 188, 195, 196]. B symptoms, a low haemoglobin, and an elevated serum LDH at relapse are also significant [178, 181, 185, 190, 197, 198]. A poor performance status is an important adverse prognostic feature [177, 179, 183], whereas age has not been significant in most series, probably due to the fact that most patients are relatively young at transplantation [188, 199–203]. Paediatric patients have the same outcome as adults [204].

The seven factor included in the IPS for advanced Hodgkin lymphoma have been examined [152]. Only low serum albumin, anaemia, age ≥45, and lymphocytopenia were independently significant. A simplified prognostic score including these four factors has been proposed, but it has not yet been tested in analyses including chemosensitivity and extent of prior therapy.

The prognostic factors known to be independently significant for outcome after high-dose chemotherapy and stem cell transplantation are shown in Table 8.5.

Table 8.5 Prognostic factors for outcome after high-dose chemotherapy and stem cell transplantation for refractory or recurrent disease

Chemosensitivity of the disease
Response to initial or salvage therapy
Duration of initial remission
Number of failed prior regimens
(FDG-PET scan after salvage therapy before transplant)
Disease burden before salvage
Stage of disease at salvage
Bulky disease at salvage
Extranodal relapse
B symptoms at relapse
Haemoglobin at relapse
Serum lactic dehydrogenase at relapse

For patients with disease recurrence after high-dose chemotherapy and autologous stem cell transplantation, prognosis is poor. Refractory disease at second-line treatment and short disease-free interval after transplant are poor prognostic factors [205, 206].

8.6 Use of Prognostic Factors in Clinical Trials

Optimising the treatment strategy for Hodgkin lymphoma is an attempt to make all prognostic factors disappear [207]. Ideally, when the amount and aggressiveness of therapy is adequately tailored to the patient's risk and disease burden, nearly all patients should have the same excellent prognosis. For example, in data of the German Hodgkin Study Group, early-, intermediate-, and advanced-stage patients nearly have the same failure-free survival with the advanced-stage curve visually in the middle, but many patients are probably overtreated [207]. Thus, with therapeutic progress prognostic factors should be expected to lose their prognostic value and become mere disease burden indicators.

As such, prognostic factors help to stratify the patient population into more homogeneous groups which are then treated with disease burden adapted treatment options. Together with strategies of response adaptation, this hopefully will lead to increasingly individualised and more adequate treatment.

8.6.1 Prognostic Factor Combinations Currently Used by Major Trial Groups

In clinical trials prognostic factors are primarily used in the definition of the study population (entry and exclusion criteria). Further uses include description of study population and adjustment for prognostic imbalances in the final analysis.

Inclusion criteria that are currently used differ by trial and study group. The Hodgkin lymphoma patients' population does not fall into naturally defined groups. Instead, prognosis varies on a continuum scale from low-risk minimal disease to high-risk maximally advanced disease. The delineation of study populations depends on the prognosis, the respective therapeutic approach, and the study group history.

The classical Ann Arbor [9] or Cotswold [19] staging systems are based on the anatomic distribution of the disease. The Ann Arbor staging system is well established and universally accepted and still forms the reference system for most definitions of study entry criteria. Most study groups currently use hybrid systems to define their study entry criteria, basically using stage and in addition presence or absence of unfavourable prognostic factors (also called risk factors in this context).

Most study groups divide Hodgkin lymphoma patient population into two (early versus advanced stages) or three (early versus intermediate versus advanced stages) separate trials or treatment groups. Attempts to use a fourth 'very favourable' early-stage group with minimal treatment have been abandoned by the EORTC [208]. Tables 8.6 and 8.7 describe inclusion criteria currently or recently used by study groups in early-stage and advanced disease, respectively.

Table 8.6 Eligibility criteria of recent or current studies in early stages. 'Early-stage' disease is typically defined by stage I or II and the absence of certain unfavourable prognostic factors

Study group	'Early stage' vs. 'intermediate stage'/'advanced disease' Early stage = stages I or II without any of the listed risk factors
EORTC (H7 study, H8 study, H9 study, H10 study)	Age >50 4+ involved nodal sites Erythrocyte sedimentation rate >50 mm/h or B symptoms and erythrocyte sedimentation rate >30 mm/h Bulky mediastinum (mediastinal thoracic ratio ≥0.35) (Infradiaphragmatic disease)
Milano	B symptoms
R-ABVD vs. ABVD-RT	Large mediastinal mass (>0.33 of the thoracic aperture)
GHSG (HD7 study, HD10 study, HD13 study, HD16 study)	Large mediastinal mass (>0.33 of the thoracic aperture) Massive spleen involvement E lesions Erythrocyte sedimentation rate >50 mm/h or B symptoms and erythrocyte sedimentation rate >30 mm/h 3+ involved lymph node areas
SWOG (9133) CALGB (9391) Cancer research UK RAPID study	B symptoms Mediastinal mass ≥1/3 maximum thoracic diameter Infradiaphragmatic presentation
NCI-C	B symptoms Mixed cellularity or lymphocyte depletion Age >40 years Erythrocyte sedimentation rate >50 mm/h 4+ disease sites
Stanford (G1 study, G5 study)	Constitutional (B) symptoms present at diagnosis Mediastinal mass equal to or greater than one-third the maximum intrathoracic diameter on a standing posteroanterior chest x-ray Any lymph node mass >10 cm in greatest trans-axial diameter Two or more extranodal sites of disease

EORTC European Organization for Research and Treatment of Cancer, *GHSG* German Hodgkin Lymphoma Study Group, *SWOG* Southwest Oncology Group, *CALGB* Cancer and Leukemia Group B, *NCI-C* National Cancer Institute of Canada, *ECOG* Eastern Cooperative Oncology Group

Table 8.7 Eligibility criteria of recent or current studies in advanced disease

Study group	Eligibility criteria for trials in advanced disease
EORTC (H34 study)	III/IV
BNLI Stanford V protocol Cancer research UK international RATHL study	Stage IB, IIB, IIIA, IIIB, or IV OR Stage IA or IIA with locally extensive disease (e.g. bulky mediastinal disease (e.g. greater than 0.33 of the maximum transthoracic diameter on routine chest x-ray or at least 2 extranodal sites of disease) or 'other poor risk features')
Manchester Lymphoma Group (VAPEC-B study)	I/II with B symptoms or bulk, III, IV
GHSG (HD9, HD12, HD15, HD18 studies)	IIB with bulk, massive spleen, or E lesion PS IIIA S PS IIIA, N with bulk, E lesion or elevated erythrocyte sedimentation rate CS IIIA bulk, massive spleen, E lesions, elevated erythrocyte sedimentation rate, or ≥3 lymph node areas IIIB/IV

Table 8.7 (continued)

Study group	Eligibility criteria for trials in advanced disease
Milano (MAMA study)	IB, IIA bulk, IIB, III, IV
GELA (H89 study) Milano (HD0801)	IIIB, IV
Stanford V study ECOG-2496 NCT00003389, CALGB-59905, CAN-NCIC-HD7, SWOG- E2496 Stanford	Stage I–IIA/B with massive mediastinal adenopathy Stage III or IV
'BEACOPP' intergroup study EORTC-20012 NCT00049595, ALLG-HD04, BNLI-EORTC-20012, CAN-NCIC-EORTC-20012, GELA-EORTC-20012, GELCAB-EORTC-20012, NORDICLG-EORTC-20012	Only higher-risk advanced stages III, IV with International Prognostic Score >2

EORTC European Organization for Research and Treatment of Cancer, *BNLI* British National Lymphoma Investigation, *GHSG* German Hodgkin Study Group, *GELA* Groupe d'Etudes des Lymphomes de l'Adulte, *NCI-US* National Cancer Institute of the United States, *SWOG* Southwest Oncology Group, *CALGB* Cancer and Leukemia Group B, *ECOG* Eastern Cooperative Oncology Group, *NCI-C* National Cancer Institute of Canada

Early stages comprise patients in whom full systemic treatment is considered overtreatment. As the prognosis in this group is excellent, study questions focus on how to cure with minimal toxicity or cost. Table 8.6 illustrates that early stages are typically defined as stage I or II without risk factors, with lists of unfavourable prognostic factors that vary by study group.

Studies in advanced stage include patients from the unfavourable end of the prognostic scale in which full systemic treatment is required. Trials either focus on improving results in high-risk advanced stages or minimising side effects of treatments felt to be satisfactory. Most study groups have stages IIIB/IV as the core group of advanced disease (Table 8.7). Studies differ in whether they include all stage IIIA patients, none, or only selected stage IIIA patients with unfavourable prognostic factors. Some groups also include stages I and II with 'systemic' risk factors.

Stages I and II with risk factors and stage IIIA form what may be called 'intermediate stages'. 'Intermediate stage' essentially denotes a grey zone between early and advanced disease. Study aims and the treatment modalities therefore overlap.

8.7 Conclusion and Future Aspects

As demonstrated above, a large number of variables have been shown to possess prognostic significance in Hodgkin lymphoma, both at presentation and in the relapse situation. Today, treatment is tailored to prognostic factors, with the aim of decreasing treatment intensity for patients with favourable characteristics in order to reduce toxicity, and increasing treatment intensity for patients with unfavourable characteristics with the aim of increasing cure rates. Different centres and groups use slightly differing criteria for treatment selection, which may make direct comparisons problematic. Some form of international harmonisation would therefore be desirable. The introduction of functional imaging with FDG-PET very early in the course of treatment as a marker for chemosensitivity may open up possibilities for tailoring treatment, but further research is needed before it is implemented for routine use. Recent research into molecular abnormalities in either tumour cells or non-malignant background cells has demonstrated important biomarkers that may in the future enable us to predict prognosis and response to specific treatment strategies up front. Such biomarkers will hopefully enable us to individualise treatment from the outset.

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Principles of Radiation Therapy for Hodgkin Lymphoma

9

Joachim Yahalom and Richard T. Hoppe

Contents

Abbreviations

3DCRT	Three-dimensional conformal radiotherapy
ABVD	Adriamycin (doxorubicin) bleomycin, vinblastine, and dacarbazine
AP-PA	Opposed anterior and posterior fields
ASCT	Autologous stem cell transplantation
BEACOPP	Bleomycin etoposide, doxorubicin, cyclophosphamide, procarbazine, prednisone
CR	Complete response
CT	Computed tomography
CTV	Clinical treated
EBVP	Epirubicin, bleomycin, vinblastine, and dacarbazine
EFS	Event-free survival
EORTC	European Organisation for Research and Treatment of Cancer

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_9, © Springer International Publishing 2015

FFTF	Freedom from treatment failure
GELA	Groupe d'Études des Lymphomes Adultes
GHSG	German Hodgkin Study Group
HL	Hodgkin lymphoma
IFRT	Involved-field radiation therapy
IMRT	Intensity-modulated radiation therapy
INRT	Involved-node radiation therapy
ISRT	Involved-site radiation therapy
LPHL	Lymphocyte-predominant HL
MOP-BAP	Mechlorethamine, Oncovin [vincristine], prednisone, bleomycin, Adriamycin (doxorubicin), and procarbazine
MOPP	Mustargen, Oncovin, procarbazine, prednisone
MSKCC	Memorial Sloan Kettering Cancer Center
NCCN	National Comprehensive Cancer Network
OS	Overall survival
PET	Positron emission tomography
PTV	Planned treatment volume
RT	Radiation therapy
STLI	Subtotal lymphoid irradiation
TLI	Total lymphoid irradiation
TSH	Thyroid-stimulating hormone

9.1 Principles of Radiation Therapy of Hodgkin Lymphoma

Radiation therapy (RT) is a major component of the current successful treatment of Hodgkin lymphoma (HL). For decades, radiation was used alone to cure the majority of patients with HL; RT is still the most effective single agent in the oncologic armamentarium for this disease, and RT alone remains the treatment of choice for patients with early-stage lymphocyte predominance HL (LPHL) and for selected patients with classical HL who have contraindications to chemotherapy [1]. Currently, most patients with HL are treated with combined-modality programs in which RT is given as consolidation after chemotherapy. As the role of RT has transformed over the years from a single modality into a component of combined-modality therapy, the classic principles of RT fields, dose, and technique have fundamentally changed.

The following principles guide the current strategy of using RT in HL:

1. RT as a part of a combined-modality program is radically different from the large-field, high-dose RT that was used in the past. The volume and doses that are required following chemotherapy are significantly less than when RT was used alone. In addition, the planning and delivery of RT has improved considerably over the last two decades.
2. Adding RT to chemotherapy improves disease control and allows the administration of shorter and less toxic chemotherapy programs for all stages of HL.
3. The new "mini-radiotherapy" for HL is well tolerated and results in a decreased risk for long-term morbidities that were associated with large-field, high-dose RT in the past [2].

9.2 The Evolution of Radiotherapy for HL

RT has been used in the management of HL since shortly after the discovery of X-rays [3, 4]. Initially it was used for local palliation, but careful study by pioneers in the field including Rene Gilbert and Vera Peters demonstrated that more aggressive treatment with higher doses and larger fields resulted in the cure of many patients, especially those who presented with limited disease [5, 6]. At Stanford, Henry Kaplan, advantaged by access to the medical linear accelerator, refined the RT concepts and together with Saul Rosenberg advocated strongly for the curative potential of RT [7]. RT remained the standard therapy for patients until effective chemotherapy was developed in the second half of the twentieth century. The success of chemotherapy and appreciation of adverse late events linked to RT such as secondary solid tumors and cardiac disease led to a decrease in the use of RT, but the eventual realization that its judicious application in lower doses and more tailored fields could

enhance curability and allow decrease in chemotherapy doses led to the development of programs of refined combined-modality therapy.

This refinement includes the use of very limited RT fields and the employment of advanced RT techniques that improve conformity and dose homogeneity. These field reductions require detailed clinical information to delineate the target accurately. Pre- and post-chemotherapy imaging is essential to define the tumor volume. The integration of computed tomography (CT) and positron emission tomography (PET)/CT treatment planning improves accurate RT volume design. A margin of safety to address subclinical disease and random and systematic positioning error is still necessary in field setup, but techniques to minimize inaccuracies in treatment planning and delivery continue to improve. The new concept of involved-site radiotherapy (ISRT), of tailoring of the radiation fields to include only the initially involved lymph node sites, further reduced the previously customary RT fields. Involved-node radiation therapy (INRT) is an even more restricted form of ISRT and is recommended only when detailed pre-chemotherapy imaging in the treatment position is available [8]. The volumes for ISRT and INRT were designed to be smaller than the classic IFRT that encompassed entire predefined anatomical regions. Recommendations for ISRT and INRT design have been established, and INRT has already been incorporated in combined-modality clinical trials in the European Organisation for the Research and Treatment of Cancer (EORTC) and the German Hodgkin Study Group (GHSG) [9]. Recommendations for ISRT design have recently been established by the International Lymphoma Radiation Oncology Group (ILROG), and ISRT has been incorporated into guidelines and clinical trials in North America and Europe [10].

9.3 Indications for Radiation Therapy in HL

It is important to distinguish between classical HL and nodular lymphocyte-predominant HL (LPHL). The management of each entity is different. Most patients with stage I–II LPHL may be treated with radiation alone, with curative intent, whereas combined-modality therapy is the standard approach for the majority of patients with classical HL.

9.3.1 Lymphocyte-Predominant HL

Most (>75 %) patients with LPHL present with stage IA or IIA disease; the disease is commonly limited to one peripheral site (neck, axilla, or groin) and involvement of the mediastinum is extremely rare. The National Comprehensive Cancer Network (NCCN) guidelines [10], the German Hodgkin Lymphoma Study Group (GHSG), and the European Organization for Research and Treatment of Cancer (EORTC) currently recommend limited radiation (IFRT or ISRT) as the treatment of choice for early-stage LPHL. Since the mediastinum is rarely involved, it need not be treated, thus avoiding the site most responsible for radiation-related short- and long-term side effects. In a recent retrospective study of 131 patients with stage IA disease, 98 % of patients obtained a complete response (CR), 98 % after extended-field RT alone, 100 % after involved-field RT alone, and 95 % after combined-modality therapy [11]. With a median follow-up of 43 months, only 5 % of patients relapsed and only three patients died. Toxicity of treatment was generally mild and was the greatest in association with combined-modality therapy. Two other studies, one from the Peter MacCallum in Australia [12] and another from the Dana-Farber in Boston, supported the adequacy of limited-field RT for LPHL and suggested a reduced risk of second tumors compared to extended-field RT [13].

Although there has not been a prospective study comparing extended-field RT (commonly used in the past) with involved-field RT, retrospective data suggest that the more limited fields are adequate [11, 14]. The radiation dose recommended is 30–36 Gy, with the higher dose reserved for bulky sites.

9.3.2 Classical Hodgkin: Early Stage

Over the last two decades, the treatment of stage I–II classical HL has changed markedly.

Combined-modality therapy consisting of short-course chemotherapy (most often ABVD) followed by reduced-dose radiation carefully directed only to the involved lymph node(s) has replaced radiation alone as the treatment of choice. Combined modality is the standard treatment for favorable and unfavorable presentations of early-stage disease in Europe, including the EORTC and GHSG. In the United States, chemotherapy followed by involved-site radiation therapy (ISRT) is the preferred treatment recommended by the NCCN guidelines [8, 10].

Several randomized studies have demonstrated that excellent results in stages I–II may be obtained with combined-modality treatment that includes only IFRT – more extensive fields of total or subtotal lymphoid irradiation (STLI and TLI) are not required.

The strategy to reduce the number of chemotherapy cycles and/or the radiation dose was tested by two large-scale randomized studies conducted by the GHSG. In the HD10 study, 1,370 patients with early favorable HL were randomly assigned in a 2×2 factorial design to receive either four or two cycles of ABVD followed by 30 or 20 Gy IFRT. The 8-year freedom from treatment failure (FFTF) and overall survival (OS) for all patients were 87 and 95 %, respectively. Most importantly, there were no significant differences between patients receiving the minimal treatment of ABVDX2 followed by IFRT of only 20 Gy and patients receiving more chemotherapy and/or more RT [15].

Patients with unfavorable early-stage HL ($n=1,395$) were randomized on the GHSG HD11 to receive either four cycles of ABVD or four cycles of baseline BEACOPP, followed by IFRT of either 30 or 20 Gy. Five-year FFTF and OS for all patients were 85 and 94.5 %, respectively. There was no difference in FFTF when BEACOPPX4 was followed by either 30 or 20 Gy, and similar excellent results were obtained with ABVDX4 and IFRT of 30 Gy. Patients who received ABVDX4 and only 20 Gy had a FFTF that was lower by 4.7 %. OS was similar in all treatment groups [16]. These large trials of the GHSG, as well as studies of the EORTC, have established combined-modality therapy with limited RT as the treatment of choice for patients with stage I–II disease.

Recently, trials utilizing results of interim PET scans that were performed after two or three cycles of ABVD to identify possible patients who may be treated with chemotherapy alone have been reported [17, 18]. In the UK RAPID trial, a management program with ABVD alone for patients with favorable stage I–II disease who had a negative PET after three cycles of ABVD was non-inferior (when analyzed as "intent-to-treat") to the use of combined-modality therapy [17]; however, when randomized groups were analyzed as treated, progression-free survival was significantly better for patients who received consolidative RT (HR 2.39 in favor of IFRT, $p=0.03$) [19]. Furthermore, the ABVD-alone arms of the EORTC HD10 trials for both favorable and unfavorable stage I–II patients who obtained a PET-negative status were terminated early due to an excess number of events when radiation therapy was not incorporated into the therapy (although substituted with more cycles of ABVD) [18]. In a recent systematic review, combined-modality treatment was found to improve tumor control and overall survival in patients with early stage Hodgkin lymphoma [20].

9.3.3 Advanced-Stage HL

Although the role of consolidative RT after induction chemotherapy in stages III–IV remains controversial, irradiation is often added in patients who present with bulky disease or remain in uncertain complete remission after chemotherapy [10]. The results of prospective studies testing the concept have been conflicting. A meta-analysis of several randomized studies demonstrated that the addition of radiotherapy to chemotherapy reduces the rate of relapse but did not show survival benefit for combined modality compared to chemotherapy alone [21].

The EORTC 20884 trial was a randomized study that evaluated the role of IFRT in patients with stage III–IV Hodgkin disease who obtained a CR after MOPP/ABV [22]. Patients received six or eight cycles of MOPP/ABV chemotherapy

(number of cycles depended upon the response). Patients who did not achieve a CR (40 %) were not randomized but were assigned to receive IFRT. Among the 333 randomized patients, the 5-year overall survival rates were 91 % (no RT) and 85 % (RT) ($p=0.07$). The authors concluded that IFRT did not improve outcome for patients with stage III–IV HL who achieved a CR after six to eight courses of MOPP/ABV chemotherapy.

The data indicated more cases of leukemia among patients who achieved a CR and were treated with RT, compared to those treated with chemotherapy alone, but surprisingly this was not in the case for the large group of patients who did not achieve a CR with chemotherapy, all of whom received RT. This suggests that the increased mortality on the randomized RT arm was a statistical aberration resulting from small number of events. Interestingly, among the partial responders after six cycles of MOPP/ABV, the addition of IFRT yielded overall survival and event-free survival rates that were similar to those obtained among patients who achieved a CR to chemotherapy. This suggests a key role for consolidative RT in stages III–IV when patients fail to achieve a complete response to chemotherapy.

There are other issues related to the EORTC study that compromise its interpretation. An unexpectedly small proportion of patients achieved a CR and were eligible for randomization. The MOPP/ABV regimen is quite toxic and has been abandoned for use in North America [23]. Relatively few patients with bulky disease were randomized on the trial, making interpretation of results in this important subgroup challenging. Lastly, the increase for secondary malignancy following combined-modality therapy was not evident in the PR patients, all of whom received even higher doses of RT to initially involved sites.

Another randomized study that evaluated the role of consolidation RT after CR to chemotherapy used ABVDX6 (the most common regimen currently used for advance-stage HL). This trial was conducted at the Tata Medical Center in India [24]. It included patients of all stages, but almost half were stages III–IV. A subgroup analysis of the advanced-stage patients showed a statistically significant improvement of both 8-year event-free survival (EFS) and 8-year overall survival with added RT compared to ABVD alone (EFS 78 vs. 59 %; $p<0.03$ and OS 100 vs. 80 %; $p<0.006$).

More recently, an analysis of 702 patients that participated in the UKLG LY09 prospective study to evaluate different chemotherapy regimens in advanced-stage and obtained a CR where analyzed according to the use of consolidation RT. Although more patients with bulky disease and partial response were in the RT group, PFS and overall survival were significantly better for 43 % of the patients who received RT in this study. Subgroup as well as multivariate analysis confirmed this benefit from additional RT [25].

PET imaging may also help to identify patients who will benefit from the addition of consolidative irradiation. In the GHSG HD15 trial, patients with advanced disease were treated with different schedules of BEACOPP chemotherapy. Following completion of chemotherapy, patients with residual disease greater than 2.5 cm underwent PET imaging. If the PET scan was negative, patients received no further therapy. If the PET scan was positive, the patients received 30 Gy consolidative RT. Although the group with a positive PET scan had a worse PFS than the PET-negative group (86.2 % vs. 92.6 %), the results in the PET-positive group were actually quite good, supporting the routine use of RT for patients in PR following chemotherapy [26].

The ECOG E2496 intergroup clinical trial tested treatment with ABVD versus Stanford V for patients with locally advanced (stages I–II with bulky mediastinal disease) or stage III–IV [27]. In this trial, the standard was for all patients (ABVD or Stanford V) with large mediastinal adenopathy to be treated with RT following chemotherapy. In addition, patients treated with Stanford V, which includes lower doses of doxorubicin and bleomycin than ABVD, were irradiated to other sites of disease initially greater than 5 cm [28]. The ECOG study showed equivalence for the ABVD and Stanford V treatment arms [27]. When these RT guidelines were not followed and RT was completely or partially omitted, the results were inferior [29].

In summary, patients in CR after full-dose chemotherapy program like MOPP/ABV or escalated BEACOPP may not need RT consolidation [26]. Yet, patients with bulky disease, incomplete or uncertain CR, or patients treated on brief chemotherapy programs will benefit from involved-field RT to originally bulky or residual disease [25].

9.3.4 RT in Salvage Programs for Refractory and Relapsed HL

High-dose therapy supported by autologous stem cell transplantation (ASCT) has become a standard salvage treatment for patients who relapse or remain refractory to primary therapy. Many of these patients have not received prior radiotherapy or have relapsed at sites outside the original radiation field. These patients could benefit from integrating radiotherapy into the salvage regimen.

Poen and colleagues from Stanford analyzed the efficacy and toxicity of adding cytoreductive or consolidative RT to 24 of 100 patients receiving high-dose therapy [30]. When involved sites were irradiated in conjunction with transplantation, no in-field failures occurred. While only a trend in favor of IF-RT could be shown for the entire group of transplanted patients, analysis restricted to patients who had no prior RT or those with relapse stages I–III demonstrated significant improvement in freedom from relapse. Fatal toxicity in this series was not influenced significantly by IF-RT.

At Memorial Sloan Kettering Cancer Center (MSKCC), a program that integrated RT into the high-dose regimen for salvage therapy was developed and included accelerated hyperfractionated irradiation (b.i.d. fractions of 1.8 Gy each) to start after the completion of reinduction chemotherapy and stem cell collection and prior to the high-dose chemotherapy and stem cell transplantation. Patients who had not been previously irradiated received involved-field RT (18 Gy in 5 days) to sites of initially bulky (>5 cm) disease and/or residual clinical abnormalities, followed by total lymphoid irradiation (TLI) of 18 Gy (1.8 Gy per fraction, b.i.d.) during an additional 5 days. Patients who had prior RT received only involved-field RT (when feasible) to a maximal dose of 36 Gy. This treatment strategy has been in place since 1985 with over 350 patients treated thus far. The first-generation program demonstrated an EFS of 47 % [31]. The recent report of the second-generation two-step high-dose chemoradiotherapy program indicated that after a median follow-up of 34 months, the intent-to-treat event-free survival and overall survival were 58 and 88 %, respectively. For patients who underwent transplantation, the EFS was 68 % [32]. Treatment-related mortality was 3 % with no treatment-related mortality over the last 10 years. The results of this treatment program in refractory patients were similar to those of relapsed patients [33]. Both groups showed favorable EFS and overall survival compared to most recently reported series. Recent report on quality of life and treatment-related complications of long-term survivors of the MSKCC program disclosed only a small number of late complications and is highly encouraging [34].

9.4 Radiation Fields: Principles and Design

In the past, radiation-field design attempted to include multiple involved and uninvolved lymph node sites. The large fields known as *mantle, inverted Y,* and *TLI* were synonymous with the radiation treatment of HL. These fields are now only rarely treated. *IFRT* encompasses a significantly smaller volume that was incorporated into many clinical trials of the past two decades. Extending this concept further, even more limited radiation fields termed INRT and ISRT have been introduced into investigational combined-modality programs and endorsed by guideline groups as the new standard RT field for HL [8–10]. Even when radiation is used as primary management for LPHL, the treatment fields should be limited to the involved site or to the involved sites and immediately adjacent lymph nodes.

The terminologies that define radiation fields may be confusing and create difficulties in

comparing treatment programs. However, general definitions and guidelines are now available and should be followed [8].

The following are definitions of types of radiation fields used in HL.

9.4.1 Extended-Field Radiotherapy

This field includes the involved lymph node group *plus* the adjacent clinically uninvolved region(s). For extranodal disease, it includes the involved organ plus the clinically uninvolved lymph node region.

It was common during the era of treatment with RT alone to treat large fields encompassing multiple lymph node regions, both involved and uninvolved. The field design that includes all of the supradiaphragmatic lymph node regions was referred to as the *mantle* field. The field that includes all lymph nodes sites below the diaphragm (with or without the spleen and called after its shape) is the *inverted Y*.

When all the major lymph node regions above and below the diaphragm were irradiated, this was referred to as *total lymphoid irradiation* (Fig. 9.1). If the pelvic nodes were not included, this was referred to as *subtotal nodal irradiation*. Extended fields are rarely used in modern treatment of HL.

9.4.2 Involved-Field Radiotherapy

These fields are limited to the clinically involved lymph node *regions* [35]. It was influenced by lymphoid regions that were defined in the Ann Arbor staging system for Hodgkin's disease [36]. An example of involved field of the neck is shown in Fig. 9.2 For extra-nodal sites, the field includes the organ alone (if no evidence for lymph node involvement). IFRT was commonly employed in clinical trials during the past two decades, but fields have now become even more restricted, termed *involved-node radiation therapy (INRT)* and *involved-site radiation therapy (ISRT).*

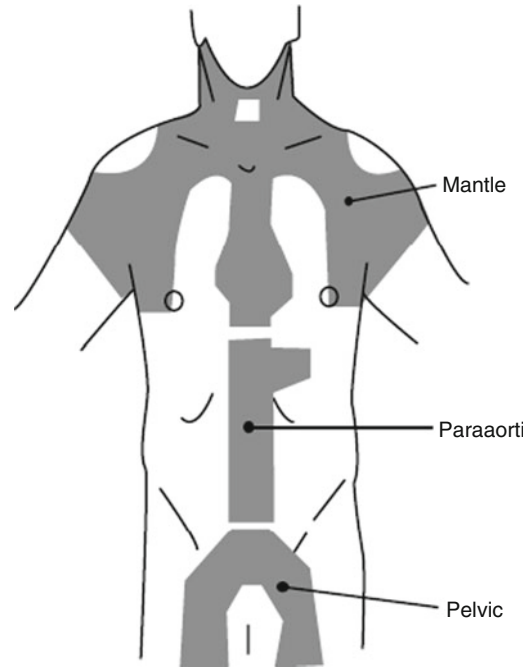

Fig. 9.1 Illustration of extended RT fields used in the past

9.4.3 Involved-Site Radiotherapy (ISRT): The New Standard Field for HL

The International Lymphoma Radiation Oncology Group (ILROG) has recently introduced a new field concept termed ISRT [8]. ISRT has already been adopted as the standard field by several organizations like NCCN [10]. In most cases, under the same clinical presentation and response, ISRT is smaller than IFRT and treatment volumes are determined by modern imaging information (like PET/CT) rather than by standard bony landmarks of the involved location. The concept of ISRT was developed as an extension of the INRT field concept that was conceived earlier (see below) [9]. In comparison to INRT, ISRT allows for more flexibility and use of clinical judgment when the strict criteria for INRT pre-chemotherapy imaging cannot be met. Indeed, in many practices pre-resection or pre-chemotherapy precise imaging is not available in the radiation treatment position. ISRT allows correcting for this deficiency. INRT

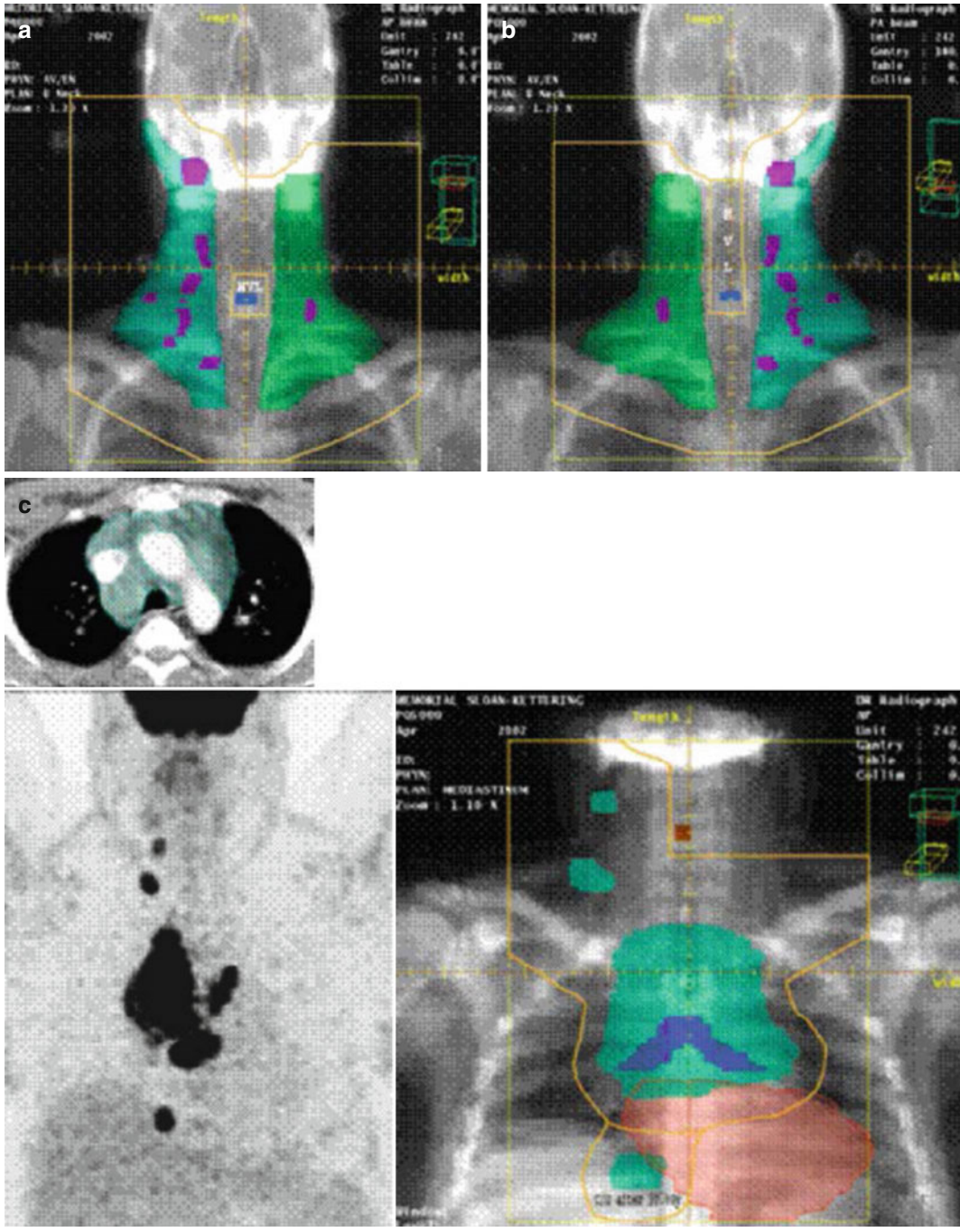

Fig. 9.2 Involved-field radiation therapy. (**a**) Stage I HL involving the right neck. (**b**) Stage II HL involvement of the right neck and the left lower neck. (**c**) Stage IIX HL with involvement of the right neck, bulky mediastinum, right hilum, and right cardiophrenic area. *Top*: CT scan display of the mediastinum; *bottom left*, FDG-PET mapping of disease involvement; *bottom right*, involved field covering the right neck, left supraclavicular area, mediastinum, and right costophrenic area

practically is a more optimal case of ISRT when accurate imaging allows tighter margins around the original volumes using the same concept discussed below.

Unlike IFRT that uses predetermined anatomical regional "borders" determined by bony landmarks that are easy to visualize during conventional 2-D simulation (now obsolete and replaced by CT or PET/CT simulation), ISRT and INRT incorporate the current concepts of volume determination as outlined in the ICRU Report 83 [37]. The modern fields are based on defining a gross tumor volume (GTV), a clinical target volume (CTV) that is expanded to a planning target volume (PTV). The PTV is then used to define beam coverage. This approach allows direct comparison with the diagnostic imaging, increasing the accuracy with which lymph node volumes are defined.

9.4.3.1 ISRT When RT Is the Primary Treatment

RT as single modality in HL is relevant for early stage lymphocyte-predominant Hodgkin lymphoma (LPHL). It may also be relevant in selected cases of early stage classical HL in patients who are not candidates for primary chemotherapy due to serious comorbidities.

In most clinical situations that require RT as the primary modality, the GTV should be readily visualized during simulation. In this situation the clinical target volume (CTV) should be more generous since microscopic or subclinical disease is more likely to be present without chemotherapy. The absence of effective systemic therapy in such cases should also influence dose decisions.

9.4.3.2 ISRT When RT Is Part of Combined-Modality Treatment

RT is often part of the treatment program for early stage classical HL following adequate systemic chemotherapy in all age groups. RT improves freedom from treatment failure even in PET-negative patients [17, 18] and allows treatment with smaller number of chemotherapy cycles [15]. In a recent systematic review, combined-modality treatment was found to improve tumor control and overall survival in patients with early stage Hodgkin lymphoma [20]. In patients with advanced-stage disease, localized RT may be used for residual lymphoma after full chemotherapy, or RT may be an integral part of some regimens for advanced-stage disease.

In this situation the GTV may be markedly affected by systemic chemotherapy, and it is therefore particularly important to review the pre-chemotherapy imaging and to outline the pre-chemotherapy volume on the simulation CT study as "pre-chemotherapy GTV" as well as the post-chemotherapy remaining CT and/or PET abnormality as "post-treatment" GTV.

9.4.3.3 Volume Definitions for Planning ISRT and INRT

These principles apply whether RT is used as primary treatment or as part of combined modality and are relevant when either involved-site radiotherapy (ISRT) or involved-node radiotherapy (INRT) is applied (see below). The difference between the two is the quality and accuracy of the pre-chemotherapy imaging which determine the margins needed to allow for uncertainties in the contouring of the clinical target volume (CTV).

Volume of Interest Acquisition

Planning RT for lymphoma is based on obtaining a three-dimensional (3D) simulation study using either a CT simulator, a PET/CT simulator, or an MRI simulator. If PET and/or CT information has been obtained separately or prior to simulation, it is possible to transfer the data either manually or electronically into the simulation CT data. Ideally, imaging studies that may provide planning information should be obtained in the treatment position and using the planned immobilization devices.

Determination of Gross Tumor Volume (GTV)

Pre-chemotherapy (or Presurgery) GTV

Imaging abnormalities obtained prior to any intervention that might have affected lymphoma volume should be outlined on the simulation study, as these volumes should (in most situations) be included in the CTV.

No Chemotherapy or Postchemotherapy GTV

The primary imaging of untreated lesions or post-chemotherapy residual GTV should be outlined on the simulation study and is always part of the CTV.

Determination of Clinical Target Volume (CTV)

CTV encompasses in principle the original (prior to any intervention) GTV. Yet, normal structures such as lungs, kidneys, and muscles that were clearly uninvolved should be excluded from the CTV based on clinical judgment. In outlining the CTV the following points should be considered:

(a) Quality and accuracy of imaging and transfer of volumes to simulation images
(b) Concerns of changes in volume since imaging
(c) Spread patterns of the disease
(d) Potential subclinical involvement
(e) Adjacent organs constraints

If separate nodal volumes are involved, they can potentially be encompassed in the same CTV. However, if the involved nodes are >5 cm apart, they can be treated with separate fields using the CTV-to-PTV expansion guidelines as outlined below.

Determination of Internal Target Volume (ITV)

ITV is defined in the ICRU Report 62 [37] as the CTV plus a margin taking into account uncertainties in size, shape, and position of the CTV within the patient. The ITV is mostly relevant when the target is moving, most commonly in the chest and upper abdomen with respiratory movements. The optimal way is to use 4D CT simulation to obtain the ITV margins. Alternatively, the ITV may be determined by fluoroscopy or estimated by an experienced clinician. In the chest or upper abdomen, margins of 1.5–2 cm in the superior-inferior direction may be necessary. In sites, e.g., the neck, that are unlikely to change shape or position during or in between treatments, outlining the ITV is not required.

Determination of Planning Target Volume (PTV)

PTV is the volume that takes into account the CTV (or ITV, when relevant) and also accounts for setup uncertainties in patient positioning and alignment of the beams during treatment planning and through all treatment sessions.

The practice of determining the PTV varies across institutions. The clinician and/or treatment planner adds the PTV and applies standard margins that depend on estimated setup variations that are a function of immobilization device, body site, and patient cooperation.

Determination of Organ at Risk (OAR)

The OARs are critical normal structures that, if irradiated, could suffer significant morbidity and might influence treatment planning or the prescribed dose. They should be outlined on the simulation study. Dose-volume histograms (DVH) and normal tissue complication probability (NTCP) should be calculated by the planner and the plan vetted by the clinician in consideration of this information.

9.4.4 Involved Nodal Radiotherapy (INRT): A Special Case of ISRT

INRT was originally developed and implemented by the EORTC to replace IFRT in prospective randomized studies (EORTC/GELA/IIL H10). It mandated accurate PET/CT information prior to chemotherapy and in a position similar the subsequent post-chemotherapy radiation therapy treatment position. The INRT technique reduces the treated volume to a minimum, but in order to be safe, optimal imaging both before and after

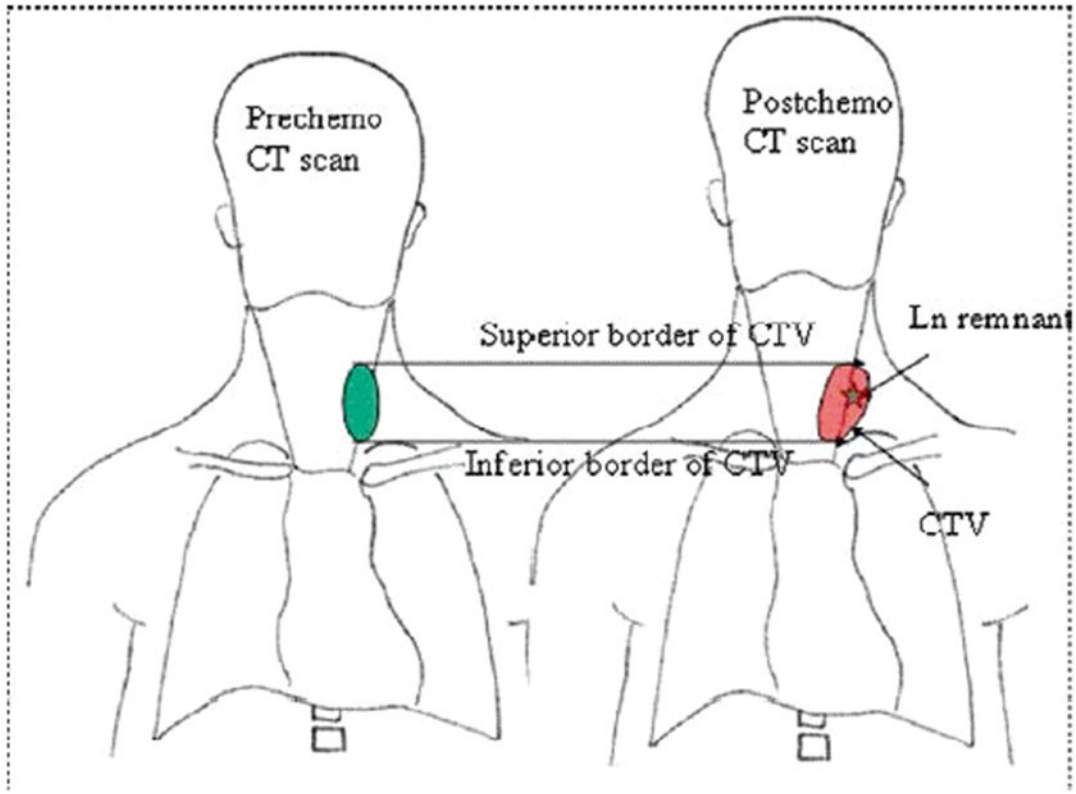

Fig. 9.3 Involved lymph nodes field. Single lymph node in the left lower neck prior to chemotherapy (*left*) and following chemotherapy (*right*). The border of the field encompasses the original volume of the node and not of the whole unilateral neck (as in IFRT approach) (Courtesy of Dr. Theodore Girinsky from Institute Goustave-Roussy)

chemotherapy is needed [9, 38]. INRT can therefore be regarded as a special case of ISRT where optimal imaging is available. PET/CT up front for staging purposes is mandatory as it has been demonstrated that PET/CT is the most accurate imaging method for determining disease extent in HL [39]. In order to enable image fusion of the pre-chemotherapy and the post-chemotherapy planning images, the pre-chemotherapy PET/CT scan should be acquired with the patient in the treatment position and using the same breathing instructions that will be used later for RT. Ideally, the patient should be scanned on a flat couch top, with the use of appropriate immobilization devices and using markers at skin positions which are visible in the imaging. During or following the completion of chemotherapy, a response assessment using PET/CT or contrast-enhanced CT should be performed. A planning CT scan is acquired with the patient in the same position as in the pre-chemotherapy CT scan. This highly conformal treatment technique has been shown to be safe, provided strict adherence to the principles above is maintained [40, 41]. INRT represents a special case of ISRT, where pre-chemotherapy imaging is ideal for post-chemotherapy treatment planning (Fig. 9.3).

9.5 Dose Considerations and Recommendations

Although doses in the range of 40–44 Gy were at one time recommended for the definitive treatment of patients with HL, these recommendations have been modified over time, especially in the context of combined-modality therapy or the treatment of patients with LPHL.

Clinical factors likely to impact disease control include tumor size, use of chemotherapy, disease extent, and technical considerations related to field design and accuracy of patient setup. The radiation dose is typically delivered in 1.8–2.0 Gy fractions. If significant portions of lung or heart are included, the dose per fraction can be reduced to 1.5 Gy. The available data indicate that the choice of fractionation is not critical for tumor control and that a schedule with minimal risk of damage to normal structures should be selected.

The GHSG evaluated dose in patients with stage IA to IIB disease without risk factors in a randomized trial of 40 Gy extended-field radiation alone vs. 30 Gy extended-field radiation with a boost of 10 Gy to the involved site of disease [42, 43]. There was no significant difference in outcome between the two arms of the study indicating that 30 Gy is sufficient for clinically uninvolved areas when RT is used alone. The optimum dose for clinically involved sites of disease with radiotherapy alone has not been tested in a randomized trial.

More relevant to current practice is the determination of the adequate radiation dose after treatment with chemotherapy. In many early studies, radiation doses were kept at ~40 Gy even after achieving a CR to chemotherapy; others reduced the dose in the combined-modality setting to 20–24 Gy with excellent overall results [44]. Studies of combined modality in advanced stage also used reduced doses of RT for patients who achieved a CR to chemotherapy and higher doses (~30 Gy) for patients in PR [22]. The pediatric groups addressing the concern of radiation effects on skeletal and muscular development also effectively reduced the dose of RT after combination chemotherapy to 21–24 Gy [45].

Several recent studies addressed the adequacy of low-dose IFRT following chemotherapy. A study conducted by the EORTC/GELA [46] randomized patients with favorable early-stage HL to 36, 20, or 0 Gy IFRT after achieving a CR to six cycles of EBVP. Because an excessive number of relapses occurred in the no-RT arm, this arm was closed early. There was no difference in EFS at 4 years between patients receiving IFRT 36 Gy (87 %) vs. 20 Gy (84 %).

A recent GHSG randomized study (HD 10) addressed the radiation dose question after short-course chemotherapy [15]. Patients with favorable stages I–II were randomized to receive either four or only two cycles of ABVD followed by IFRT of 30 or 20 Gy. At a median follow-up of 7 years, there was no difference in FFTF among the four arms. FFTF at 5 years was 93.4 % in patients treated with 30 Gy (91.0–95.2 %) and 92.9 % in those receiving 20 Gy (90.4–94.8 %). These results, taken together with the better tolerability and the lack of inferiority in secondary efficacy endpoints, lead to the conclusion that 20 Gy IFRT, when combined with even only two cycles of ABVD, is equally effective to 30 Gy IFRT in this very favorable group of patients [15]. The GHSG HD11 study targeted patients with unfavorable early stage and randomized them to either ABVDX4 or BEACOPPX4; either program was followed by either 20 or 30 Gy to the involved field. Five-year FFTF and OS for all patients were 85 and 94.5 %, respectively. There was no difference in FFTF when BEACOPPX4 was followed by either 30 or 20 Gy and similar excellent results were obtained with ABVDX4 and IFRT of 30 Gy. Patients who received ABVDX4 and only 20 Gy had FFTF that was lower by 4 %. OS was similar in all treatment groups [16]. These results suggest that 30 Gy should remain the standard IFRT dose following ABVD in unfavorable early-stage HL [16].

For patients with early stage LPHL, no advantage has been shown for doses over 30–35 Gy, which is the recommended dose to the CTV [12].

For patients with residual lymphoma after chemotherapy, the residual mass may represent a more refractory disease, and increasing the dose to the CTV to 36–40 Gy should be considered.

9.5.1 The Significance of Reducing the Radiation Dose

Recent studies clearly indicate that the risk of secondary solid tumor induction is radiation dose related. This was carefully analyzed for secondary breast and lung cancers as well as for other tumors [47–51]. While it will take more years of careful follow-up of patients in randomized studies to

display the full magnitude of risk tapering by current reduction of radiation field and dose, recent data suggest that this likely to be the case. In a recent Duke University study, two groups of patients with early-stage HL were treated with different radiation approaches over the same period. One group received radiotherapy alone, given to extended fields with a median dose of 38 Gy; the second group received chemotherapy followed by involved-field low-dose (median of 25 Gy) radiotherapy. While 12 patients developed second tumors in the first group and 8 of them died, no second tumors were detected in the second group. The median follow-up was 11.7 and 8.1 years, respectively [52]. Similar observations with an even longer follow-up were made by the Yale group [53]. In a study that used data-based radiobiological modeling to predict the radiation-induced second cancer risk, lowering the dose from 35 to 20 Gy and reducing the extended field to IFRT reduced lung cancer risk and breast cancer risk by 57 and 77 %, respectively [47].

More recently, a randomized study by a French Collaborative Lymphoma group (GOELAM) randomized favorable early stage HL patients to receive after ABVDX3 a conservative RT dose of 40 Gy to involved sites and 30 Gy to adjacent sites (CA) or in the "experimental group" (EA) to receive only 36 Gy and 24Gy to the adjacent sites [54]. Surprisingly, the 10-year incidence of severe or fatal complications was nil in the EA but reached 15.5 % in the CA ($p<.003$) and 11.1 % in the historical controls that received the higher dose. The 10-year FFTF and overall survival rates were similar for the 89 patients in the EA (88.6 and 97.8 %, respectively), for the 99 patients in the conservative arm (92.6 and 95 %, respectively), and for the 202 patients in the historical control group (91.9 and 92.9 %, respectively).

9.5.2 Dose Recommendations

Radiation alone (as primary treatment for LPHL) using ISRT
- Clinically involved and adjacent uninvolved nodes: 30–36 Gy

Radiation alone (as primary treatment for cHL [uncommon])
- Clinically involved sites: 30–36 Gy
- Clinically uninvolved sites: 30 Gy

Radiation following chemotherapy in a combined-modality program

Patients in CR after chemotherapy: 20–30 Gy
- For pediatric or adolescent patients: 15–24 Gy
- In some programs of short chemotherapy for bulky or advanced-stage disease (e.g., Stanford V), the recommended RT dose is 30–36 Gy

Patients in PR after chemotherapy: 30–40 Gy

9.6 New Aspects of Radiation Field Design and Delivery

The abandonment of large-field irradiation for most patients with HL permits the use of more conformal RT fields and introduction of other innovative RT techniques.

The change in the lymphoma radiotherapy paradigm coincided with substantial improvement in imaging and treatment planning technology that has revolutionized the field of radiotherapy. The integration of fast high-resolution computerized tomography into the simulation and planning systems of radiation oncology has changed how treatment volumes and relationship to normal critical structures are determined and planned. In the recent past, tumor volume determinations were made with fluoroscopy-based simulators that produced often poor-quality imaging requiring wide "safety margins" that detracted from accuracy and sparing of critical organs. Most modern simulators are in fact high-resolution CT scanners with software programs that allow accurate conformal treatment planning and provide detailed information on the dose volume delivered to normal structures within the treatment field and the homogeneity of dose delivered to the target. More recently, these simulators are integrated also with a PET scanner that provides additional tumor volume information for consideration during radiation planning.

Intensity-modulated radiotherapy (IMRT) is the most advanced planning and radiation delivery mode and is mainly used for small-volume

cancers that require high radiation doses (e.g., prostate and head neck cancers) or are adjacent to critical organs. IMRT allows for accurately enveloping the tumor with either a homogenous radiation dose ("sculpting") or delivering higher doses to predetermined areas in the tumor volume ("painting"). The end result of this new modality is highly accurate treatment with maximal sparing of normal tissues. In the radiotherapy of lymphoma, there are several clinical situations where IMRT provides a benefit: treatment of very large or complicated tumor volumes in the mediastinum and abdomen and head and neck lymphomas. IMRT also allows re-irradiation of sites prior to high-dose salvage programs that otherwise will be prohibited by normal tissue tolerance, particularly of the spinal cord [55] (Figs. 9.4a–d and 9.5a–c).

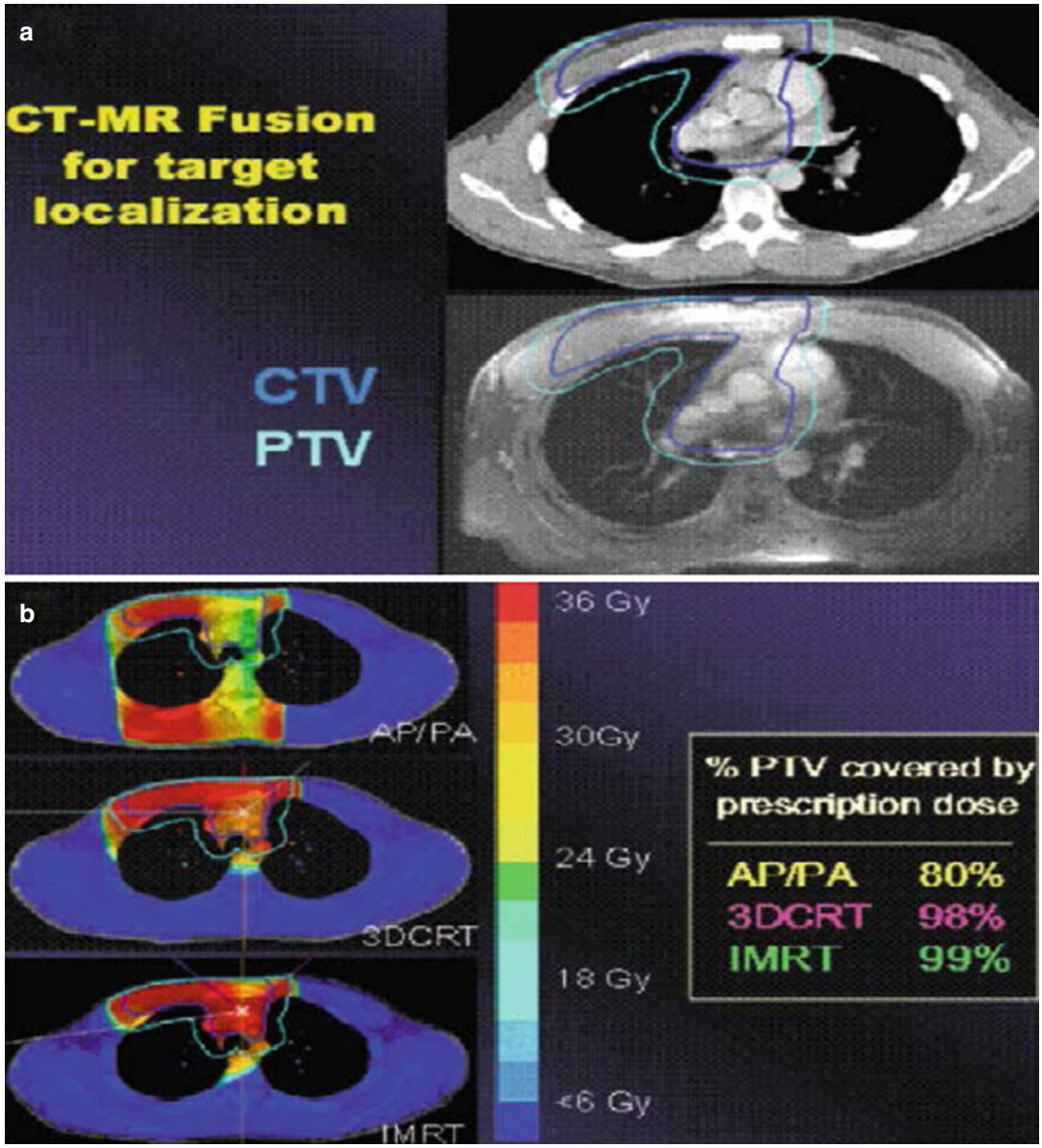

Fig. 9.4 (**a**) CT-MR fusion for target localization of HL involving the mediastinum and right chest wall. *CTV* clinical treatment volume, *PTV* planning treatment volume. (**b**, **c**) Treatment plans comparing AP/PA, 3D-CRT, and IMRT. *PTV* planning treatment volume, *AP/PA* opposed anterior and posterior fields, *3DCRT* three-dimensional conformal radiotherapy, *IMRT* intensity-modulated radiotherapy. (**d**) Comparison of lung complication probability of different plans

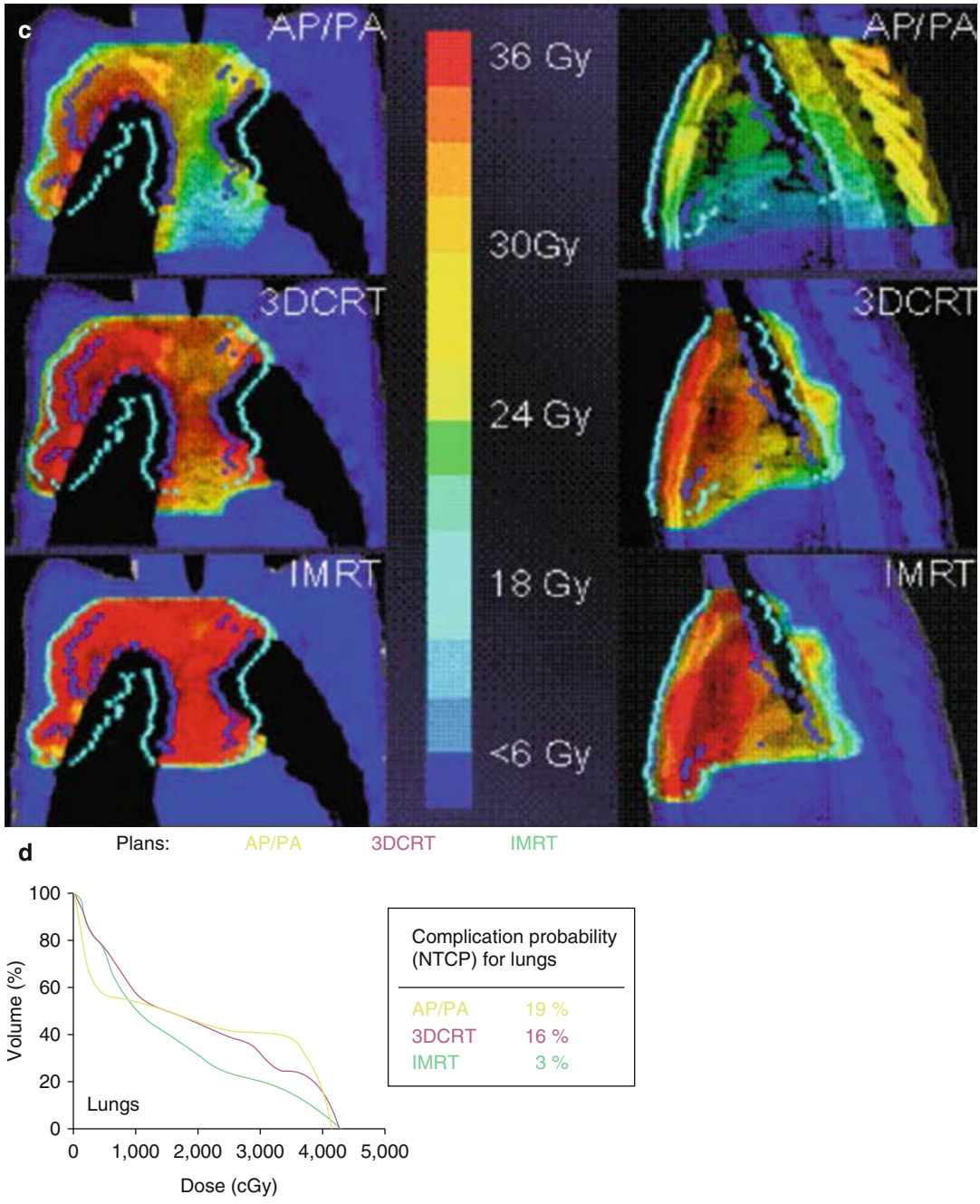

Fig. 9.4 (continued)

Another technical advance is the use of particle therapy (protons). Protons have the advantage of a more defined depth of penetration than photons (X-rays), which eliminates the "exit dose" of photons. Protons are potentially useful in re-treatment when dose constraints of critical organs have may be exceeded. Proton therapy is being evaluated for treating sites such as the mediastinum, where significant sparing of OARs including the heart, lungs, and esophagus may be better realized [56].

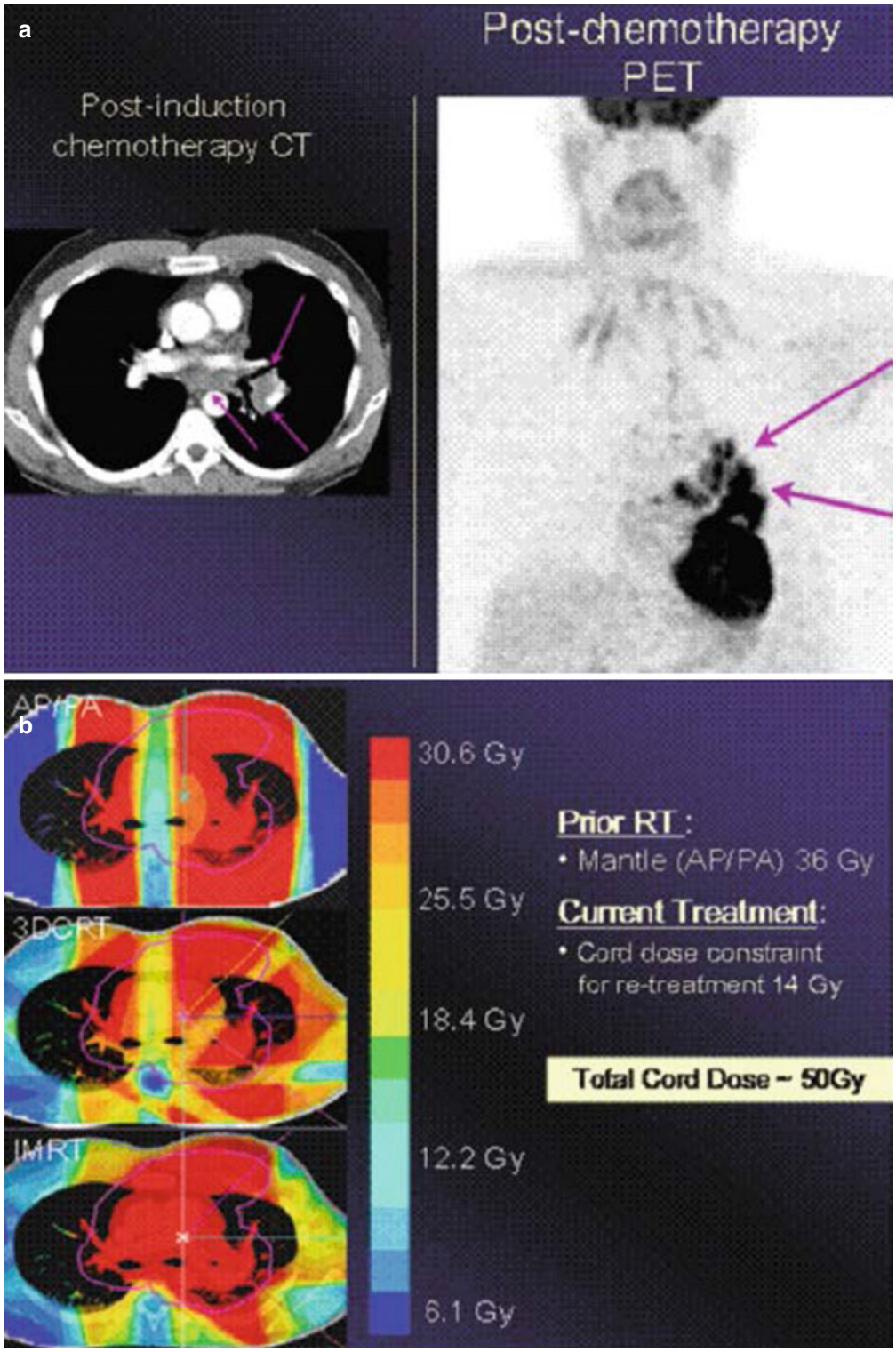

Fig. 9.5 (**a**) Use of IMRT for re-irradiation of a patient relapsing after ABVD and mantle-field irradiation to 36 Gy. (**b**, **c**) Treatment planning options for re-irradiation. *AP/PA* opposed anterior and posterior fields, *3DCRT* three-dimensional conformal radiotherapy, *IMRT* intensity-modulated radiotherapy

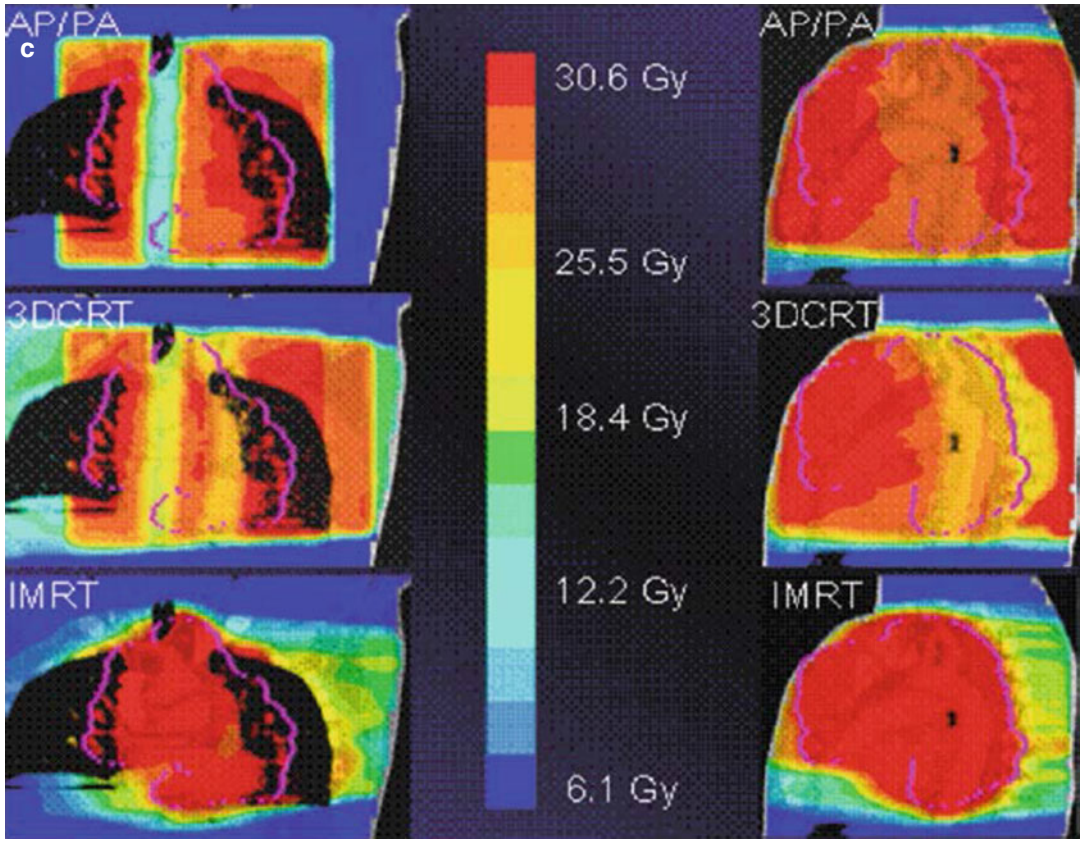

Fig. 9.5 (continued)

9.7 Common Side Effects and Supportive Care During Radiotherapy

Side effects of radiotherapy depend on the irradiated volume, dose administered, and technique employed. They are also influenced by the extent and type of prior chemotherapy, if any, and by the patient's age. Most of the information that we use today to estimate risk of radiotherapy is derived from strategies that used radiation alone. The field size and configuration, doses, and technology have all drastically changed over the last decade. It is thus misleading to judge current radiotherapy for HL, and inform patients on risks of radiotherapy using information of past radiotherapy that is no longer practiced.

It is of interest that most of the data of long-term complications associated with radiotherapy and particularly second solid tumors and coronary heart disease were reported from databases of patients with HL treated more than 25 years ago. It is also important to note that we have very limited long-term follow-up data on patients with HL who were treated with chemotherapy alone.

9.7.1 Acute Effects

Radiation, in general, may cause fatigue and areas of the irradiated skin may develop mild sun exposure-like dermatitis. The acute side effects of irradiating the full neck and portions of the mouth include dryness, change in taste, and pharyngitis. With the doses and techniques of irradiation currently employed in HL, these side effects are usually mild and transient. The main potential side effects of subdiaphragmatic irradiation are loss of

appetite, nausea, and increased bowel frequency. These reactions are usually mild and can be minimized with standard antiemetic medications.

Irradiation of more than one field, particularly after chemotherapy, can cause myelosuppression, which may necessitate short treatment interruption and very rarely administration of G-CSF.

9.7.2 Early Side Effects

Lhermitte's sign: Less than 3 % of patients who have treatment that includes long lengths of the spinal cord may note an electric shock sensation radiating down the backs of both legs when the head is flexed (Lhermitte's sign) 6 weeks to 3 months after mantle-field radiotherapy. Possibly secondary to transient demyelinization of the spinal cord, Lhermitte's sign resolves spontaneously after a few months and is not associated with late or permanent spinal cord damage. The risk is likely increased in the presence of prior neurotoxic chemotherapy such as vincristine or vinblastine.

Pneumonitis and pericarditis: During the same period, radiation pneumonitis and/or acute pericarditis may occur in <5 % of patients; these side effects occur more often in those who have extensive mediastinal disease. Both inflammatory processes have become rare with modern radiation techniques.

The consideration and discussion of radiotherapy and chemotherapy potential late side effects and complications is of prime importance and is detailed in Chap. 20.

9.7.3 Supportive Care During Treatment

It is important to prepare the patient to the potential side effects, and many organizations and cancer centers also provide written patient information regarding radiotherapy of lymphomas. Since some level of xerostomia may be associated with radiotherapy that involves the upper neck and/or lower mandible and mouth, attention to dental care is advised. If dryness is a concern, it is advised to arrange for an expert dental appointment for overall dental evaluation and consideration of mouth guards (from scatter) and/or supplemental fluoride treatment during and after radiotherapy.

Soreness of the throat and mild to moderate difficulty of swallowing solid and dry food may also occur during neck irradiation, with onset at a dose of ~20 Gy. These side effects are almost always mild, self-limited, and subside shortly after completion of radiotherapy. Skin care with and use of sunscreen is advised for all patients undergoing radiotherapy. Temporary hair loss is expected in irradiated areas and recovery is observed after several months.

We normally recommend a first post-RT follow-up visit 6 weeks after the end of treatment and obtain post-RT baseline blood count, standard biochemistry tests, as well as TSH levels (if there was neck irradiation) and lipid profile (if applicable) at that visit. Follow-up imaging studies normally commence 3 months after completion of treatment. Other follow-up studies are included in the NCCN guidelines for HL [10].

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Principles of Chemotherapy in Hodgkin Lymphoma

10

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Contents

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10.1 Historical Introduction

Hodgkin lymphoma was the malignant disease for which the possibility of cure with combination chemotherapy in the majority of patients was first realized. As such it has provided a model upon which studies in many other types of malignancy have been based, and it is interesting to follow the trajectory of knowledge from early single-agent work through combinations, combined modalities, increasing complexity, and most recently selective de-escalation. Patients with advanced disease represent a minority of those affected by Hodgkin lymphoma. However, these patients represent the group in which the development and effects of chemotherapy are most readily appreciated, since the role of radiation therapy is markedly less than in those with localized disease.

As early as 1942, four patients with HL were treated with nitrogen mustard by Wilkinson and Fletcher at Manchester Royal Infirmary, although a military embargo prevented the dissemination of this information [1]. Similar considerations applied to the bombing of the ship "USS Liberty" on December 3, 1943, in Bari and the hematological consequences of a nitrogen mustard gas leak among the survivors. Cornelius Rhoads, an American cancer researcher, was involved in their care and understood from his observations of the effects on the bone marrow and lymphoid tissue that nitrogen mustard derivatives might be effective against lymphoid and hematological

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_10,

malignancies [2, 3]. In 1958 another alkylating agent, cyclophosphamide, proved effective in non-Hodgkin lymphoma [4]. Shortly after this vinblastine was first shown to be an effective drug in HL, as was vincristine. Although encouraging, the early results of chemotherapy were modest, with most responses short lived after corticosteroids, alkylating, and spindle-cell agents [5–7] There was a prevalent view that only extensive irradiation could yield complete cures [8, 9].

One of the first modern randomized studies was the EORTC H1 trial, which investigated whether "adjuvant" chemotherapy (weekly vinblastine for 2 years) could improve the results over radiotherapy alone [10]. A durable advantage was seen in the chemotherapy arm for relapse-free survival (at 15 years 60 % vs. 38 %, $p<0.001$), although more than 50 % of patients with mixed cellularity histology developed recurrences [11]. To reduce the relapse rate, irradiation was extended to infradiaphragmatic nodal and spleen areas. Single-agent or doublet chemotherapy was added after radiotherapy, but no immediate attempt was made to use polychemotherapy, based upon the idea that the cure rate would depend upon the adequacy of irradiation [12, 13]. Two factors gradually undermined the dominance of strict pathological delineation and extensive irradiation as the basis of curative therapy in HL: The advent of accurate cross-sectional imaging by computed tomographic (CT) scanning and the recognition that relapses after irradiation alone had minimal impact on survival owing to the efficacy of salvage chemotherapy [14]. With the development of 4-drug combination therapy, which for the first time resulted in cures for advanced HL without the need for irradiation, the transition to systemic therapy began in earnest.

10.2 Chemotherapy Applied to Advanced-Stage HL: Theories and Practice

10.2.1 Classes of Active Classical Agents in HL (Table 10.1)

Almost every class of chemotherapy drug has been shown to have some efficacy in Hodgkin lymphoma, with the possible exception of the antimetabolite drugs such as 5-fluorouracil [15]. The original combination treatments were based upon evidence of single-agent activity among alkylating agents, vinca alkaloids, corticosteroids, and the hydralazine monoamine oxidase inhibitor, procarbazine. All of these produced response rates of over 50 % when used singly in patients not previously exposed to multi-agent chemotherapy (Table 10.1). Later entrants to this field included the antibiotic drugs doxorubicin and bleomycin, the nitrosoureas and dacarbazine, and the podophyllotoxins, all of which showed appreciable single-agent activity after prior combination regimens. More recently, newer cytotoxics such as gemcitabine have been introduced, often in combination with platinum drugs, and found to produce significant response rates in recurrent disease. In 2011 brentuximab vedotin, an antibody–drug conjugate, was approved in the United States and conditionally in Europe for treatment of relapsed or refractory Hodgkin lymphoma after autologous stem cell transplant or after at least two combination chemotherapy reg-

Table 10.1 Single-agent activity of cytotoxic drugs in Hodgkin lymphoma [15]

Drug	Overall response rate (%)	Complete response rate (%)
Single agents tested before combination chemotherapy		
Alkylating agents		
Chlorambucil	61	16
Mustine	63	13
Cyclophosphamide	54	12
Vinca alkaloids		
Vinblastine	68	30
Vincristine	60	36
Agents mainly tested after prior multi-agent therapy		
Dacarbazine	56	6
Nitrosoureas		
Carmustine	44	5
Lomustine	48	12
Antibiotics		
Doxorubicin	30	5
Bleomycin	38	6
Podophyllotoxin		
Etoposide	27	6
Antimetabolite		
Gemcitabine	22	0
Antibody–drug conjugate		
Brentuximab vedotin	75	34

imens in patients who are not transplant candidates. Approval was granted on the basis of an overall response rate of 75 % and a complete response (CR) of 34 % in a phase II trial in 102 Hodgkin lymphoma patients relapsed after or refractory to autologous stem cell transplantation, response rates approximately twice as high as those reported for other single agents [16]. This antibody–drug conjugate attaches an anti-CD30 antibody to a potent antimicrotubular agent, monomethyl auristatin (MMAE), by a protease cleavable linker. MMAE binds to tubulin and disrupts the microtubule network inducing cell cycle arrest and apoptosis, a mechanism of action similar to those for vincristine and vinblastine [17].

It is clear that Hodgkin lymphoma is broadly sensitive to phase-specific, cycle-specific, and non-cycle-specific agents, although it is less clear whether this is a feature of the malignant cells themselves or their associated inflammatory infiltrate, which may be critical to sustaining them. The development of combination therapies has been based mainly upon the use of agents with nonoverlapping toxicity as far as possible, and as cure rates have risen, the emphasis has fallen increasingly upon avoiding long-term side effects. The most important among these are infertility and myelodysplasia, mainly caused by the alkylating agents, pulmonary fibrosis caused by bleomycin and nitrosoureas, and cardiomyopathy related to anthracyclines, a risk increased by the concomitant use of mediastinal radiotherapy.

10.2.2 Polychemotherapy: Models and Comparative Clinical Studies (Tables 10.2 and 10.3)

10.2.2.1 The Skipper and Schabel L1210 Model

One of the earliest models to influence the design of chemotherapy treatments was the L1210 leukemia in mice studied by Skipper and Schabel: repeated administrations of a single effective drug result in a proportionally identical tumor cell kill with each treatment, so that if the cells proliferate with a constant tumor doubling time, cure can be obtained and time to cure can be predicted by knowing the initial tumor burden and the proportion of cells killed for a given dose and interval [43, 44]. Conversely if death will occur when reaching a specific number of malignant cells, there is a predictable likelihood of death based upon initial cell dose and treatment: "The cardinal rule of chemotherapy, the invariable inverse relationship between cell number and curability." Unfortunately, human tumors are far more complex than the L1210, the model confounded by the presence of resting stem cells, variable growth factors, and apoptosis along the tumor course, together with tumor cell heterogeneity, putting the cure of advanced HL beyond the reach of single chemotherapy agents, with inevitable relapse even after complete remission has been achieved [45, 46].

10.2.2.2 MOPP and Derivatives

Combination chemotherapy was first tested clinically in childhood acute lymphoblastic leukemia by Jean Bernard [47] who designed two doublets of cortisone–methotrexate and prednisone–vincristine at the same time as pursuing work on chemotherapy for Hodgkin lymphoma. Lacher and Durant were the first to use doublet combination chemotherapy in Hodgkin lymphoma with vinblastine and chlorambucil [48]. At the NCI, Freireich, Frei, and Katon added 6-mercaptopurine into the more effective VAMP regimen [7]. This led on to MOMP (cyclophosphamide, vincristine, methotrexate, and prednisone) and MOPP (mechlorethamine, vincristine, procarbazine, prednisone), developed by DeVita and Carbone, also at the NCI [49, 50]. Some of the critical features of success were prolonged treatment (6 months, more than any other regimen at the time); use of each drug at "optimal" dose and schedule with a sliding scale for dose adjustment according to marrow suppression; an interval of 2 weeks for recovery of normal tissue (marrow, GI epithelium), hopefully before HL recovery; and treatment with curative intent rather than palliation. MOPP provided an 80 % response rate and long-term disease-free and overall survival of almost 50 and 40 %, respectively [18]. The results have held up, and the 20-year analysis confirmed among 198

Table 10.2 Chemotherapy regimens designed for advanced Hodgkin lymphoma

Drugs	Dose mg/m^2	Route	Schedule
4-Drug regimen			
MOPP			q. 28 days
Mechlorethamine	6	iv	Days 1 and 8
Vincristine	1.4 (cap 2 mg)	iv	Days 1 and 8
Procarbazine	100	po	Days 1–14
Prednisolone	40	po	Days 1–14
MVPP			q. 42 days
Mechlorethamine	6	iv	Days 1 and 8
Vinblastine	6 (cap 10 mg)	iv	Days 1 and 8
Procarbazine	100	po	Days 1–14
Prednisolone	40	po	Days 1–14
ChlVPP			q. 28 days
Chlorambucil	6 (cap 10 mg)	po	Days 1–14
Vinblastine	6 (cap 10 mg)	iv	Days 1 and 8
Procarbazine	100	po	Days 1–14
Prednisolone	40	po	Days 1–14
COPP			q. 28 days
Cyclophosphamide	650	iv	Days 1 and 8
Vinblastine	6	iv	Days 1 and 8
Procarbazine	100	po	Days 1–14
Prednisolone	40	po	Days 1–14
ABVD			q. 28 days
Doxorubicin	25	iv	Days 1 and 15
Bleomycin	10 iu/m^2	iv	Days 1 and 15
Vinblastine	6	iv	Days 1 and 15
Dacarbazine	375	iv	Days 1 and 15
Hybrid regimens			
MOPP/ABV			q. 28 days
Mechlorethamine	6	iv	Day 1
Vincristine	1.4	iv	Day 1
Procarbazine	100	po	Days 1–7
Prednisolone	40	po	Days 1–14
Doxorubicin	35	iv	Day 8
Bleomycin	10 iu/m^2	iv	Day 8
Vinblastine	6	iv	Day 8
ChlVPP/EVA			q. 28 days
Chlorambucil	6 (cap 10 mg)	po	Days 1–7
Vincristine	1.4 (cap 2 mg)	iv	Day 1
Procarbazine	90	po	Days 1–7
Etoposide	75	po	Days 1–5
Prednisolone	50	po	Days 1–7
Doxorubicin	50	iv	Day 8
Vinblastine	6 (cap 10 mg)	iv	Day 8

Table 10.2 (continued)

Drugs	Dose mg/m^2	Route	Schedule
BEACOPP baseline			q. 21 days
Bleomycin	10 iu/m^2	iv	Day 8
Etoposide	100	iv	Days 1–3
Doxorubicin	25	iv	Day 1
Cyclophosphamide	650	iv	Day 1
Vincristine	1.4 (cap 2 mg)	iv	Day 8
Procarbazine	100	po	Days 1–7
Prednisolone	40	po	Days 1–14
Escalated regimens			
Escalated BEACOPP			q. 28 days
Bleomycin	10 iu/m^2	iv	Day 8
Etoposide	200	iv	Days 1–3
Doxorubicin	35	iv	Day 1
Cyclophosphamide	1,250	iv	Day 1
Vincristine	1.4 (cap 2 mg)	iv	Day 8
Procarbazine	100	po	Days 1–7
Prednisolone	40	po	Days 1–14
G-CSF		sc	Days 8–14
BEACOPP-14			q. 14 days
Bleomycin	10 iu/m^2	iv	Day 8
Etoposide	100	iv	Days 1–3
Doxorubicin	25	iv	Day 1
Cyclophosphamide	650	iv	Day 1
Vincristine	1.4 (cap 2 mg)	iv	Day 8
Procarbazine	100	po	Days 1–7
Prednisolone	80	po	Days 1–7
G-CSF		sc	Days 8–13
Weekly regimens			
Stanford V			4-week cycle
Doxorubicin	25	iv	Days 1 and 15
Vinblastine	6	iv	Days 1 and 15
Mechlorethamine	6	iv	Day 1
Vincristine	1.4 (cap 2 mg)	iv	Days 8 and 22
Bleomycin	5 iu/m^2	iv	Days 8 and 22
Etoposide	60	iv	Days 15 and 16
Prednisolone	40	po	Daily to week 10 and then taper
VAPEC-B			4-week cycle
Doxorubicin	35	iv	Days 1 and 15
Cyclophosphamide	350	iv	Day 1
Etoposide	75–100	iv	Days 15–20
Vincristine	1.4 (cap 2 mg)	iv	Days 8 and 22
Bleomycin	10	iv	Days 8 and 22
Prednisolone	50	po	Daily to week 6 and then taper

Table 10.3 Summary results of combination chemotherapy regimens used in first-line therapy of advanced Hodgkin lymphoma

Regimen	% CR	% EFS 5 years	% OS 5 years	% OS ≥7 years
MOPP [18–22]	67–81	40–60	65–73	51–70
MVPP [23–25]	72–76	60	65–75	
ChlVPP [26, 27]	57–74	55–60	66	65
ABVD [20, 28–33]	68–92	61–80	73–90	77
MOPP/ABVD alternating [20, 34, 35]	83–92	65–70	75–84	74
COPP/ABVD alternating [36, 37]	85	69	83	75
MOPP/ABV Hybrid [28, 35, 38, 39]	80–88	66–75	76–83	72
Stanford V [30, 31, 40, 41]	72–91	54–94	82–96	
VAPEC-B [42]	47	62	79	
ChlVPP/EVA [29, 42]	67	82–84	89	
BEACOPP baseline [37]	88	76	88	80
escalated BEACOPP [37]	81–96	87	91	86

patients a CR rate of 81 %, induction failures 19 %, relapses 36 %, and deaths 54 %. Of the 106 deaths, 30 occurred in patients free of disease; among the 92 patients who survived (46 %), only 2 had persistent HL [19]. These results have been reconfirmed in subsequent trials (Table 10.3) [20, 21, 51, 52]. Although the rise in cures from HL can be ascribed to multiple advances and not just the introduction of effective chemotherapy, the 1970 report convinced almost all groups treating HL to accept the inclusion of polychemotherapy (MOPP or MOPP derivatives) in the treatment strategy for localized as well as advanced disease. In almost all instances where a combined treatment was compared to irradiation alone, whether patients were staged or not with laparotomy, an advantage in terms of response, disease-, and relapse-free survival was observed when MOPP or a MOPP-derived chemotherapy was used [53].

Analysis of the results with MOPP has proven a fruitful source of information to design and interpret future studies. Thus, a complete response was seen to be a prerequisite for sustained remission, and a high percentage of complete responses was correlated with higher survival rates. Capping the vincristine dose at 2 mg may have been detrimental to the results. Patient and initial disease characteristics were good predictors of outcome, with confirmation of the adverse prognostic significance of systemic "B" symptoms. Maintenance treatment with intermittent MOPP or carmustine did not appear beneficial [54]. In patients treated previously by irradiation and chemotherapy, MOPP was less well tolerated and less effective [55]. Conversely, retreatment in relapsed patients but with initial remission lasting over a year proved efficient on the second occasion [56]. MOPP therapy carries consequences in terms of carcinogenicity, in particular with secondary acute myeloid leukemia [57, 58]. It is also responsible for impaired fertility in both men and women [59]. Immunosuppression related to the treatment or to the underlying disease brings risks of different types, in particular that of opportunistic infection [60].

There were many attempts to improve upon these results. The three best known MOPP-derived regimens have been MVPP, with vinblastine instead of vincristine, ChlVPP, and COPP, with an additional substitution of mechlorethamine, replaced by chlorambucil or cyclophosphamide (Tables 10.2 and 10.3). These alternatives have never undergone direct comparison, and historical controls are difficult to interpret. In addition the proportion of patients who have also had radiotherapy varies considerably between series. For example, in the NCI series, 32/198 patients had been irradiated prior to MOPP and 28/198 patients received TNI "to prevent recurrent disease in previously involved nodes" as consolidation after chemotherapy. MVPP, devised in Great Britain, proved easier to handle than MOPP (with less constipation and neurological toxicity) but was slightly more myelotoxic [23, 61, 62].

ChlVPP appeared more patient-friendly with minimal nausea/vomiting, constipation or neurologic toxicity, limited hematotoxicity, and the number of cycles adapted to the response: a maximum of 5 beyond CR. The 66 % OS rate in advanced HL was comparable to mustine-containing regimens, at lower toxic cost, for all of these acute toxicities, except myelosuppression [26, 63]. COPP is less myelotoxic than MOPP and is often used in children [64].

10.2.2.3 ABVD and Derivatives

The ABVD regimen was devised just 10 years after MOPP, in 1973, for intravenous-only administration at fixed 2-week intervals. Like MOPP, ABVD was a combination of hematotoxic and neurotoxic drugs. Two, doxorubicin and vinblastine, had been shown highly effective in HL. The results with dacarbazine were numerous but possibly less convincing, and bleomycin was also felt to have considerable potential [10, 45, 65–67]. By comparison to MOPP, hematotoxicity after ABVD was predictable, noncumulative, and milder as a result of the intravenous dosing and short intervals. Further, ABVD was far less neurotoxic. Bonadonna developed ABVD at the Milan NCI with the intention "to compare the efficacy of ABVD with MOPP, and to demonstrate absence of cross-resistance between the two regimens" [68]. The results of MOPP were well established, and the potential of ABVD in terms of "alternative to MOPP to be used either in MOPP failures or in sequential combination with MOPP" was clearly in the mind of the authors, based on these very early results achieved in 45 patients. No significant cardiac toxicity was seen in this first series, probably because of the relatively small cumulative dose of doxorubicin (6 cycles = 300 mg/m^2), the short follow-up, and the small numbers. Conversely, bleomycin pulmonary toxicity was apparent from the outset, while the effects upon fertility were initially overestimated through short observation which did not take into account the reversal of temporary amenorrhea in some women.

It took a surprisingly long time for ABVD to be accepted as a standard of care, and it was initially considered only as a salvage treatment in MOPP failures. However, the Milan group undertook a larger trial, comparing MOPP and ABVD directly in patients with stage IIB, IIIA, and IIIB HL. In 232 patients, a combined modality approach of three cycles before and after extensive irradiation yielded an 80.7 % CR rate after MOPP/radiotherapy and 92.4 % after ABVD/radiotherapy ($p < 0.02$). At 7-year follow-up, ABVD surpassed MOPP for FFP (80.8 % vs. 62.8 %; $p < 0.002$), RFS (87.7 % vs. 77.2 %; $p = 0.06$), and OS (77.4 % vs. 67.9 %; $p = 0.03$). With longer follow-up, the disadvantages of MOPP in terms of fertility damage and second MDS/leukemia were also more apparent.

Currently, ABVD is considered by most investigators as the standard chemotherapy for most patients with HL, with the possible exception of high-risk patients with advanced disease and poor prognostic features. Reasons to avoid ABVD relate to previous lung impairment and decreased left ventricular ejection fraction. Hematological toxicity is usually moderate, and ABVD may be delivered safely at full dose and on schedule to a nonselected average population of adult patients without the need to modify doses in the presence of neutropenia [69]. The most frequent serious toxicity with ABVD is pulmonary fibrosis, which may be fatal and precludes its use in most patients over 65 [70]. The discontinuation of bleomycin for toxicity during ABVD treatment does not appear to have an adverse effect on outcome, which calls into question the importance of bleomycin in the ABVD regimen [70–73]. This has recently been tested prospectively in a randomized study of patients showing a good early response to ABVD, where patients either continued all four drugs or AVD only [17]. The initial results confirmed the excess toxicity associated with bleomycin, particularly reduced lung function and more instances of venous thromboembolism, and the results of the efficacy comparison are awaited.

10.2.2.4 Alternating and Hybrid Regimens

Although the study of drug resistance mechanisms and mathematical modeling was widely pursued during the 1970s, the first alternating regimen

emerged from the plan by Bonadonna to use the ABVD regimen together with MOPP as a means to test it in initial therapy [22]. This was based on the observation of a higher salvage rate with ABVD than with MOPP in patients previously treated with MOPP and the deduction that ABVD could be "non-cross resistant". By contrast with the pragmatic testing of alternating regimens, hybrid regimens had their origins in a more scientific approach, being designed to circumvent innate and acquired mechanisms of resistance as modeled by Goldie and Coldman [74, 75].

MOPP/ABVD Alternating Therapy

ABVD had yielded good results when compared to MOPP. Despite the small numbers of patients studied, a study comparing MOPP alone with a monthly alternation of MOPP and ABVD was considered the logical next move. The originators felt no need for a large study, nor long follow-up, because the first results were quite convincing and appeared rapidly. At 5-years MOPP/ABVD alternation, compared to MOPP alone, yielded a superior CR rate (92 % vs. 71 %; $p=0.02$), FFP (70 % vs. 37 %; $p<0.0001$), and disease-free survival (84 % vs. 54 %; $p<0.005$) [22, 34]. Similar results were found with MOPP/ABVD and involved field radiation therapy at Memorial Sloan Kettering Cancer Center [76–78]

It took more than 20 years to confirm the superiority of MOPP/ABVD over MOPP [20, 79]. There are several reasons for this: the original studies were small and lacked follow-up by comparison to the extensive evidence base for MOPP; ABVD, with bleomycin and without corticosteroids, was considered more toxic than MOPP when combined with irradiation, especially to the mediastinum, and the biological rationale behind the superiority of the alternating regimen was not clearly understood. This critical question was investigated by the CALGB through the addition of a third arm, ABVD alone, and by the SFOP in children. In neither study did the alternating regimen prove superior to ABVD alone, suggesting that it is the superiority of ABVD over MOPP which is the key determinant of outcome rather than the use of multiple chemotherapy drugs. This hypothesis is supported by the design of the CALGB trial where an unbalanced number of cycles (12 MOPP/ABVD vs. 6 ABVD) should favor the alternating arm. If Bonadonna's initial results demonstrating the superiority of ABVD over MOPP had been widely accepted, despite the small numbers, the next logical trial would have been to test ABVD versus MOPP/ABVD, which could have saved 20 years of studies. In the event, alternating MOPP and ABVD was considered a good compromise of old and new and served as the regimen to test against MOPP, at least in Europe [52].

The Goldie and Coldman Model and the "Hybrid" Regimens

Goldie and Coldman described the relationship between tumor drug sensitivity and spontaneous mutation rates. This mathematical model was the rationale for the development of "hybrid" regimens that all introduced many different drugs, with different mechanisms of action, early in the course of treatment and with a rapidly cycling schedule, to erase preexisting resistance to one or the other drug [74, 75]. The MOPP/ABV hybrid regimen and the similar ChlVPP/EVA were widely used for over two decades [24, 38, 39]. Several features explain this: a high and durable complete response rate, the short duration of the program by comparison to alternating therapies, the overall decrease in the cumulative doses of doxorubicin and mechlorethamine, and less extensive irradiation required for residual disease.

Unfortunately, although theoretically attractive, this concept did not bring any advantage compared to the conventional four-drug or alternating regimens. In the GHSG HD6 trial, HL control was similar with the hybrid COPP/ABV/IMEP and alternating COPP/ABVD, with more toxicity in the hybrid [36]. Two later trials, designed to test the benefit of the early introduction of all drugs in a rotating fashion, actually favored ABVD in that the control of lymphoma was the same, but the toxicity more severe with the hybrid regimens [28, 29]. Both the intergroup and the UK studies reported similar findings, with a hazard ratio of 10.5 for grade 3/4 mucosal toxicity and 3.94 for grade 3/4 infection in the

UK study. In the intergroup study, there was a small but worrying increase in the incidence of myelodysplasia or acute myelogenous leukemia, with 11 cases in patients randomized to the hybrid arm and two among patients randomized to ABVD (*P* 0.011). The results of these trials further established ABVD as a standard chemotherapy for advanced-stage Hodgkin lymphoma, at least in North America.

10.2.2.5 The Dose–Response Relationship: Norton and Simon Model

Much of the thinking about how to maximize the cure rate in lymphoma has centered upon the relationship between dose and response to cytotoxic therapy. Theories of tumor cell ecology have suggested that as the mass of disease is reduced, the growth fraction may rise. This, together with the assumed selection of resistant subclones, underlies the idea that tumor eradication is dependent upon the delivery of treatment at adequate dose intensity early in a course of treatment. If doses are too small or too infrequent, the fractional cell kill might be expected to decline and allow the emergence of resistance [80].

Three prospective clinical trials have directly addressed the question of dose versus response using the same chemotherapy drugs in both arms. In the first-line treatment of advanced disease, a critical study was performed by the German Hodgkin Study Group (HD9), as detailed later on, in which patients were randomized between the baseline BEACOPP regimen and an escalated regimen, with the doses of doxorubicin, cyclophosphamide, and etoposide increased to 140, 185, and 200 %, respectively. This resulted in an increase in freedom from treatment failure at 5 years from 76 to 87 % ($p<0.01$) which was translated into a small but significant improvement in survival on longer follow-up (80 % vs. 86 % at 10 years, $p=0.0053$). This was at the cost of an increased risk of myelodysplasia and acute leukemia in the escalated arm but at a frequency too low to reverse the gain in survival from better control of the lymphoma [81].

There are two randomized studies for recurrent disease which have yielded similar data on the dose–response relationship. The UK group compared the myeloablative BEAM regimen to mini-BEAM, which uses the same drugs at non-myeloablative doses. The high-dose treatment yielded superior progression-free survival ($p=0.005$) although the trial was closed with only 44 patients recruited and had insufficient power to demonstrate a survival advantage [82]. A study of similar design was conducted by the German group, and this too demonstrated superior freedom from treatment failure at 3 years (55 % for BEAM, 34 % for non-myeloablative dexa-BEAM, $p=0.019$), although once again no survival difference could be demonstrated [83].

While there is good evidence for an overall dose–response relationship, there are several areas of continuing uncertainty. For example, it is not clear whether the dose of treatment over a whole course is the critical determinant of outcome or whether initial dose intensity during the first weeks of treatment is more important. From retrospective analyses comparing outcomes to doses administered, it appears that the most influential factor is the total dose of treatment given, with some scope for compensating suboptimal early treatment by later escalation, a finding that may distinguish Hodgkin lymphoma from many other malignancies [84–86].

Dose–Response Relationships and Treatment Tolerance: An Individual Characteristic?

A dose–response for both malignant and normal tissue toxicity is well recognized, raising the question of whether the efficacy of tumor control can be related to toxic side effects, effectively using each subject as their own pharmacodynamic control. The GHSG explored hematotoxicity as a surrogate for pharmacological and metabolic heterogeneity in relation to reduced systemic dose and disease control. Patients treated with various regimens in the HD6 trial (validated on two other cohorts) were retrospectively classified as showing WHO grade of leuko-

cytopenia 0–2 and over 2, respectively. Patients with a high hematological toxicity had a 5-year FFTF rate of 68 % versus 47 % for those with low toxicity, independent of the actual drug doses received [87]. No pretreatment pharmacokinetic parameters could be found to explain these observations; however, recent work from the GELA has explored polymorphisms in a population of HL patients that might determine anticancer agent metabolism. The UGT1A1 polymorphism has been identified as a possible candidate for influencing the metabolism of several anticancer drugs and patient outcomes [88]. Unfortunately, similar dose–response relationships are also seen for long-term toxicities, for example, infertility and secondary leukemias [37, 89, 90].

10.2.2.6 Sustained/Weekly Regimens

Pursuing the idea of increased dose intensity, several groups developed novel, brief duration regimens for the treatment of advanced Hodgkin lymphoma. The underlying rationale for the development of these regimens was, firstly, an increase in the dose intensity of chemotherapy by reduction in the total duration of treatment but an increase in the number of different agents and, secondly, reduced cumulative doses of drugs responsible for long-term toxic effects, including alkylating agents, doxorubicin, and bleomycin. The PACEBOM, VAPEC-B, and Stanford V regimens were all designed to deliver weekly treatments, alternating between myelosuppressive and non-myelosuppressive agents. The preliminary results from single-arm studies appeared promising, with high response and survival rates [91]. Unfortunately, the results of randomized trials did not confirm the early promise of these regimens.

The Stanford V program developed from the close collaboration of radiotherapy and chemotherapy, endeavoring to minimize the use of each modality, aiming at improved results with less toxicity. Initial chemotherapy was composed of the standard drugs from the MOPP/ABVD scheme (mechlorethamine, doxorubicin, bleomycin) plus etoposide, with dose intensity increased for better/earlier tumor response while cumulative doses, thought to be responsible for late toxicity (marrow, heart, lung), were reduced. The use of alkylating agents was limited in order to avert gonadal damage. The final scheme was an abbreviated 12-week program with radiotherapy started 2–4 weeks after chemotherapy, restricted to sites at higher risk for relapse (bulky sites), and delivered at 36 Gy, in order to reduce the incidence of late cardiopulmonary effects, and "mini-mantle" instead of mantle fields sparing the axillae to decrease the risk of secondary breast carcinoma. The results of the initial "Stanford V" phase 2 were confirmed in the Eastern Cooperative Oncology Group (ECOG) E1492 study in 45 patients, of whom 87 % received radiotherapy; FFP was 85 % at 5 years and OS 96 % with one death from HL and one from an M5 AML [40]. Later analysis confirmed these excellent results and the relative preservation of fertility in both women and men; no case of secondary MDS/leukemia or NHL had been registered at a 65-month median follow-up [41].

A randomized trial (Italian Lymphoma Group: ILL) compared Stanford V to mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, vindesine (MOPPEBVCAD), and ABVD as the standard in 355 patients with stage IIB–IV HL. In this trial the Stanford V arm was inferior to the other two arms in terms of 5-year FFS (54 % vs. 78 % for ABVD and 81 % for MOPPEBVCAD, respectively ($p < 0.01$ for comparison of Stanford V with the other two regimens) [30]. However, only 66 % of patients in the Stanford V arm received irradiation against 87 % in the ECOG phase 2 study: this is important in a strategy that was originally designed to combine both modalities. The Stanford V program was also compared to ABVD in a large prospective trial run by the UK National Cancer Research Institute Lymphoma Group (NCRI) in 520 patients with stage IIB–IV HL. Results in the Stanford V and in the ABVD arm were similar for 5-year PFS and overall survival (OS) rates (76 and 90 %, for ABVD; 74 and 92 % for Stanford V, with radio-

therapy administered in 53 and 73 %, respectively) [31]. The North American Intergroup trial led by ECOG (E2496) compared ABVD with involved-field radiation therapy only to bulky mediastinal sites with the combined modality Stanford V. There was no difference in response rates or in 5-year failure-free or overall survival between the two arms of the trial. The relatively extensive use of radiotherapy required to achieve optimum results for weekly regimens makes them a less attractive choice for many patients: in the UK study 73 % of patients treated with Stanford V received consolidation radiotherapy compared to 37 % in the previous UK study using ABVD in a similar group of patients. In E2496 75 % of patients on the Stanford V regimen received radiation therapy, while 41 % of those on ABVD had irradiation of bulky mediastinal sites [92] The short 12-week duration of the Stanford V regimen has some appeal for patients and remains a reasonable approach for those with low-risk non-bulky disease, in whom limited or no irradiation is needed, but this is only a minority.

The only other weekly regimen to be compared with a hybrid regimen in a randomized trial was one featuring myelosuppressive (doxorubicin, cyclophosphamide, and etoposide) and relatively non-myelosuppressive (vincristine and bleomycin) drugs given on an alternating weekly basis for 11 weeks: VAPEC-B. This was compared to a hybrid ChlVPP/EVA schedule for advanced disease, expected to still be significantly more myelosuppressive and to impair fertility, and showed inferior progression-free survival for the weekly regimen in all but the best prognosis subgroup. Event-free survival at 5 years in newly diagnosed patients with advanced disease following the hybrid regimen was 78 % versus 58 % for VAPEC-B, which translated into better overall survival at 89 % versus 79 % [42].

10.2.2.7 Escalated-Dose Regimens

In order to spare patients the acute gastrointestinal and hematologic toxicities, the original recommendation of the NCI to follow a "sliding scale" of dose adaptation for MOPP was gradually superseded by fixed doses at well-tolerated levels and intervals. Retrospective studies of MOPP and MVPP suggested that the cumulative dose, as much as frequency of administration or dose intensity, might determine the outcomes [21, 93]. These observations also appear hold for ABVD [86], although all these are retrospective and need to be confirmed in a prospective study.

The German Hodgkin Study Group has pioneered the exploration of two levels of dose increment, in the conventional dose range, by reducing the length of treatment and adding etoposide to the standard regimen, COPP/ABVD [94]. Further intensification was carried out by increasing the myelosuppressive drug doses, with growth factor support. Both intensified regimens provided higher CR, freedom from treatment failure (FFTF), and, crucially, statistically higher overall survival as compared to standard COPP/ABVD [81]. The early effects of dose intensification were maintained in the long-term results at 10 years: FFTF was 64, 70, and 82 % with OS rates of 75, 80, and 86 % for patients treated with standard COPP/ABVD, BEACOPP baseline, and BEACOPP escalated, respectively ($p<0.001$) [37]. The higher overall chemotherapy doses, as given in the escalated BEACOPP scheme, appear to provide greater disease control than any of the previous or contemporary regimens. This is supported by the very low number of deaths due to the progression of lymphoma (2.8 %). The GHSG has conducted a series of studies, HD12, HD15, and HD18, all using escalated BEACOPP in advanced HL patients (under the age of 61) whose preliminary results appear to replicate closely those of the escalated BEACOPP arm in the HD9 study [95–97].

The GHSG reported early on its concerns for the immediate toxicity, especially among patients older than 65, and, in younger patients, impaired fertility and risk of myelodysplasia (MDS) or secondary acute myeloblastic leukemia (AML). A review of the HD9 results concerning the cumulative incidence of all second tumors at

10 years confirmed that the rate for AML/MDS was lower after COPP/ABVD (0.4 %) versus BEACOPP baseline (2.2 %) and BEACOPP escalated (3.2 %; log-rank test: $p=0.03$). However, counting all secondary malignancies, there was no difference (5.3 % after COPP/ABVD, 7.9 % after BEACOPP baseline, and 6.5 % after BEACOPP escalated) [37].

The immediate and long-term toxic effects of escalated BEACOPP and the reluctance of many specialists to consider COPP/ABVD as a standard comparator have hindered acceptance of escalated BEACOPP as a new standard of care. Two Italian trials, HD2000 and GSM-HD, have demonstrated superior progression-free survival (PFS) with escalated BEACOPP in comparison to ABVD. In HD2000, BEACOPP resulted in an 81 % (95 % CI, 70–89 %) 5-year PFS versus 68 % (95 % CI, 56–78 %) for ABVD, but no significant OS difference was observed [32]. Similarly, the GSM-HD trial demonstrated a higher 3-year FFP for escalated plus baseline BEACOPP (4+4) versus ABVD (87±3 and 71±4 %), respectively, but freedom from second progression (FF2P) and OS were alike [33]. ABVD was declared preferable, taking into account the lesser toxicity, including fewer toxic deaths (1 vs. 6).

The outstanding results of escalated BEACOPP, despite the toxicity, have made it most appealing for high-risk patients. A recent meta-analysis of some of the trials to report the outcomes of treatment for ABVD and BEACOPP suggested a modest 7 % 5-year survival advantage following escalated BEACOPP [73]. This has been called into question by results in two recent randomized clinical trials. In a multi-institutional Italian trial comparing ABVD with BEACOPP (4 cycles escalated dose + 4 cycles standard dose) for patients with stage IIB, III, or IV Hodgkin lymphoma, the superior freedom from first progression for BEACOPP was confirmed (at 7 years 73 % for ABVD vs. 85 % for BEACOPP, $p=0.004$) which was the primary endpoint of the trial. However, there was no significant difference in freedom from second relapse following autologous stem cell transplantation or in overall survival between the two treatment arms. The treatment-related mortality was 4 % for BEACOPP versus 1 % for ABVD [98]. This suggests that most patients can be treated initially with ABVD and only those who relapse salvaged with autologous stem cell transplantation and thus exposed to a treatment-related mortality similar to that with initial BEACOPP treatment. The EORTC randomized patients with high-risk stage III or IV Hodgkin lymphoma (International Prognostic Score ≥3) to BEACOPP (4 cycles escalated dose + 4 cycles standard dose) or ABVD. There was no significant difference in 4-year event-free or overall survival which were the primary endpoints, although this trial also confirmed a superior progression-free survival for BEACOPP [99]. Progression-free survival may not be the most clinically important treatment result, and these two trials suggest that ABVD is an acceptable initial treatment approach even for high-risk advanced-stage Hodgkin lymphoma patients because of the effectiveness of salvage autologous stem cell transplantation in the minority of patients who relapse.

As with ABVD, it was found that omission of bleomycin during treatment with BEACOPP because of toxicity did not have an adverse impact on progression-free or overall survival. In addition, with this intensive regimen, omission of vincristine during treatment because of toxicity also had no adverse impact on these outcomes [100].

10.2.2.8 High-Dose Treatment and Autologous Stem Cell Transplantation as Part of Initial Therapy

Attempts have been made to improve results by using intensified consolidation and peripheral blood stem cell (PBSC) rescue for patients considered at high risk. Three randomized studies have explored this concept for HL. The Scotland and Newcastle Lymphoma Group HD3 study randomized 65 out of 126 high-risk patients: resulting in a nonsignificant advantage for the

conventional arm (TTF 85 % vs. 79 %, $p=0.35$) [101]. A European study of similar design randomized 163 high-risk patients achieving CR or PR after four ABVD or an equivalent regimen to receive HDT plus ASCT (83 patients) or four more courses of conventional chemotherapy (80 patients). There was no evidence of a benefit to the group receiving high-dose therapy: CR 92 % vs. 89 %, 5-year FFS 75 % vs. 82 %, and OS 88 % vs. 88 %, respectively [102].

The Groupe Ouest-Est d'Etude des Leucémies et Autres Maladies du Sang (GOELAMS) undertook a randomized study in 158 high-risk patients, comparing conventional intensive chemotherapy ($n=82$) with vindesine (5 mg/m^2), doxorubicin (99 mg/m^2), carmustine (140 mg/m^2), etoposide (600 mg/m^2), and methylprednisolone (600 mg/m^2) (VABEM) followed by low-dose lymph node irradiation versus ($n=76$) 4 cycles of ABVD followed by myeloablative carmustine (300 mg/m^2), etoposide (800 mg/m^2), cytarabine (1,600 mg/m^2), and melphalan (140 mg/m^2) and ASCT. The results were remarkably similar for CR (89 % vs. 88 %), 5-year FFTF (79 % vs. 75 %), and OS (87 % vs. 86 %) [103].

In summary, there is no evidence to support the use of high-dose consolidation at first remission in HL at present.

10.3 Chemotherapy as the Sole Treatment for Early-Stage Hodgkin Lymphoma

Because of concerns about the serious late morbidity and mortality of radiotherapy, particularly second primary cancers and cardiovascular events [104–106], there has been considerable interest in using chemotherapy alone for patients with early-stage Hodgkin lymphoma. Two randomized clinical trials have demonstrated similar outcomes for ABVD with or without radiotherapy for patients with early-stage non-bulky Hodgkin lymphoma [71, 107]. In the trial conducted by the National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group, there was 5 % lower rate of progression with subtotal nodal irradiation with or without ABVD depending on risk factors as compared with ABVD alone (92 % vs. 87 %, respectively, $p=0.05$), although at a median follow-up time of 11.3 years the median survival was lower for radiotherapy with or without ABVD as compared with ABVD alone due to deaths from causes other than Hodgkin lymphoma (87 % vs. 94 %, respectively, $p=0.04$) [107]. Combined modality treatment with radiotherapy and chemotherapy and chemotherapy alone approaches will be discussed in more detail in the chapter on the treatment of early-stage Hodgkin lymphoma.

10.4 Combined Modalities: Chemotherapy with Radiotherapy Treatment

10.4.1 Early-Stage Disease

In early-stage HL, there has been a progressive shift in the relative roles of radiation and chemotherapy. There have been several factors behind this, including increasing cure rates, better means of determining the extent of disease, better prognostic indices, and most importantly the increasing recognition of the long-term risks from treatment. This has led to an increase in the use of combined modality approaches in order to reduce the toxicity from either, and in many cases the exploration of chemotherapy as the sole treatment (see above).

The first trial of ABVD in combination with radiotherapy confirmed that four cycles of ABVD with adjuvant IF RT gave results as good as those seen with STNI [108]. The GHSG HD7 study used a similar design to show that two cycles of ABVD followed by EF RT 30 Gy with a 10 Gy boost were superior to STNI in favorable localized HL [109]. The GHSG HD10 study compared the number of cycles of ABVD (4 as standard vs. 2) and the dose of IF RT (20 vs. 30 Gy) in the same early favorable group. The results were similar in all four treatment arms, contributing to the proposal that ABVD ×2 cycles + IF RT 20 Gy

could be the standard approach for favorable early-stage localized HL [110].

The results of the GHSG HD11 trial for unfavorable/intermediate localized HL strike a note of caution regarding the de-escalation of combined modality treatment. This study compared four cycles of ABVD with four BEACOPP baseline, followed by either 20 or 30 Gy IF RT. Progression-free survival was significantly inferior in the ABVD + 20 Gy arm (Hazard ratio 1.49, $p=0.03$), suggesting an interaction between the intensity of chemotherapy and the role of radiation [111].

In young patients, especially females, the Stanford V program has provided excellent results while preserving fertility in most cases. For comparison with the European experience, the Stanford V data in early-stage HL has been retrospectively analyzed: Favorable/early patients received 8 weeks of chemotherapy + 20 or 30 Gy IF RT, while unfavorable/intermediate risk patients were treated with 12 weeks of chemotherapy + 36 Gy. By comparison with European (EORTC and GHSG risk factors), this resulted in excellent FFP and OS, although second-line treatment proved less successful in the unfavorable group [112]. Fertility was preserved with 25 live births/pregnancies reported in this group of 120 patients [113, 114].

10.4.2 Advanced Disease

Up to 30 % of the patients with advanced HL will relapse, or progress, often in initially involved areas where bulky disease was present [115]. Because of this, and the undoubted efficacy of irradiation in controlling localized disease, radiotherapy has been widely used in consolidation to improve cure rates in advanced disease. Several older studies supported this approach and a meta-analysis of 14 randomized trials in all stages of HL demonstrated improved EFS but not survival, albeit with adverse survival effects when the radiation was extensive [116]. There are however concerns regarding the long-term side effects of such irradiation, which necessitate a careful review of this approach.

10.4.2.1 Does Consolidation Radiotherapy Improve Outcomes Compared to Chemotherapy Alone?

The answer here depends to a large extent on the effectiveness of the chemotherapy. Series which demonstrate an EFS advantage for combined chemotherapy–radiotherapy tend to be those with shorter or less intense regimens. For example, if the results of three different studies of the Stanford V regimen are compared, there is a correlation between the EFS and the proportion of patients receiving radiotherapy: in the Italian Lymphoma Group (IIL) study 66 % of patients received radiotherapy for a EFS of 73 %, while in the UK NCRI trial the figures were 73 % irradiated and 75 % EFS, and in the series from Stanford 91 % irradiated and 89 % EFS [30, 31, 41]. The correlation is much less evident for radiation after the more intensive escalated BEACOPP regimen: in the IIL study 45 % were irradiated for an EFS of 81 %, while in the German HL Study Group a radiotherapy rate of 71 % yielded EFS of 87 % [32, 81]. The results with ABVD appear to lie somewhere between these two: analysis of the UK NCRI trial results with ABVD showed that patients selected to receive consolidation radiotherapy had superior EFS, despite more adverse baseline prognostic factors such as bulk disease, and a lower proportion being in CR at the end of chemotherapy, a finding which held across all prognostic subgroups [117].

10.4.2.2 Following Chemotherapy for Advanced HL, Is Radiotherapy Consolidation More Effective than Additional Chemotherapy?

In adults, two well designed trials have addressed this question. In the GHSG HD3 trial, 288 patients received six cycles of COPP/ABVD, and 100 patients in radiological CR were randomized to one additional COPP/ABVD or IF RT 20 ± 20 Gy. There was no difference in terms of tumor control, but patients who did not receive any consolidation fared poorly [118]. The GELA group conducted a larger trial which gave much

the same result: 533 patients with advanced HL were randomized to six cycles of MOPP/ABV or doxorubicin, bleomycin, vinblastine, procarbazine, prednisone (ABVPP). Patients in CR or PR ≥75 % after six cycles were randomized between two additional cycles of chemotherapy or subtotal nodal irradiation (STNI). There was some interaction between the randomizations, with the best overall survival seen after ABVPP alone; however there was no significant difference overall in the second randomization: the 10-year DFS figures for patients treated with consolidation CT or STNI were 73 and 78 % ($p=0.07$). Once again, patients who received no consolidation at all had poorer survival [119].

10.4.2.3 If Complete Response Is Achieved After Chemotherapy, Does Additional Radiotherapy Provide an Advantage?

Once again the intensity and efficacy of the prior chemotherapy appear to be influential, as does the level of detail at which the response is assessed. Two trials have suggested that radiotherapy may be unnecessary for many patients.

The EORTC conducted a trial in patients with stage III–IV HL who were in CR after six or eight cycles of hybrid MOPP/ABV. Three hundred thirty-three of 421 potentially eligible patients were randomized over a 10-year period to receive either no further treatment or IF RT 24 Gy to all initially involved nodal areas and 16–24 Gy to all initially involved extranodal sites. The 5-year EFS was 84 % in the no treatment group and 79 % the IF RT group ($p=0.35$). There was a nonsignificant trend toward inferior survival in the radiated group, a finding ascribed to cardiac toxicity and second malignancies [39].

Chemotherapy or radiotherapy consolidation in CR patients enrolled in the HD3 trial was shown to be equivalent [118]. Following a series of studies in which consolidation radiotherapy continued to be used, the GHSG HD 12 trial examined the role of consolidation radiotherapy following either eight escalated BEACOPP or four escalated and four baseline. Nine hundred thirty-four patients were randomized between radiotherapy or no radiotherapy, and no difference was seen in freedom from treatment failure or overall survival [95].

The findings from the UK NCRI LY09 study are in contrast, with patients who received consolidation radiotherapy following complete remission showing a significantly greater EFS and OS, although this was not a randomized comparison. If anything the irradiated group had less favorable baseline characteristics [117].

The findings in the German HD 15 study offer an interesting perspective on the potential future role of consolidation radiotherapy for advanced HL. In this trial, patients with residual masses over 2.5 cm after BEACOPP chemotherapy which showed positive uptake on a FDG-PET scan underwent radiotherapy to 30 Gy, while those with a PET-negative mass were managed expectantly. In total only 11 % of patients went on to receive any radiotherapy and the overall results were excellent: the negative predictive power for PET was 94.1 % [78]. Overall survival at 5 years was also excellent with this approach, ranging between 91.8 % for those treated with eight cycles of escalated BEACOPP and 96.2 % for those who received only six cycles. Patients treated with eight cycles of BEACOPP-14 had intermediate OS results, at 94.8 %.

In conclusion, radiotherapy may be avoidable in patients who achieve a true CR after adequate chemotherapy. Patients without evidence of active disease can be expected to have an excellent prognosis without irradiation, while those in whom there is still an abnormality seem likely to require additional therapy, and in this situation radiotherapy may be effective. It is to be hoped that the controversy surrounding the use of consolidation radiotherapy may finally be resolved with the functional assessment of residual disease.

10.5 Chemotherapy Treatment for Recurrent and Refractory Hodgkin Lymphoma

10.5.1 Salvage Chemotherapy Regimens (Tables 10.4 and 10.5)

The variety of agents with activity against Hodgkin lymphoma has permitted the development of many salvage regimens for use in that minority of patients whose lymphoma is not eradicated by first-line therapy. The preference in

designing these regimens is to select agents with sufficiently different mechanisms of action to reduce the likelihood of cross-resistance to the prior treatment. In the majority of patients, the aim of second-line therapy is to produce a sufficient response to proceed to high-dose treatment with autologous progenitor cell rescue, as this appears to be the only means to produce long-term remission in more than 50 % of patients.

Table 10.4 Salvage regimens in common use for recurrent/refractory Hodgkin lymphoma

Drugs	Dose mg/m^2	Route	Schedule
Dexa-BEAM			q. 21 days
Dexamethasone	24 mg daily	po	Days 1–10
Carmustine	60	iv	Day 2
Etoposide	250	iv	Days 4–7
Cytarabine	100 bd	iv	Days 4–7
Melphalan	20	iv	Day 3
DHAP			q. 21 days
Dexamethasone	40 mg daily	iv	Days 1–4
Cytarabine	2,000 bd	iv	Day 2
Cisplatin	100	ivi	Day 1
ESHAP			q. 21 days
Etoposide	40	iv	Days 1–4
Cytarabine	2,000	iv	Day 5
Cisplatin	25	ivi	Days 1–4
Methylprednisolone	500 mg daily	iv	Days 1–5
ICE			q. 21 days
Ifosfamide	5,000	ivi	Day 2
Carboplatin	AUC 5	iv	Day 2
Etoposide	100	iv	Days 1–3
GDP			q. 21 days
Gemcitabine	1,000	iv	Days 1 and 8
Dexamethasone	40 mg daily	po	Days 1–4
Cisplatin	75	iv	Day 1
IGEV			q. 21 days
Ifosfamide	2,000	iv	Days 1–4
Gemcitabine	800	iv	Days 1 and 4
Vinorelbine	20	iv	Day 1
Prednisolone	100 mg daily	po	Days 1–4

There is currently no accepted standard salvage chemotherapy for Hodgkin lymphoma. The regimens in common use are listed in Table 10.4. Many regimens in wide use contain cisplatin, such as DHAP (dexamethasone, cytosine arabinoside, and cisplatin) [123] and ESHAP (etoposide, methylprednisolone, cytosine arabinoside, and cisplatin) [121] or may use an ifosfamide–etoposide backbone such as ICE (ifosfamide, carboplatin, and etoposide) [122]. There is interest in using gemcitabine following promising single-agent data from its use in refractory disease and in vitro studies showing its ability to circumvent multidrug resistance (MDR) due to increased P-glycoprotein overexpression [125]. Cells expressing MDR often have increased deoxycytidine kinase activity and reduced deoxycytidine deaminase, allowing intracellular accumulation of gemcitabine phospho-derivatives and thereby increasing its cytotoxicity. Combining gemcitabine with DNA-damaging agents such as platinum drugs and other alkylating agents is a logical approach for disease that has recurred after prior treatment with anthracycline and vinca alkaloid drugs. It should be noted however that the combination of gemcitabine with bleomycin, while superficially attractive for HL, was accompanied by severe lung toxicity, and should be avoided [126].

The response rate to salvage regimens is generally high irrespective of the combination chosen, with between 60 and 90 % overall response rates and between 20 and 30 % complete responses, depending upon the selection of

Table 10.5 Published results of salvage regimens used in Hodgkin lymphoma

		Responses (%)			Grade ¾ toxicity (%)			
Regimen	No. of patients	CR	PR	ORR	Neutropenia	Thrombocytopenia	Vomiting	Toxic deaths (%)
Dexa-BEAM [83]	144	27	54	81	NS	NS	NS	5
Mini-BEAM [82]	55	49	33	82	86	60	NS	2
ASHAP [120]	56	34	36	70	100	NS	NS	0
ESHAP [121]	22	41	32	73	59	NS	NS	4
ICE [122]	65	26	59	85	NS	NS	NS	0
DHAP [123]	102	21	68	89	88	69	26	0
GDP [124]	23	17	52	69	9	13	13	0
IGEV [48]	91	54	28	81	28	20	3	0

patients. Table 10.7 gives details of the reported response rates and toxicity of a variety of regimens reported in the literature.

10.5.2 High-Dose Therapy (Tables 10.6 and 10.7)

The principles of high-dose therapy for Hodgkin lymphoma are similar to those for other chemosensitive malignancies. Combinations are chosen to include agents which are active against the lymphoma; have different mechanisms of action, where possible, from the previous therapy; show a steep dose–response curve; and have hematologic toxicity as their dose-limiting characteristic. The most widely used regimens are based upon alkylating agents and nitrosoureas, often with etoposide. Total body irradiation has been incorporated with some regimens, but is no longer widely used following the demonstration of increased toxicity in several series. Two regimens have dominated the published literature for high-dose therapy and autologous progenitor cell rescue, CBV and BEAM [129]. Details of the most widely used regimens are given in Table 10.6.

The outcomes of treatment with these have been widely reported, with long-term remissions in 30–60 % of cases (Table 10.7). The likelihood of durable remission can be estimated from the antecedent features of the lymphoma [134]. Several retrospective studies have identified risk factors that stratify patients based on disease characteristics, such as the presence of B symptoms, extranodal disease, and duration of remission from frontline chemotherapy. The 5-year event-free survival rate for patients with low-risk disease ranges from 65 to 80 %, whereas EFS for patients with intermediate- or high-risk disease is less than 30 %, with the majority of relapses occurring within the first 2 years after high-dose therapy. Even for patients with disease that does not enter remission with first-line therapy, however, there are some long-term remissions achieved using high-dose treatment, with a retrospective study of the European Bone Marrow Transplant registry reporting a 5-year progression-free survival of 32 % among 175 such cases [130].

There has been no formal comparative study to determine the best high-dose regimen, although analyses of transplant registries have been used and suggest a marginal advantage for BEAM over CBV. Raising the doses of the individual drugs within a high-dose regimen has not in general been effective. A study in which the drugs in the CBV regimen were increased, yielded significant pulmonary toxicity when the

Table 10.6 High-dose regimens commonly used for Hodgkin lymphoma

Regimen	Drugs included	Total dose administered (mg/m^2)
CBV	Cyclophosphamide	4,800–7,200
	Carmustine	300–600
	Etoposide	750–2,400
BEAM	Carmustine	300
	Etoposide	800–1,200
	Cytarabine	1,600
	Melphalan	140
BEAC	Carmustine	200–300
	Etoposide	600–1,200
	Cytarabine	800–1,200
	Cyclophosphamide	6,000
LACE	Lomustine	200
	Cytarabine	4,000
	Cyclophosphamide	1,800
	Etoposide	1,000

Table 10.7 Published results of treatment with high-dose therapy and autologous progenitor cell rescue in Hodgkin lymphoma

Regimen	No. of patients	Status of disease	EFS/FFTF (%)	OS	Reference
CBV	128	Relapse/refractory	25	45	[127]
BEAM	280	Relapse	60	66	[128]
BEAM	139	Relapse	45	50	[129]
BEAM	175	Primary refractory	32	36	[130]
BEAM	86	Primary refractory	25	35	[131]
BEAM	76	Primary refractory	23	30	[132]
LACE	67	Relapse/refractory	64	68	[133]

dose of carmustine exceeded 450 mg/m^2 [127]. A similar study of increasing etoposide dose in the BEAM regimen resulted in higher transplant-related mortality and gastrointestinal complications at a total dose of 2,400 mg/m^2.

10.5.3 New Systemic Treatments

There have been relatively few new conventional cytotoxic agents developed recently for HL, but both monoclonal antibodies and small molecule therapeutics targeting specific abnormal pathways in HL have recently started to show some promising results.

Antibody therapies have been directed at relatively specific molecules such as CD30 on the surface of Reed–Sternberg cells, but the results with unconjugated anti-CD30 were discouraging, probably because it targets only a small proportion of the cells within a mass of lymphoma [135]. On the other hand, antibody–drug conjugate therapy has shown very promising results, with a response rate of 75 % reported using the anti-CD30–monomethylauristatin E (SGN-35) for patients with recurrent and refractory disease as described in Sect. 10.2.1 [16].

Anti-CD20, given with the intention of targeting the infiltrating B cells and interrupting autocrine growth factor loops, has shown some promise in an early pilot study [136] but awaits confirmatory data from a prospective trial. This approach may find more application in the treatment of nodular lymphocyte predominant disease, in which CD20 is present on the surface of the malignant cells [137].

Among the small molecule therapies being tested, proteasome inhibitors have been disappointing in HL [138], whereas inhibitors of histone deacetylase (HDACis) have resulted in significant responses in early-phase studies, despite significant marrow toxicity [139]. It is not clear whether the principal target of HDACis is the malignant cell itself or the surrounding inflammatory infiltrate, but further studies using a range of more or less specific agents targeting different members of the HDAC family may yield further information.

Conclusions

A variety of pharmacologic hypotheses have been tested in the course of the last 50 years, and none has been found entirely satisfactory for predicting the outcomes of treatment. The superiority of ABVD over MOPP is established, but the place of the more intensive multi-agent regimens such as BEACOPP is still to be conclusively proven, and high-dose therapy as a component of initial treatment was unrewarding. There appears to be a potential trade-off between the intensity of chemotherapy and the value of consolidation radiotherapy in advanced disease: it is not clear whether any chemotherapy is intensive enough for radiation to be dropped altogether, but functional imaging holds promise for lowering the proportion of patients irradiated very significantly.

As treatment has evolved so the balance between toxicity and efficacy has been established. New approaches using response-adapted therapy hold the promise of identifying the minority of patients for whom early intensification is a necessity, while allowing de-escalation of treatment in those destined to do well. Finally, there are a small number of novel reagents currently undergoing testing against recurrent and refractory disease which appear to hold some promise.

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Treatment of Early Favorable Hodgkin Lymphoma

11

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Contents

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11.1 Introduction

Historically, Hodgkin lymphoma (HL) was the first malignant disease that could be cured. In the past century, the first successful outcomes of radiotherapy employing large radiation fields were reported, in particular in patients with limited disease. Even bulky tumors melted away during intense irradiation. One might hypothesize that this can be explained by the radiosensitivity of the few malignant cells in HL (Hodgkin and Reed–Sternberg [H-RS] cells) amidst the majority of nonmalignant surrounding cells in the microenvironment.

Further refinement of this initial treatment approach was achieved through carefully designed prospective randomized phase III clinical trials. In this context, the step-by-step development of uniformly accepted staging procedures and clear definitions of stages and response criteria was a major achievement. This allowed direct comparison of study results performed in different consortia worldwide.

Focusing on stage-adapted treatment of HL, these trials allowed the definition of clinical prognostic factors. These, in turn, lead to risk-adapted treatment, which became more refined with subsequent studies. In line with these advances, treatment strategies changed from radiotherapy only using extended-field radiotherapy (EFRT) and later involved-field radiotherapy (IFRT) to combined modality treatment (CMT) and limited chemotherapy only.

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_11,

Thanks to the long-term follow-up of thousands of patients treated within clinical trials over decades, significant late effects of treatment became apparent, in particular secondary malignancies and damage to the cardiovascular and respiratory systems. Based on these unexpected findings, which could only be retrieved for the first time in oncology due to the high cure rate and accurately documented long-term follow-up of HL patients, the ingredients of curative regimens were further adjusted. As far as possible, noncarcinogenic cytostatic agents were introduced in newly developed chemotherapy regimens and radiation doses were further reduced. This has lead to the current major challenges in the treatment of early stage HL: maintaining the very high cure rates and at the same time reducing the incidence of devastating late effects. To define an optimal balance, it is thus strongly advocated to treat early stage HL patients within clinical trials and not ad hoc according to local guidelines.

This chapter deals with recent developments in the treatment of stage I and II HL with favorable prognostic factors comprising 40 % of all early stage HL patients.

11.2 Defining Favorable Early Stage Disease

11.2.1 Staging

In HL patients, prognosis is distinctly worse with each progressive stage of disease and the selection of appropriate treatment depends on accurate staging of the extent of disease. The Ann Arbor staging classification was formulated in 1971 and is still the most commonly used staging system for HL [1]. During the Cotswold meeting in 1989, some modifications were introduced to account for new imaging techniques such as computerized tomography (CT) scanning. In addition, clinical involvement of the liver and spleen was redefined, to formally introduce the concept of bulky disease and to draw the attention to the problem of equivocal complete remission [2]. Stage I indicates involvement of a single lymph node region or a single extranodal organ or site. In stage II disease, two or more lymph node regions on the same side of the diaphragm are involved, or there is localized involvement of an extranodal organ or site and of one or more lymph node regions on the same side of the diaphragm. The stage number is followed by the letter A or B indicating the absence (A) or presence (B) of one or more of the following constitutional symptoms: (a) unexplained fever with temperatures above 38 °C during the previous month, (b) drenching night sweats during the previous months, and (c) unexplained weight loss of more than 10 % of body weight in the previous 6 months. Mediastinal bulk was defined by the ratio of the maximum transverse tumor diameter to the internal thoracic diameter at the level of the T5–T6 vertebral interspace. A ratio exceeding one-third was considered bulky.

For the initial staging of HL, a detailed history, complete physical examination, and imaging studies with whole body positron emission tomography using [18F]-fluoro-2-deoxy-d-glucose (FDG-PET, here referred to as PET) scanning and CT scans of the neck, thorax, abdomen, and pelvis, are generally recommended [3, 4]. In patients with PET-CT-assessed stage I–II disease, routine bone marrow biopsy can be omitted [5]. In case of specific symptoms or physical signs, special investigations and imaging studies may be performed to confirm clinical involvement at a given site. See Chaps. 6 and 7 for a more comprehensive review of clinical evaluation and functional imaging.

About 7 % of stage I–II HL patients present with infradiaphragmatic disease [6]. The specific features and treatment of stage I–II infradiaphragmatic HL patients are described in Chap. 12.

11.2.2 Prognostic Factors

The stage of the disease is not the only prognostic tool in HL. Several studies describing prognostic factors in early stage HL have been performed [7, 8]. They were derived from long-term follow-up of patient cohorts treated in a variety of phase III prospective randomized trials. These prognos-

tic factors predict the likelihood of occult disease in the abdomen and the effectiveness of treatment. The prognostic significance of bulky disease particularly in the mediastinum has been well documented [7]. The presence of constitutional symptoms has always been considered one of the main prognostic indicators. There is also a strong correlation between erythrocyte sedimentation rate (ESR) and the number of involved lymph node regions (see Chap. 8 for prognostic factors). Different Lymphoma Collaborative Groups worldwide use varying combinations of prognostic factors to identify prognostic risk groups. These prognostic factors allow patients to be stratified into favorable or unfavorable prognostic groups. The current definitions of a favorable treatment group according to the different study groups in Europe and the United States are presented in Table 11.1. The Lymphoma Group of the European Organization for Research and Treatment of Cancer (EORTC) and the French–Belgian Groupe d'Etude des Lymphomes de l'Adulte (GELA) define clinical stage I–II patients as favorable if they present with the following characteristics: age <50 years and low ESR (<50 mm/h without and <30 mm/h with B symptoms), no more than three involved lymph node regions, and no large mediastinal mass [9]. All these criteria need to be met to be "favorable." The German Hodgkin Study Group (GHSG) criteria differ slightly in that they substituted age <50 years with no extranodal disease and specify no more than two involved nodal regions rather than ≤3 as in the EORTC [10]. In Canada and North America, it is common to define an early or limited stage risk group as stage I and IIA disease without bulky disease (see Table 11.1).

11.3 Radiotherapy Alone

The use of radiation therapy, pioneered at Stanford University in the 1960s by Henry Kaplan and Saul Rosenberg, offered patients with HL the first hope for cure. In the treatment of early stages, EFRT was considered the standard treatment modality for many years. With this technique, radiation was delivered not only to the clinically involved but also to the adjacent, clinically uninvolved sites. Because it was known that HL spreads to contiguous nodal sites, mantle field RT encompassed all nodal sites above the diaphragm. The combination of mantle field with inverted-Y field and spleen irradiation was termed "subtotal nodal irradiation" (STNI). See Chap. 9 for definitions of field size.

Significant advances in the treatment of HL were then derived from clinical trials. Investigators at Stanford demonstrated that radiation therapy alone using total lymphoid irradiation or STNI is an adequate treatment for nearly all patients with pathologic stages I–II. In a series of 109 patients, the freedom from relapse rate at 10 years was 77 %. The likelihood of relapse after treatment

Table 11.1 Definition of early stage favorable HL

EORTC–GELA	GHSG	NCI-C/ECOG
CS I–II without risk factors (supradiaphragmatic)	CS I–II without risk factors	CS I–IIA without risk factors (supradiaphragmatic)
No large mediastinal mass	No large mediastinal mass	No large mediastinal mass
Age <50 years	No extranodal disease	Age <40 years
No elevated ESR[a]	No elevated ESR[a]	ESR <50 mm/h
1–3 involved nodal regions	1–2 involved nodal regions	1–3 involved nodal regions
		LPHL or NS histology

EORTC European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *NCI-C* National Cancer Institute of Canada, *ECOG* Eastern Cooperative Oncology Group, *CS* clinical stage, *ESR* erythrocyte sedimentation rate, *LPHL* nodular lymphocyte-predominant Hodgkin lymphoma, *NS* nodular sclerosis

[a]ESR <50 mm/h without B symptoms or ESR <30 mm/h with B symptoms

with irradiation alone was much higher for patients with extensive mediastinal disease than minimal mediastinal involvement [11].

The Princess Margaret Hospital in Toronto, Canada, conducted a retrospective study of patients with clinical stage I and II treated between 1978 and 1986 to determine the impact of patient selection and EFRT on outcome. The study involved 250 patients with supradiaphragmatic disease and no adverse prognostic factors selected for treatment with radiation alone. Patients with favorable prognostic features (age <50 years, ESR <40 mm/h, and lymphocyte-predominant or nodular sclerosing histology) treated with mantle and para-aortic-splenic irradiation had only 12.7 % actuarial risk of relapse at 8 years [12].

Between 1964 and 1987, the EORTC performed four consecutive randomized clinical trials aiming to delineate the subsets of patients who could be safely treated with RT alone [13, 14] (Table 11.2). In the EORTC H1 trial, all 288 patients had clinical stage I or II disease [15]. No staging laparotomy was performed. Patients received mantle field RT in case of supradiaphragmatic disease and inverted-Y RT for subdiaphragmatic disease. Patients in complete remission were randomized between no further treatment and 2 years of a weekly vinblastine.

Table 11.2 Early stage favorable HL: selection of randomized studies of radiotherapy alone

Trial	Year	Study arms	Number of patients	Outcome	Overall survival	Reference
EORTC HI	1964–1971	A. Mantle field or inverted-Y RT	288	A. 38 % DFS (15 years)	A. 58 % OS (15 years)	Tubiana et al. [15]
		B. The same RT followed by vinblastine		B. 60 % DFS (15 years)	B. 65 % OS (15 years)	
				$p<0.001$	$p=0.15$ (NS)	
EORTC H2	1972–1976	A. Laparotomy and mantle field + para-aortic lymph node RT	300	A. 76 % DFS (12 years)	A. 79 % OS (12 years)	Tubiana et al. [14, 16]
		B. STNI		B. 68 % DFS (12 years)	B. 77 % OS (12 years)	
				$p=0.18$ (NS)	$p=0.38$ (NS)	
EORTC H5F	1977–1982	Laparotomy negative patients	198	A. 69 % DFS (9 years)	A. 94 % OS (9 years)	Carde et al. [17]
		A. Mantle field RT		B. 70 % DFS (9 years)	B. 91 % OS (9 years)	
		B. STNI		$p>0.50$ (NS)	$p>0.50$ (NS)	
EORTC H6F	1982–1987	A. Laparotomy, if negative: mantle field RT for LP or NSc histology	262	A. 84 % RFS (6 years)	A. 89 % OS (6 years)	Carde et al. [18]
		STNI for MC or LD histology		B. 80 % RFS (6 years)	B. 93 % OS (6 years)	
		B. STNI		$p=0.25$ (NS)	$p=0.24$ (NS)	
EORTC H7VF-H8VF	1988–1993	Mantle field RT	40	RFS 73 % (6 years)	OS 95 % (6 years)	Noordijk et al. [19], abstract
GHSG HD4	1988–1994	A. STNI 40 Gy	376	A. 78 % RFS (7 years)	A. 91 % OS (7 years)	Dühmke et al. [20]
		B. STNI 30 Gy + IFRT 10 Gy		B. 83 % RFS (7 years)	B. 96 % OS (7 years)	
				$p=0.093$ (NS)	$p=0.16$ (NS)	

EORTC European Organization for Research and Treatment of Cancer, *GHSG* German Hodgkin Study Group, *DFS* disease-free survival, *OS* overall survival, *RFS* relapse-free survival, *STNI* subtotal nodal irradiation, *RT* radiotherapy, *IFRT* involved-field radiotherapy, *Gy* Gray, *NS* not significant, *LP* lymphocyte predominant, *NSc* nodular sclerosing, *MC* mixed cellularity, *LD* lymphocyte depleted

The 15-year follow-up showed a significant advantage in disease-free survival for the combined treatment compared with RT alone (60 vs. 38 %). The incidence of relapse in the para-aortic region was high in patients who received supradiaphragmatic RT only. However, the benefit of the combined treatment was more evident in patients with unfavorable characteristics. The overall survival did not differ significantly between both arms (65 vs. 58 %).

The EORTC H2 trial compared staging laparotomy including splenectomy followed by mantle field and para-aortic RT with STNI without staging laparotomy in 300 patients with supradiaphragmatic clinical stage I–II disease [14, 16]. To assess the prognostic significance of the laparotomy findings, the results of the staging laparotomy did not change the treatment policy. It was found that positive laparotomy was associated with a higher relapse rates. However, the impact of positive laparotomy on disease-free survival was observed only in patients with favorable prognostic factors. At 12-year follow-up, the disease-free survival and overall survival did not differ significantly between the laparotomy and the no-laparotomy groups (76 vs. 68 % and 79 vs. 77 %, respectively). This trial showed that staging laparotomy could be omitted in certain subsets of patients, provided STNI was given instead of mantle field RT. Together with data from the H1 trial, a new set of clinical prognostic factors could be derived that identified groups of patients with a more favorable and unfavorable prognosis. This gave the opportunity to develop treatment regimens tailored to these prognostic factors, with the aim to minimize treatment intensity as much as possible in the favorable subgroups to spare them from unnecessary treatment toxicity.

In the next EORTC trial (H5F), patients with favorable characteristics (age ≤40 years, ESR ≤70 mm/h, clinical stage I or stage II without mediastinal involvement, and lymphocyte-predominant or nodular sclerosing histology) underwent staging laparotomy [14, 17]. The laparotomy was used to select a group of patients with a good prognosis for whom RT alone might be sufficient. Patients ($n=198$) with negative laparotomy remained in the favorable group and were randomized between mantle field RT and STNI. At 9-year follow-up there was no significant difference in disease-free survival and overall survival between the two treatment arms (69 vs. 70 % and 94 vs. 91 %, respectively). This trial showed that favorable patients with negative staging laparotomy could safely be treated with relatively limited RT alone.

The EORTC H6F trial investigated whether staging laparotomy was mandatory for the identification of the subset of patients that could be treated by STNI and splenic irradiation alone [18]. The favorable subgroup was characterized by clinical stages I or II with a maximum of two involved areas and no bulky mediastinum and ESR ≤50 mm/h if no B symptoms present or ≤30 mm/h in case of B symptoms. These patients ($n=262$) were randomized between clinical staging plus STNI (mantle, spleen, and para-aortic RT) and staging laparotomy plus treatment adaptation. If the laparotomy was negative, patients with lymphocyte-predominant or nodular sclerosing subtypes were treated with mantle field RT, and patients with mixed cellularity or lymphocyte depleted histology received mantle field and para-aortic RT (STNI). Again, no significant differences between the two treatment arms were found in this trial in disease-free survival and overall survival at 6-year follow-up (80 vs. 84 % and 93 vs. 89 %, respectively).

Taken together, these four randomized trials demonstrated that staging laparotomy could be safely omitted in patients with favorable clinical characteristics in early favorable HL and that these patients could be treated by STNI (40 Gy) with a similar outcome as obtained by staging laparotomy followed by mantle field RT (40 Gy). Another important finding was that the overall outcome had gradually improved over the years (Fig. 11.1).

The total radiation dose in these EORTC trials was always 40 Gy. The HD4 trial of the GHSG tested the hypothesis that dose reduction from 40 to 30 Gy in the extended field would be possible without a clinically relevant increase in the recurrence rate [20]. All patients ($n=376$) with pathologically staged stage I or II without adverse prognostic factors received 40 Gy radiation dose

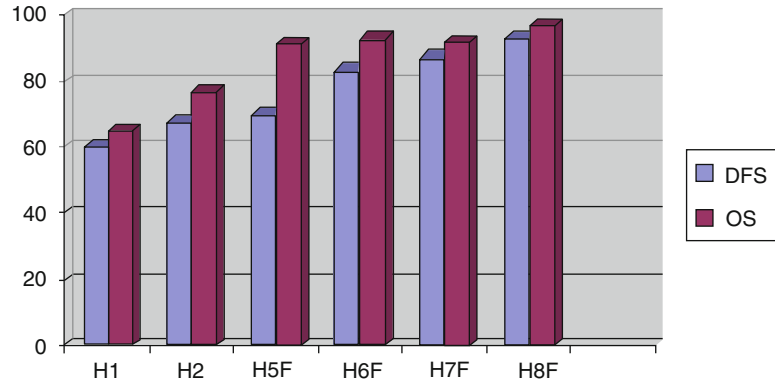

Fig. 11.1 Disease-free survival and overall survival in consecutive EORTC Lymphoma Group trials on early stage favorable Hodgkin lymphoma (HL). *DFS* disease-free survival, *OS* overall survival

to the involved field, but were randomly assigned to receive either 40 or 30 Gy to the noninvolved extended field. The 7-year relapse-free and overall survival rates did not differ (78 vs. 83 % and 91 vs. 96 %, respectively). Hence, 30 Gy seems a sufficient dose for treating subclinical involvement of HL with RT alone.

Radiation in mantle field technique can potentially cause less long-term toxicity compared with STNI. However, in clinically staged patients, results with mantle irradiation alone have been disappointing. In the EORTC H7-VF and H8-VF trials, 40 female patients were treated with mantle field RT only. The respective prognostic factors were stage IA, aged <40 years, nodular sclerosing or lymphocyte-predominant histology, and ESR <50 mm/h. These patients were expected to have a very low risk of occult abdominal involvement (5 %). The relapse-free survival was however lower than expected: a total of 23 % had relapsed at 6 years [19]. Because of this unacceptable rate, the very favorable subgroup has since been treated according to the EORTC strategy for the favorable subgroup.

Specht et al. reported on the influence of radiation field size on long-term outcome in early stage disease in a meta-analysis of eight randomized trials evaluating larger vs. smaller radiation fields [21]. These trials included almost 2,000 patients with both favorable and unfavorable prognosis stage I–II disease. A definite and substantial reduction in the risk of treatment failure was demonstrated if more extensive radiotherapy was used. The 10-year risk of recurrence was 43 % for patients treated with smaller-field irradiation compared to 31 % for those treated with larger-field radiation therapy. The size of reduction in risk for failure in patients with different stages of disease, with and without B symptoms, of different ages, and staged with and without laparotomy was remarkably similar. Although the additional radiotherapy prevented a substantial proportion of recurrences, it did not significantly affect overall mortality. The lack of survival difference suggests that salvage chemotherapy for relapse after initial radiotherapy is effective enough to minimize the impact of any increase in relapse on survival.

To summarize, STNI was considered a standard treatment for early favorable HL until the 1990s. However, 25–30 % of patients eventually relapsed with subsequent 10-year survival rates of only 63 % [22].

11.4 Late Treatment Effects and Mortality

As the number of patients surviving HL increased and there was longer follow-up, it became evident that their life expectancy did not revert completely to that of the age-matched general population. The higher mortality of HL patients is largely a result of the long-term effects of treatment. Important late effects comprise secondary malignancies, cardiovascular diseases, pulmonary problems, gonadal dysfunction, infectious complications, and fatigue. The incidence of the most life-threatening late side effects, i.e., secondary cancers and cardiovascular diseases, is

significantly related to the radiation dose and field size, choice of cytostatic drugs, and total amount of drugs administered.

In patients with early favorable disease, mortality from causes other than HL has increased over time, exceeding HL-related mortality after 10–15 years [23, 24]. A large study with a median follow-up of more than 17 years examined case-specific mortality and absolute excess mortality, compared to population rates, in a cohort of 1,261 Dutch patients [23]. These patients were younger than 40 years when treated between 1965 and 1987. HL was the most frequent cause of death (55 %), followed by secondary malignancies (22 %) and cardiovascular diseases (9 %). In the first 10 years following initial treatment, the excess mortality rate is largely due to the primary disease, while after 10 years causes other than HL contribute most to excess mortality. The actuarial risk of death is shown in Fig. 11.2. Even after 30 years of follow-up, there was no evidence of a decline in the relative risk of death from causes other than HL. In 30-year survivors, the annual excess mortality rate from all causes other than HL was nearly 3 per 100 patients. Solid tumors, especially in the digestive and respiratory tract, contributed most to this excess risk, followed by cardiovascular diseases [23]. Recently, the EORTC and the GELA published their results of a study analyzing the cause-specific excess mortality in adult patients with respect to treatment modality [25]. The study population consisted of 4,401 patients aged 15–69 in all stages, who were treated between 1964 and 2000. In patients with early stage disease, the overall excess mortality was associated with age ≥40 years ($p=0.007$), male gender ($p<0.001$), unfavorable prognostic features ($p<0.001$), treatment with EBVP (epirubicin, bleomycin, vinblastine, prednisone) plus IFRT ($p=0.002$), and mantle field irradiation alone ($p=0.003$). Therefore, excess mortality was linked to treatment modalities that were associated with poor failure-free survival resulting in a higher need for salvage treatment. Late treatment effects are covered in more detail in Chaps. 23, 24, 25, and 26.

11.5 Combined Modality Treatment

With the observation of high relapse rates and fatal long-term effects, most study groups abandoned STNI and EFRT from the treatment of early stage HL. Studies were developed in an attempt to reduce long-term toxicity without increasing disease-specific mortality. Most randomized studies evaluated CMT in an attempt to define the optimal chemotherapy, number of cycles needed, as well as radiation field size and

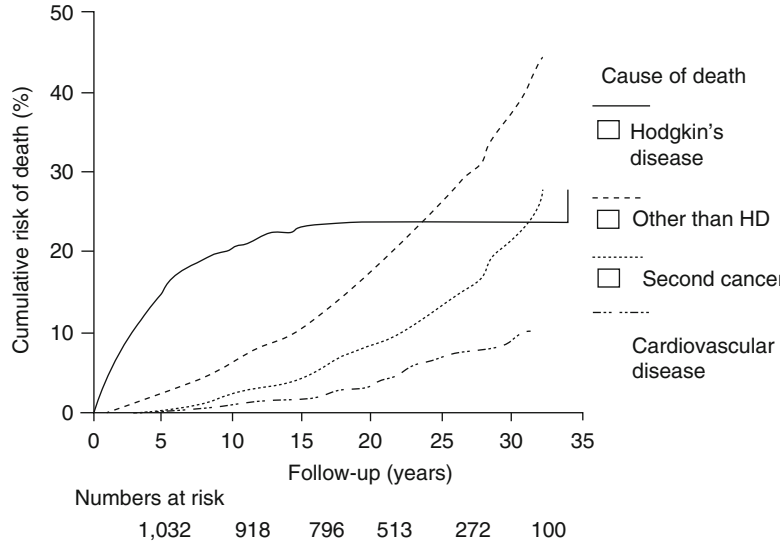

Fig. 11.2 The actuarial risks of death from major disease categories in 1,261 Dutch HL patients. Data from Dutch database on Hodgkin lymphoma (Reprinted from Aleman et al. [23] with permission)

dose when combined with chemotherapy. Commonly used regimen and drug combinations are listed in Table 11.3.

11.5.1 Radiotherapy Alone Versus CMT

The high relapse rates after treatment with radiotherapy alone prompted several groups to study CMT as induction therapy. An earlier meta-analysis of individual patient data showed that CMT reduced the relapse risk compared with radiotherapy alone, but did not improve overall survival [21]. Most of the trials included in this analysis were conducted between 1967 and 1988 using MOPP or MOPP-like regimens, which produced unacceptable hematologic toxicity, frequently induced secondary malignancies, and rendered most recipients infertile. These studies were therefore only of historical interest and will not be discussed further. Later, based mainly on results of studies in advanced HL, the ABVD regimen became the standard of care in early favorable HL. When compared with MOPP, ABVD had a better efficacy and produced less toxicity [26]. In particular, secondary leukemias and infertility are less frequently observed than after alkylating agent-containing regimens.

Two randomized studies, one in Europe and one in the United States, showed the benefit of adjuvant chemotherapy with a short course of ABVD or ABVD-like chemotherapy in early favorable patients: GHSG HD7 trial compared EFRT alone with CMT consisting of two cycles of ABVD followed by EFRT in 650 early favorable patients [10]. A significant advantage in freedom from treatment failure (FFTF) was seen after CMT, mainly related to fewer relapses as compared with EFRT only (3 vs. 22 %). There were no differences in overall survival between treatment arms. Importantly, with a median follow-up of 87 months, CMT was not associated with significantly more acute or long-term toxicity. The US trial included more than 300 patients and confirmed the benefit of adjuvant radiotherapy given after a short course of limited chemotherapy in clinically staged IA and IIA patients [27]. The study showed that three cycles of doxorubicin and vinblastine (AV) followed by STNI were well tolerated and gave a superior failure-free survival compared with STNI alone. The conclusion from these two studies is that the number of relapses can be reduced by the addition of ABVD or ABVD-like chemotherapy to large radiation fields. However, these extensive radiation fields can cause severe late side effects.

In a small randomized US trial, the VBM regimen was combined with mantle field radiotherapy and produced comparable results to STNI in clinically favorable stage I–II patients [28]. However, VBM was later abandoned due to concern of pulmonary toxicity. The Group Pierre-et-Marie-Curie showed that it was possible to replace the classic mantle field irradiation by a more limited radiotherapy to initially involved areas only. This novel approach termed IFRT involved the addition of chemotherapy to control occult disease in uninvolved areas [29]. IFRT reduced the irradiation of normal tissues, such as breast, heart, and lungs.

Therefore, several groups performed randomized trials comparing STNI with a combined modality approach in which patients received smaller radiation fields and combination chemotherapy. The results of a selection of some of the largest trials are listed in Table 11.4.

In the EORTC H7F trial in 333 patients with early favorable disease, six cycles of EBVP were followed by IFRT and randomly compared with

Table 11.3 Chemotherapy regimens used in early stage favorable HL

Regimen	Drug combinations
ABVD	Doxorubicin, vinblastine, bleomycin, dacarbazine
EBVP	Epirubicin, bleomycin, vinblastine, prednisone
MOPP	Mechlorethamine, vincristine, procarbazine, prednisone
MOPP–ABV	Mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine
Stanford V	Vinblastine, doxorubicin, vincristine, bleomycin, mechlorethamine, etoposide, prednisone
VBM	Vinblastine, methotrexate, bleomycin

STNI [30]. EBVP was assumed to be potentially less toxic but similarly effective compared to ABVD. There were significantly more treatment failures in the STNI arm, especially in nonirradiated lower abdominal and extranodal areas. EBVP combined with IFRT proved to be effective in these favorable patients; the 10-year event-free survival rate after EBVP and IFRT was 10 % better than after STNI alone, whereas overall survival was 92 % in both arms. This trial demonstrated that EFRT could be replaced by CMT including IFRT. However, in early unfavorable patients, EBVP was significantly less efficient than MOPP–ABV [30]. Randomized comparisons of EBVP and ABVD have not been performed.

In the subsequent H8F trial by the EORTC–GELA, more than 500 favorable HL patients were randomized between STNI or CMT consisting of three cycles of MOPP–ABV hybrid followed by IFRT [9]. Patients in the CMT arm had a lower relapse rate, which resulted in a significantly higher event-free survival rate than for patients in the STNI arm (93 vs. 68 % at 10 years). Importantly, patients in the combined modality arm also had a significantly higher overall survival than patients in the STNI arm (97 vs. 92 % at 10 years) (see Fig. 11.3). The results of this study again demonstrated the superiority of CMT over EFRT alone and showed that IFRT is a sufficient treatment after chemotherapy for early favorable HL. However,

Table 11.4 Early stage favorable HL: selection of studies comparing STNI alone with combined modality treatment (CMT)

Trial	Year	Study arms	Number of patients	Outcome	Overall survival	Reference
SWOG/CALGB	1989–2000	A. STNI (36–40 Gy)	326	A. 81 % FFS (3 years)	Follow-up too short	Press et al. [27]
		B. 3 AV + STNI (36–40 Gy)		B. 94 % FFS (3 years)		
				$p<0.001$		
Stanford–Kaiser Permanente	1988–1995	A. STNI (30–44 Gy)	78	A. 92 % PFS (5 years)	A. 98 % OS (5 years)	Horning et al. [28]
		B. 6 VBM + mantle field RT		B. 87 % PFS (5 years)	B. 94 % OS (5 years)	
				$p=0.73$ (NS)	$p=0.05$ (NS)	
EORTC H7F	1988–1993	A. STNI (36 Gy)	333	A. 78 % EFS (10 years)	A. 92 % OS (10 years)	Noordijk et al. [30]
		B. 6 EBVP + IFRT (36 Gy)		B. 88 % EFS (10 years)	B. 92 % OS (10 years)	
				$p=0.0113$	$p=0.79$ (NS)	
EORTC–GELA H8F	1993–1999	A. STNI (36 Gy)	542	A. 68 % EFS (10 years)	A. 92 % OS (10 years)	Fermé et al. [9]
		B. 3 MOPP–ABV + IFRT (36 Gy)		B. 93 % EFS (10 years)	B. 97 % OS (10 years)	
				$p<0.001$	$p=0.001$	
GHSG HD7	1994–1998	A. EFRT 30 Gy (IFRT 40 Gy)	627	A. 67 % FFTF (7 years)	A. 92 % OS (7 years)	Engert et al. [10]
		B. 2 ABVD + EFRT 30 Gy (IFRT 40 Gy)		B. 88 % FFTF (7 years)	B. 94 % OS (7 years)	
				$p<0.0001$	$p=0.43$ (NS)	

SWOG Southwest Oncology Group, *CALGB* Cancer and Leukemia, *EORTC* European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *STNI* subtotal nodal irradiation, *IFRT* involved-field radiotherapy, *EFRT* extended-field radiotherapy, *Gy* Gray, *FFS* failure-free survival, *PFS* progression-free survival, *EFS* event-free survival, *FFTF* freedom from treatment failure, *OS* overall survival, *NS* not significant

due to its carcinogenic potential, MOPP–ABV was abandoned in favor of ABVD. Therefore, this trial cannot be used to draw firm conclusions regarding the number of cycles of ABVD required as part of CMT.

11.5.2 Optimal Number of Cycles of Chemotherapy

The use of fewer cycles of ABVD could potentially reduce late side effects of combined modal-

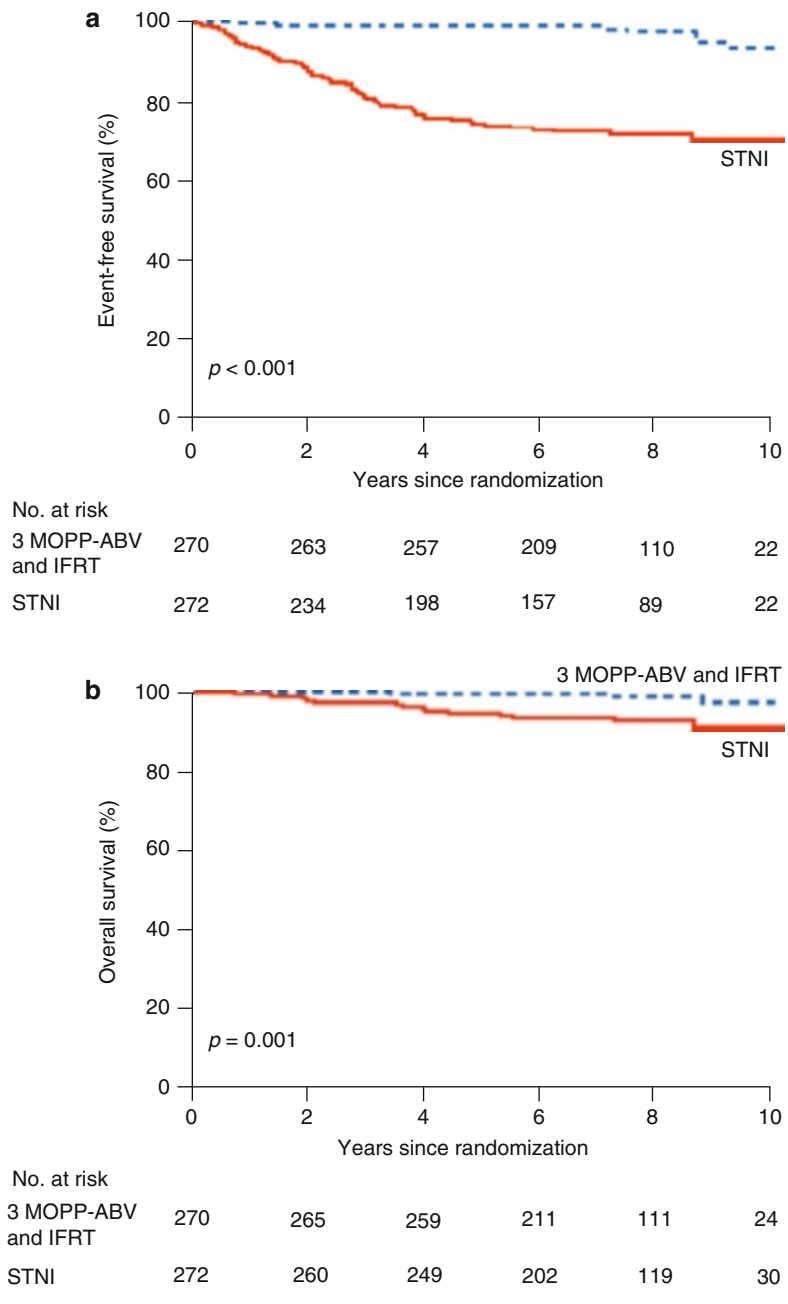

Fig. 11.3 Kaplan–Meier estimates of event-free and overall survival among 542 patients with a favorable prognosis in the EORTC–GELA H8F trial. At 10 years, event-free survival was 93 % in the group that received MOPP–ABV–IFRT and 68 % in the STNI group ($p < 0.001$) (**a**) and overall survival was 97 and 92 %, respectively ($p = 0.001$) (**b**) (Reprinted from Ferme et al. [9] with permission)

ity therapy. Between 1998 and 2003, the GHSG HD10 trial accrued more than 1,300 favorable prognosis stage I–II HL patients. Patients were randomized to four arms in a 2×2 factorial design: two cycles of ABVD followed by 30 Gy IFRT; two cycles of ABVD followed by 20 Gy IFRT; four cycles of ABVD followed by 30 Gy IFRT; and four cycles of ABVD followed by 20 Gy IFRT. This trial tested a possible reduction in the number of ABVD cycles as well as reduction of radiation dose when using IFRT. With a median follow-up of 90 months, there were no significant differences in FFTF and overall survival at 5 years between four or two cycles of ABVD. In addition, there was also no difference between 30 and 20 Gy IFRT [31]. Importantly, there was also no significant difference in terms of overall survival, FFTF, and progression-free survival when all four arms were compared. The results were robust with longer follow-up (8 years). The treatment arms with four cycles of ABVD and 30 Gy IFRT showed significantly more acute toxicity in comparison with two cycles of ABVD and 20 Gy IFRT. Two cycles of ABVD followed by 20 Gy IFRT are thus the new GHSG standard of care for HL patients in early favorable stages.

11.5.3 Optimal Chemotherapy Combination

Reduction of chemotherapy-induced toxicity was pursued in the GHSG HD13 trial. This trial investigated whether drugs can be omitted from the ABVD regimen and randomized patients with early favorable HL to two cycles of either ABVD, AVD, ABV, or AV with all arms followed by 30 Gy IFRT. The final results were presented in 2013 at the 9th International Symposium on Hodgkin Lymphoma in Cologne. Compared with ABVD, the 5-year FFTF was reduced up to 11.7 % (ABV) or 16 % (AV) when dacarbazine was deleted and reduced up to 3.9 % (AVD) by the deletion of bleomycin. The reduction in FFTF did not translate into poorer OS [32]. Therefore, it seems that dacarbazine and bleomycin are important therapeutic agents in ABVD. The Stanford group has reported good results in 87 patients with stage I or IIA non-bulky HL treated with an abbreviated Stanford V regimen administered weekly for 8 weeks followed by 30 Gy modified IFRT [33]. At a median follow-up of 10 years, the FFP was 94 %.

11.5.4 Optimal Radiation Dose

Apart from the choice of cytostatic agents and the number of courses, the question of radiation field size and dose has also been evaluated (for a selection of randomized trials, see Table 11.5). A decline in late complications is expected with lower radiation doses as their incidence is correlated with the amount of radiation given.

Two randomized trials have investigated radiation doses in early favorable HL patients treated with CMT. In the EORTC–GELA H9F trial, 783 patients with stage I–II disease and favorable characteristics received six cycles of EBVP. Patients in complete remission after chemotherapy were randomized to receive standard dose IFRT (36 Gy), low-dose IFRT (20 Gy), or no RT at all. This trial thus evaluated the role of IFRT and potential differences in the radiation dose delivered. The experimental arm without RT was closed early due to an excess failure rate compared with the two RT arms: only 70 % event-free survival at 4 years for the non-RT arm vs. 84 and 87 % for the 20 and 36 Gy IFRT arms, respectively [35]. Therefore, it can be concluded that in favorable patients who achieve a complete remission after six cycles of EBVP, omission of IFRT leads to an unacceptable failure rate. Although no differences in outcome were reported between the two radiation dose levels, follow-up is too short to draw definite conclusions, including those on late effects.

As discussed in Sect. 11.5.2, the GHSG HD10 trial compared doses of 30 and 20 Gy IFRT after two or four cycles of ABVD. No significant differences were observed between patients receiving 30 Gy IFRT and 20 Gy IFRT in terms of overall survival (97.7 vs. 97.5 %), FFTF (93.4 vs.

Table 11.5 Early stage favorable HL: selection of studies of RT field size and dose in CMT

Trial	Year	Study arms	Number of patients	Outcome	Overall survival	Reference
Milan	1990–1997	A. 4 ABVD + STNI 36–40 Gy	133	A. FFP 93 % (12 years)	A. OS 96 % (12 years)	Bonadonna et al. [34]
		B. 4 ABVD + IFRT 36–40 Gy		B. FFP 94 % (12 years)	B. OS 94 % (12 years)	
EORTC–GELA H9F	1998–2004	A. 6 EBVP + IFRT 36 Gy	783	A. EFS 87 % (4 years)	A. OS 98 % (4 years)	Noordijk et al. [35], abstract
		B. 6 EBVP + IFRT20 Gy		B. EFS 84 % (4 years)	B. OS 98 % (4 years)	
		C. 6 EBVP (no RT)		C. EFS 70 % (4 years)	C. OS 98 % (4 years)	
		Median follow-up 33 months		No RT arm closed because of excess failure rate ($p<0.001$)		
GHSGHD10	1998–2003	A. 2 ABVD + IFRT 30 Gy	1.370	No differences in FFTF between patients given two or four cycles of ABVD or 20 or 30 Gy IFRT (FFTF 91–93 %)	No survival differences between patients given two or four cycles of ABVD or 20 or 30 Gy IFRT (OS 96–97 %)	Engert et al. [31]
		B. 2 ABVD + IFRT 20 Gy				
		C. 4 ABVD + IFRT 30 Gy				
		D. 4 ABVD + IFRT 20 Gy				
		Median follow-up 91 months				

EORTC European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *STNI* subtotal nodal irradiation, *IFRT* involved-field radiotherapy, *RT* radiotherapy, *Gy* Gray, *FFP* freedom from progression, *OS* overall survival, *EFS* event-free survival, *FFTF* freedom from treatment failure

92.9 %), and progression-free survival (93.7 vs. 93.2 %), respectively [31]. Therefore, IFRT with a dose of 20 Gy seems to be sufficient after two cycles of ABVD.

11.5.5 Optimal Radiation Field Size

The rationale for reduced radiation therapy field size is to further improve the therapeutic ratio. Smaller radiation fields should also lead to a decrease in late complications such as cardiovascular and secondary cancers as the amount of irradiated normal tissue was reduced. Several randomized trials in early unfavorable HL have shown that after effective chemotherapy, IFRT is as effective as EFRT in terms of overall survival and FFTF [9, 36]. However, data from randomized trials in patients with early favorable HL are scarce.

Bonadonna et al. reported the long-term follow-up of 133 patients with early HL randomly assigned to IFRT or STNI after four cycles of ABVD and found no significant differences in overall survival (94 vs. 96 %) or freedom from progression (94 vs. 93 %) at 12 years [34] (see Table 11.5). The limited size of the patient sample, however, had no adequate statistical power to test for non-inferiority of IFRT vs. STNI.

Is it possible to further reduce the field size beyond IFRT? Based on the observation that in patients treated with chemotherapy alone, recurrences typically occur in sites of initial nodal involvement, the EORTC–GELA group introduced the concept of involved-node radiotherapy (INRT) [37, 38]. INRT only includes the initially involved lymph nodes with a small isotropic margin. Identifying and contouring involved lymph

nodes is of outmost importance. Therefore, it is recommended that all patients have cervical and thoracic CT scans pre- and post-chemotherapy, preferably in the treatment position, and must be examined by the radiation oncologist before the start of the chemotherapy [37, 39]. Better sparing of normal tissues such as the salivary glands, heart, coronary arteries, and breast in female patients is expected with the use of INRT compared to IFRT (Fig. 11.4). The new INRT concept was applied in the EORTC–GELA–FIL H10 randomized trial for patients with early stage HL (see Fig. 11.5 for the trial design).

Canadian researchers reported promising results with INRT in a retrospective study, although the definition of INRT was not exactly the same as that of the EORTC–GELA–FIL group and a greater radiation margin was applied [40]. In British Columbia, patients with limited stage HL, defined as stage IA or IIA with tumor bulk less than 10 cm, are treated according to province-wide guidelines consisting of combined chemotherapy and radiation therapy. The extent of the radiation therapy field size underwent serial changes during the last decades, from EFRT to IFRT and eventually since 2001 to INRT with margins from 1.5 to 5 cm. There were no statistically significant differences among the three groups for progression-free survival and overall survival. There were also no marginal recurrences in the INRT patient group [40]. Clearly, the exact definition

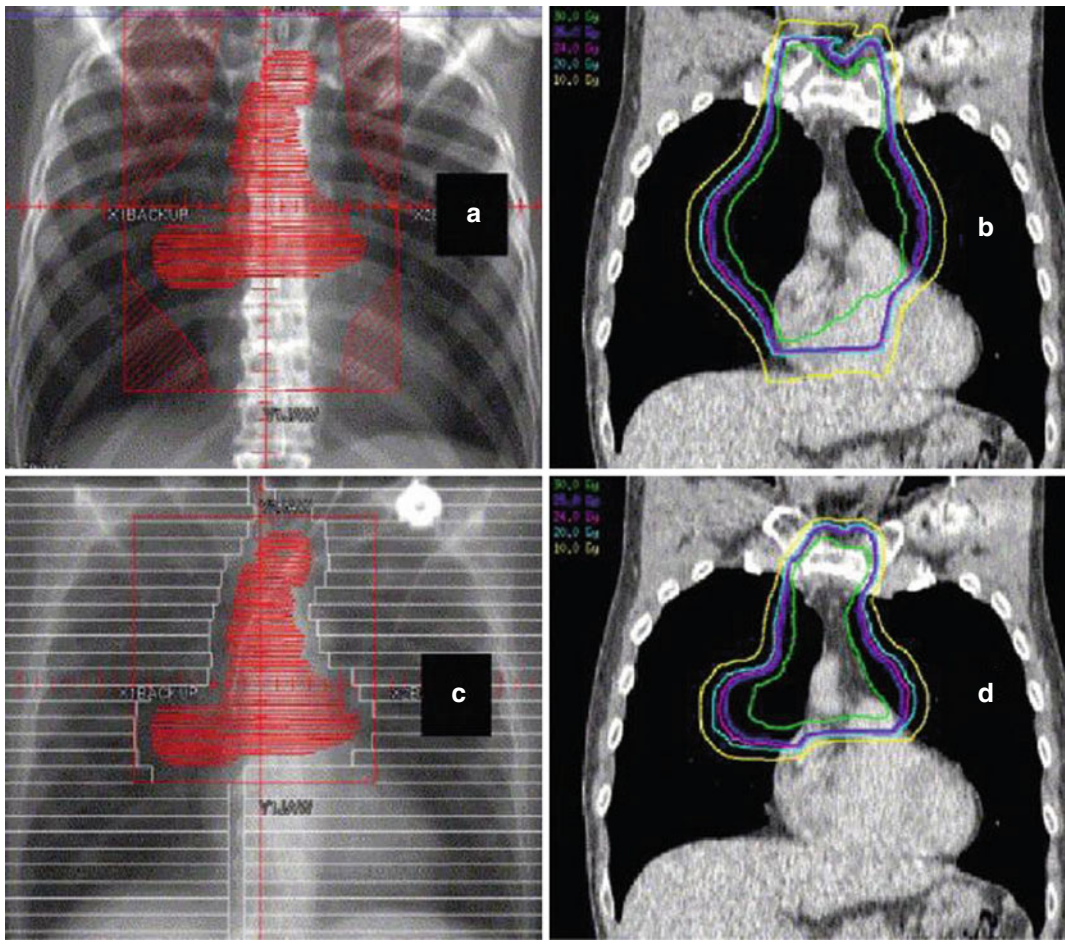

Fig. 11.4 Comparison between radiation field sizes and the volume of heart irradiation using either IFRT (**a**, **b**) or INRT (**c**, **d**) for a mediastinal tumor mass (PTV in *red color*) (Reprinted from Girinsky et al. [37] with permission)

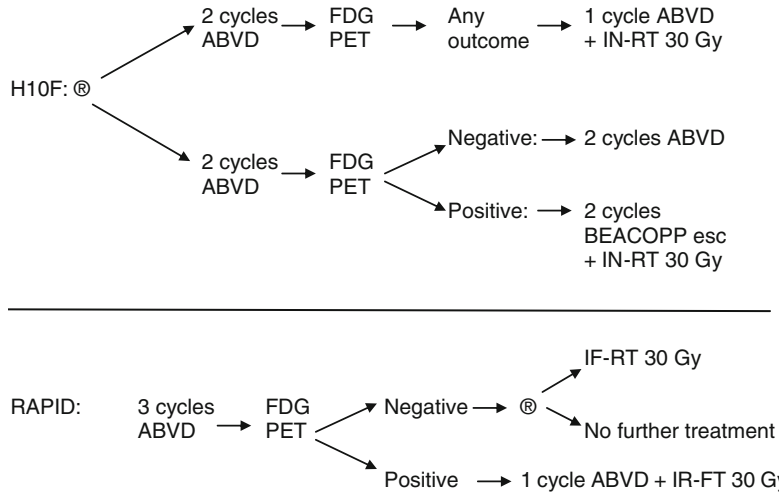

Fig. 11.5 Designs of the EORTC/LYSA/FIL H10 favorable trial and the RAPID/UK trial (62.6 % favorable) for early stage HL. ® randomization, *INRT/IFRT* involved-node/involved-field radiotherapy

of INRT is still in evolution and requires further investigation prior to its incorporation into routine practice.

11.6 Chemotherapy Alone

The potentially life-threatening late side effects of radiotherapy for HL patients have raised the question whether those in early stage disease can be treated with chemotherapy alone. This question is particularly relevant for patients in whom the risk of RT-induced toxicity is deemed less acceptable. Chemotherapy-only protocols have been successfully used in children and adolescents (see Chap. 15 on pediatric HL). However, few data exist on their role in adults. Table 11.6 shows a selection of randomized trials performed in adult patients with early favorable HL dealing with the issue of chemotherapy alone. These trials encountered a number of problems with design, patient accrual, as well as variations in the type of chemotherapy and field size of radiation therapy utilized.

The use of chemotherapy alone is not a new concept. Two randomized trials published in the early 1990s compared MOPP as first-line therapy in early stage HL with radiotherapy: a preliminary analysis of a small randomized US trial in laparotomy-staged patients suggested that MOPP alone was at least as effective as radiation in a subset of patients with more favorable prognostic features [41]. Another small trial from Italy performed in laparotomy-staged early favorable and unfavorable patients showed a very low overall survival at 8 years after MOPP (56 %) compared with 93 % in the EFRT arm, whereas freedom from progression- and relapse-free survival were similar in both groups. In contrast to the US study, the rescue rate of patients who relapsed after MOPP was significantly lower than that observed after radiotherapy [42]. However, the two studies are not comparable, because of the distinct criteria adopted for the selection of patients.

The National Cancer Institute of Canada (NCI-C) and the Eastern Cooperative Oncology Group (ECOG) conducted a randomized phase III trial addressing the role of chemotherapy alone (ABVD) for early favorable and unfavorable HL. Favorable patients had the following characteristics: age <40 years, ESR <50 mm/h, lymphocyte-predominant or nodular sclerosing histology, no bulky disease, and less than four nodal sites involved. The experimental arm consisted of four cycles of ABVD alone if a complete remission was achieved after two cycles. Otherwise, patients received six cycles. The standard arm was STNI with 35 Gy. Among the favorable-risk patients, there was no difference between the two arms for event-free survival, freedom from disease progression, and overall

Table 11.6 Early stage favorable HL: selection of randomized studies of chemotherapy alone in adult patients

Trial	Year	Study arms	Number of patients	Outcome	Overall survival	Reference
NCI-US	1978–1989	A. 6–8 MOPP	84	A. DFS 82 % (10 years)	A. OS 90 % (10 years)	Longo et al. [41]
		B. Radiotherapy		B. DFS 67 % (10 years)	B. OS 85 % (10 years)	
				p=NS	p=NS	
Rome–Florence	1979–1982	A. Mantle field + para-aortic RT (36–44 Gy)	89	A. RFS 70 % (8 years)	A. OS 93 % (8 years)	Biti et al. [42]
		B. 6 MOPP		B. RFS 71 % (8 years)	B. OS 56 % (8 years)	
				p=NS	p<0.001	
NCI-C/ECOG HD6	1994–2002	A. 4–6 ABVD	123	A. EFS 87 % (5 years)	A. OS 97 % (5 years)	Meyer et al. [43]
		B. STNI		B. EFS 88 % (5 years)	B. OS 100 % (5 years)	
				p=0.6 (NS)	p=0.3 (NS)	
EORTC–GELA H9F	1998–2004	A. 6 EBVP + IFRT 36 Gy	783	A. EFS 87 % (4 years)	A. OS 98 % (4 years)	Noordijk et al. [35], abstract
		B. 6 EBVP + IFRT 20 Gy		B. EFS 84 % (4 years)	B. OS 98 % (4 years)	
		C. 6 EBVP (no RT)		C. EFS 70 % (4 years)	C. OS 98 % (4 years)	
		Median follow-up 33 months		No RT arm closed because of excess failure rate (p<0.001)		
Memorial Sloan Kettering Cancer Center	1990–2000	A. 6×ABVD	152	A. FFP 81 % (5 years)	A. OS 90 % (5 years)	Strauss et al. [44]
		B. 6×ABVD + RT		B. FFP 86 % (5 years)	B. OS 97 % (5 years)	
				p=0.61 (NS)	p=0.08 (NS)	

NCI-US National Cancer Institute United States, *EORTC* European Organization for Research and Treatment of Cancer, *NCI-C* National Cancer Institute of Canada, *ECOG* Eastern Cooperative Oncology Group, GELA Groupe d'Etude des Lymphomes de l'Adulte, *STNI* subtotal nodal irradiation, *IFRT* involved-field radiotherapy, *RT* radiotherapy, *Gy* Gray, *NS* not significant, *FFP* freedom from progression, *OS* overall survival, *DFS* disease-free survival, *RFS* relapse-free survival, *EFS* event-free survival

survival after a median follow-up of 11.3 years [43]. However, longer follow-up is still needed to determine late toxicities.

Only two randomized trials comparing CMT with chemotherapy alone in early favorable patients have been published. As discussed in Sect. 11.5.4, one was the EORTC–GELA H9F trial in which IFRT in 36 Gy was compared with 20 Gy or no radiotherapy in CR patients after six cycles of EBVP. The chemotherapy-only arm was prematurely closed due to an excessive number of relapses [35].

The Memorial Sloan Kettering Cancer Center randomized early non-bulky HL patients between six cycles of ABVD alone and six cycles of ABVD plus 36 Gy radiotherapy. Of the 76 patients randomized to radiotherapy, 11 received IFRT; the rest received modified EFRT. Due to the poor accrual rate, the trial was closed before completion and only 152 patients were randomized. No significant differences were observed between CMT and chemotherapy alone, but the sample size was insufficient [44].

11.7 Treatment Adaptation Based on PET Scan Response

PET is becoming an important tool for staging and response assessment in HL (see Chap. 7). Functional imaging with FDG-PET enables evaluation of early metabolic changes rather than the morphologic changes occurring later during treatment. Several studies using PET after two or three cycles of ABVD have shown that early metabolic changes are predictive of the final treatment response and progression-free survival [45–47]. Most studies with early interim PET were performed in patients with advanced stages. A negative interim PET has been associated with an event-free survival of 90 % and higher, whereas a positive interim PET has been associated with event-free survival of only 0–13 %. The negative predictive value of interim PET in HL is high with 94–100 % rates reported on relatively short follow-up. However, the positive predictive value of interim PET has varied from 61 to 100 % [48]. This understanding has led to the use of PET scanning for early treatment response assessment as surrogate test of chemosensitivity. Given that a substantial fraction of patients with early favorable HL might currently be overtreated, there is a potential benefit in identifying patients who might be eligible for less intensive treatment. However, reduction of treatment based on negative interim PET has not been proven safe yet. Likewise, no data exist to support the hypothesis that intensification of therapy based on a positive interim PET improves the clinical outcome.

Several large randomized controlled trials have incorporated PET response-adapted therapy into their designs. Results of two large randomized phase III clinical trials investigating the effect of reducing treatment intensity by omitting radiotherapy for patients with negative interim PET scans have been communicated, i.e., the EORTC/LYSA/FIL H10F trial and the NCRI Lymphoma Group RAPID trial performed in the United Kingdom [49–52]. The trial designs are presented in Fig. 11.5.

The preliminary results of these two trials are briefly summarized in Table 11.7.

The European H10 trial closed prematurely with a median follow-up of only 13 months due to futility based on 33 events. The difference between PET-negative patients as regards 1-year PFS was 5.1 % in favor of patients receiving INRT [49, 50]. The follow-up in the RAPID trial was much longer (48.6 months) and the final analysis based on 36 events showed a difference in 3-year PFS of only 3.7 % in favor of PET-negative patients receiving IFRT [51, 52]. The H10 trial was closed early due to futility; the RAPID trial was considered to be positive. However, comparing the outcome of both trials shows a quite similar reduction in disease control if no additional radiotherapy is given to PET-negative patients. Obviously, this was to be expected prior to the start of these studies and should be outweighed against a possible improved long-term survival (less late toxic deaths; less secondary malignancies) in those patients who

Table 11.7 Preliminary results of H10-F and RAPID trials

European H10-F trial	UK RAPID trial
Trial closed early due to futility	Trial considered positive
444 patients	600 patients
Median follow-up 13 months	Median follow-up 48.6 months
Futility analysis based on 33 events	Final analysis based on 36 events
Non-inferiority margins 10 %	Non-inferiority margins 7 %
PET2-negative patients:	PET2-negative patients:
1-year PFS 94.9 % if no RT	3-year PFS 90.8 % if no RT
1-year PFS 100 % if INRT	3-year PFS 94.5 % if IFRT
No OS analysis	PET2-negative patients:
	3-year OS 99.5 % if no RT
	3-year OS 97.0 % if IFRT

PFS progression-free survival, *OS* overall survival, *INRT* involved-node radiotherapy, *IFRT* involved-field radiotherapy

received no additional radiotherapy. Results from at least 10–20 years follow-up are needed to support this hypothesis.

The GHSG HD16 trial in early stage favorable patients who have become PET-negative after two cycles of ABVD compares 20 Gy IFRT with no further treatment. All PET-positive patients will receive 20 Gy IFRT. Results are not yet available.

11.8 Recommendations and Future Directions

In most parts of the world, CMT strategies including two to three cycles of ABVD followed by 20–30 Gy IFRT are the current standard treatment for patients with early favorable HL. With this approach, FFTF rates of more than 90 % and an overall survival of nearly 95 % are reached. HL-related death is unusual and mortality is mainly due to late toxicity. Even strategies that provide very high freedom from recurrence may not be optimal, since, depending on the strategy used, treatment-related mortality at 10–20 years may exceed HL mortality in this low-risk group. Therefore, the choice of a given strategy must not only be judged by the tumor control but also be weighed against acute and chronic morbid side effects. New criteria such as quality of life are also becoming more important [53]; (Chap. 23).

Over the last decades, several strategies have attempted to reduce late complications in HL patients by giving less chemotherapy or radiotherapy. It should be realized that most long-term results are not known yet. Therefore, it remains to be seen which strategy provides the best balance between treatment efficacy and toxicity. At present, the goal in early favorable HL is to maintain the excellent efficacy with as little complications as possible. One of the key questions in early favorable HL is which patients might be safely treated with chemotherapy alone. In this respect, results from two recent large, randomized trials (H10/RAPID) deleting additional radiotherapy in patients achieving a PET-negative complete remission after two or three cycles of ABVD are encouraging, i.e., 4–5 % loss of local tumor control which might be compensated for by less (lethal) late side effects induced by radiation. However, longer follow-up is needed to reach firm conclusions.

In summary, it is clear that HL is the ultimate type of malignancy in which the consecutive improvement in outcome was achieved by carefully planned subsequent prospective phase III randomized clinical trials performed by the various lymphoma groups throughout the world. The challenge for the next decade is to focus on targeted treatment, thereby preventing early and late toxicities due to damage of normal tissues by the cytostatic agents and radiation employed. In this respect, a variety of new developments in the treatment arena are currently recognized, among others, targeting the microenvironment in HL, developing and testing new antibodies which specifically target Reed–Sternberg cells (Chap. 21), and exploring a number of small molecules interfering with specific signal pathways that maintain the proliferation of Hodgkin cells (Chap. 22), etc. These and future strategies are all based on better insight into the molecular pathology of HL. Further intensification of translational research is therefore of utmost importance, to provide our patients with patient-tailored treatment leading to the highest possible cure rates and at the same time preventing major toxic side effects.

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Treatment of Early Unfavorable HL

12

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Contents

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12.1 Introduction

Early unfavorable or intermediate-stage Hodgkin lymphoma usually includes patients in stages I and IIA with clinical risk factors such as large mediastinal mass, extranodal disease, high ESR, or more than three or four nodal areas involved. In addition, selected stage IIB patients are also included in this risk group. The current treatment for these patients is based on four cycles of ABVD chemotherapy followed by involved-field radiotherapy. A more aggressive approach with two cycles of BEACOPP escalated followed by two cycles of ABVD has recently shown better tumor control but no advantage in overall survival yet. More cycles of chemotherapy have not resulted in better outcome in early unfavorable patients. One of the major current controversies in this risk group is the use of PET to guide treatment intensity or the use of additional radiotherapy in PET-negative patients. This chapter will give you an overview on the past and current treatment approaches and will highlight the discussion on PET-guided treatment in these patients.

12.2 Why Early Unfavorable?

The Ann Arbor staging system with the 1989 Cotswolds modifications [1] is still being used worldwide in the staging of patients with HL. Modern staging procedures recommend the

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_12,

routine use of FDG-PET/CT scanning at diagnosis [2]. Through the introduction of FDG-PET/CT scanning at diagnosis, patients will be upstaged in up to 30 % mainly from early to advanced stages. In addition, the extent of radiation fields in CS I/II disease can be influenced by identifying additional lesions by FDG-PET scanning [2, 3]. In the past, patients with limited-stage I/II disease were treated with extended-field radiotherapy (RT), whereas those with more advanced stage III or IV received multi-agent chemotherapy. Up to the 1990s of the twentieth century, staging laparotomy was performed to more reliably identify patients with disease truly limited to one side of the diaphragm. The successful introduction of chemotherapy in advanced stages and its potential to eradicate occult disease, the relapse rates of up to 30 % after extended-field RT alone, and the increasing awareness of serious long-term toxicity after extended-field RT promoted the development of combined modality treatment approaches. Combined modality has the evident advantage of combining two efficacious treatment modalities. It is given as combination of a fixed number of chemotherapy cycles followed by a certain dose and extent of RT. As a result, the extent of both RT and chemotherapy could be reduced in the combined treatment design as compared to administering single-treatment modalities. However, even in stage I/II, the extent of disease varies substantially requiring a risk-adapted treatment. In many early-stage patients, mediastinal bulky disease is present, which has been demonstrated as prognostically unfavorable. Other poor prognostic clinical factors include higher age, increased number of involved nodes, and elevated erythrocyte sedimentation rate (ESR), accompanied by B symptoms. Though slight differences in definition exist between major cooperative groups, CS I/II HL patients in Europe are generally divided into an early favorable and an early unfavorable (intermediate) subgroup. In contrast, patients in North America presenting with adverse factors (mainly the presence of bulky disease) are treated like stage III–IV disease and are not included in clinical trials for CS I/II disease. At present, progression-free survival rates of 85–90 % are common for patients with unfavorable CS I/II disease treated with a combined modality approach.

12.3 Prognostic Factors

The factors used by the European Organisation for Research and Treatment of Cancer (EORTC) Lymphoma Group, the German Hodgkin Study Group (GHSG), the National Cancer Institute of Canada (NCIC), and the Eastern Cooperative Oncology Group (ECOG) are shown in Table 12.1 [1, 4]. We have to bear in mind that these risk factors and the resulting prognostic groups were originally defined in the context of treatment with extended-field RT. In a combined modality setting, the differences in prognosis between favorable and unfavorable disease are likely to be smaller. Moreover, in more recent series, the treatment had already been tailored according to the prognostic groups. Thus, one would have anticipated that these prognostic factors today have less independent prognostic significance. However, a large randomized trial included a joint experimental treatment arm for both favorable and unfavorable subgroups, thus possibly addressing the current impact of predictive factors. In this trial, EORTC H7 [5], the unfavorable subset of patients was randomized between six cycles of EBVP (epirubicin, bleomycin, vinblastine, prednisone), a combination presumed to be less toxic and equally effective to ABVD [6], and six cycles of MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone, Adriamycin, bleomycin, vinblastine, and dacarbazine), both followed by 30–36 Gy involved-field RT (IF-RT). After a median follow-up of 9 years, patients treated with EBVP had a significantly higher rate of tumor progression and relapse than those treated with MOPP/ABV resulting in a significantly inferior 10-year event-free survival (EFS) of 68 vs. 88 % ($p<0.001$) (Fig. 12.1, upper chart). The favorable subset of patients was randomized between six cycles of EBVP followed by IF-RT and subtotal nodal irradiation (STNI), considered standard treatment at the time of initiation of the trial. Those treated with EBVP had a superior 10-year

Table 12.1 Definition of favorable and unfavorable (intermediate) early-stage Hodgkin lymphoma

	EORTC	GHSG	NCIC/ECOG
Risk factors	(a) Large mediastinal mass	(a) Large mediastinal mass	(a) Histology other than LP/NS
	(b) Age ≥50 years	(b) Extranodal disease	(b) Age ≥40 years
	(c) ESR ≥50 without B symptoms or ≥30 with B symptoms	(c) ESR ≥50 without B symptoms or ≥30 with B symptoms	(c) ESR ≥50
	(d) ≥4 nodal areas	(d) ≥3 nodal areas	(d) ≥4 nodal areas
Favorable	CS I–II (supradiaphragmatic) without risk factors	CS I–II without risk factors	CS I–II without risk factors
Unfavorable	CS I–II (supradiaphragmatic) with ≥1 risk factors	CS I or CS IIA with ≥1 risk factors, CS IIB with (c) or (d) but without (a) and (b)	CS I–II with ≥1 risk factors

EORTC European Organisation for Research and Treatment of Cancer, *GHSG* German Hodgkin Study Group, *NCIC* National Cancer Institute of Canada, *ECOG* Eastern Cooperative Oncology group, *ESR* erythrocyte sedimentation rate, *LP* lymphocyte predominance, *NS* nodular sclerosis, *CS* clinical stage

EFS compared to patients treated with STNI alone: 88 vs. 78 % ($p=0.01$) (Fig. 12.1 lower chart). While the less toxic EBVP regimen produced superior results in the favorable subset of patients, the poor results in the unfavorable patients reflect the necessity for a more potent and intense treatment for this subgroup. Thus, the clinical relevance of the prognostic factors appeared to be maintained. Indirect evidence for the impact of discriminating between favorable and unfavorable early stages can be found in two other trials including patients with adverse prognostic factors, though differently defined. In a trial performed by the Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA), the less intense AOPE (Adriamycin, vincristine, prednisone, and etoposide) proved inferior to CVPP (cyclophosphamide, vincristine, procarbazine, prednisone) [7]. The Southwestern Oncology Group trial 9051 tested a less toxic combination of etoposide, vinblastine, and Adriamycin (EVA) followed by STNI and found an unacceptably high relapse rate mainly in non-irradiated areas indicating the inferiority of the chemotherapy [8]. Klimm et al. analyzed the impact of the three different staging and prognostic subgroup definitions on the outcome of 1,173 early-stage patients treated homogeneously in the HD10 and HD11 trials of the GHSG [9]. Figure 12.2 shows the PFS of these patients related to the GHSG, EORTC, and NCCN prognostic risk factors score, respectively: all three staging systems identified the unfavorable risk group. Especially tumor-specific (rather than patient-specific) risk factors such as mediastinal bulk and high tumor activity were predictive for poor outcome. For overall survival, the scores reflected the unfavorable risk profile as well (figures not shown). These data underline the continued usefulness of identifying a poor-risk group within the group of stage I/II disease though new risk factors with a higher specificity are needed.

12.4 Chemotherapy Regimens

After the initial Bonadonna report on ABVD [10] and the randomized trial on ABVD vs. MOPP vs. MOPP/ABVD in advanced disease [11], the NCIC/ECOG intergroup trial on ABVD vs. MOPP/ABV hybrid set the stage for ABVD as standard chemotherapy due to equal efficacy but less toxicity as compared with MOPP/ABV [12]. In an attempt to reduce toxicity even further, the GOELAMS (Groupe Ouest-Est d'Étude des

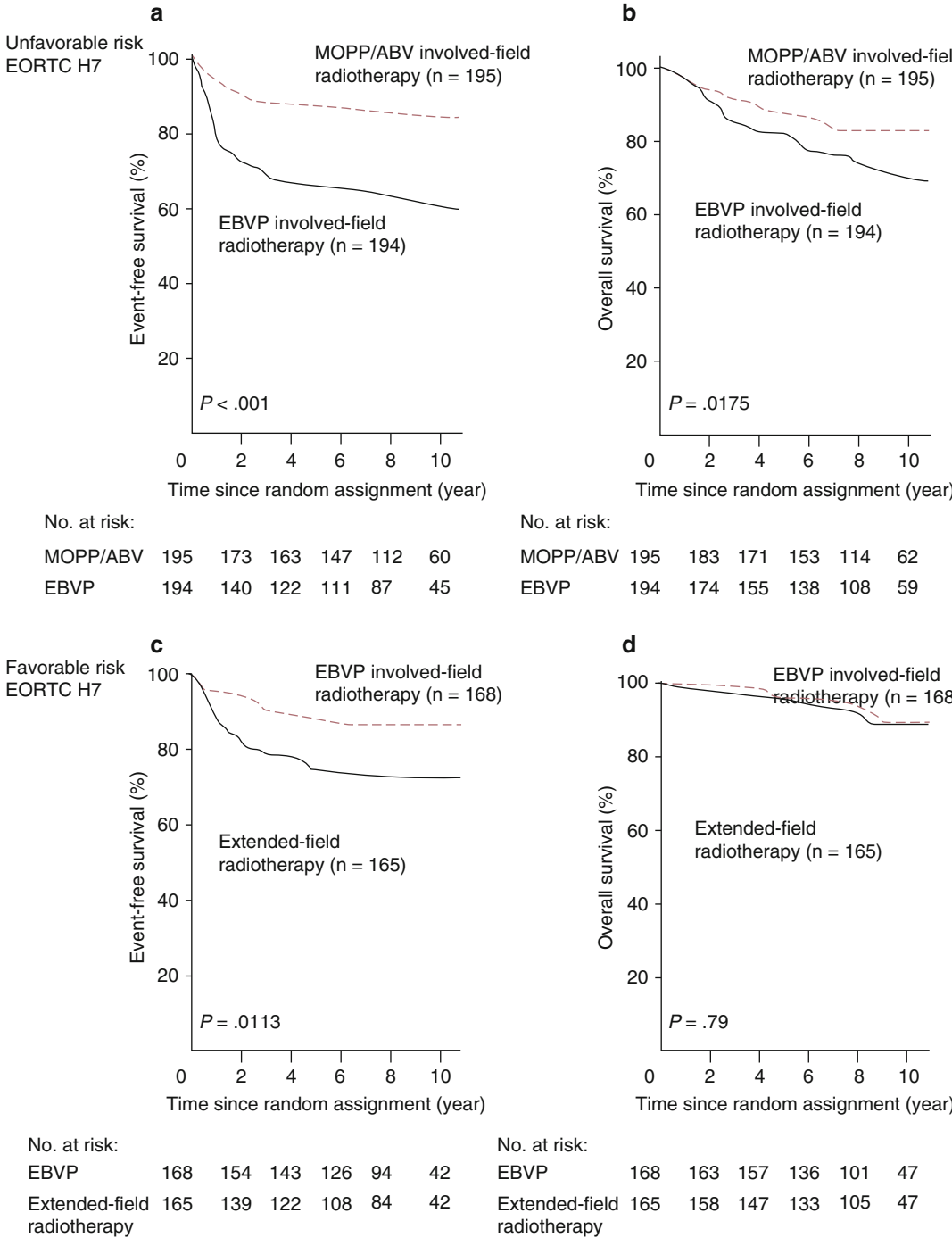

Fig. 12.1 In the *upper chart*, the estimated progression-free (PFS) (a) and overall survival (OS) (b) of the European Organisation for Research and Treatment of Cancer (*EORTC*) H7 randomized trial: MOPP/ABV vs. EBVP + involved-field radiotherapy in the unfavorable risk group are given; for comparison in the *lower chart*, the PFS (c) and OS (d) of the favorable risk groups are given for the EBVP + involved-field radiotherapy treatment arm vs. extended-field radiotherapy alone treatment arm [5]

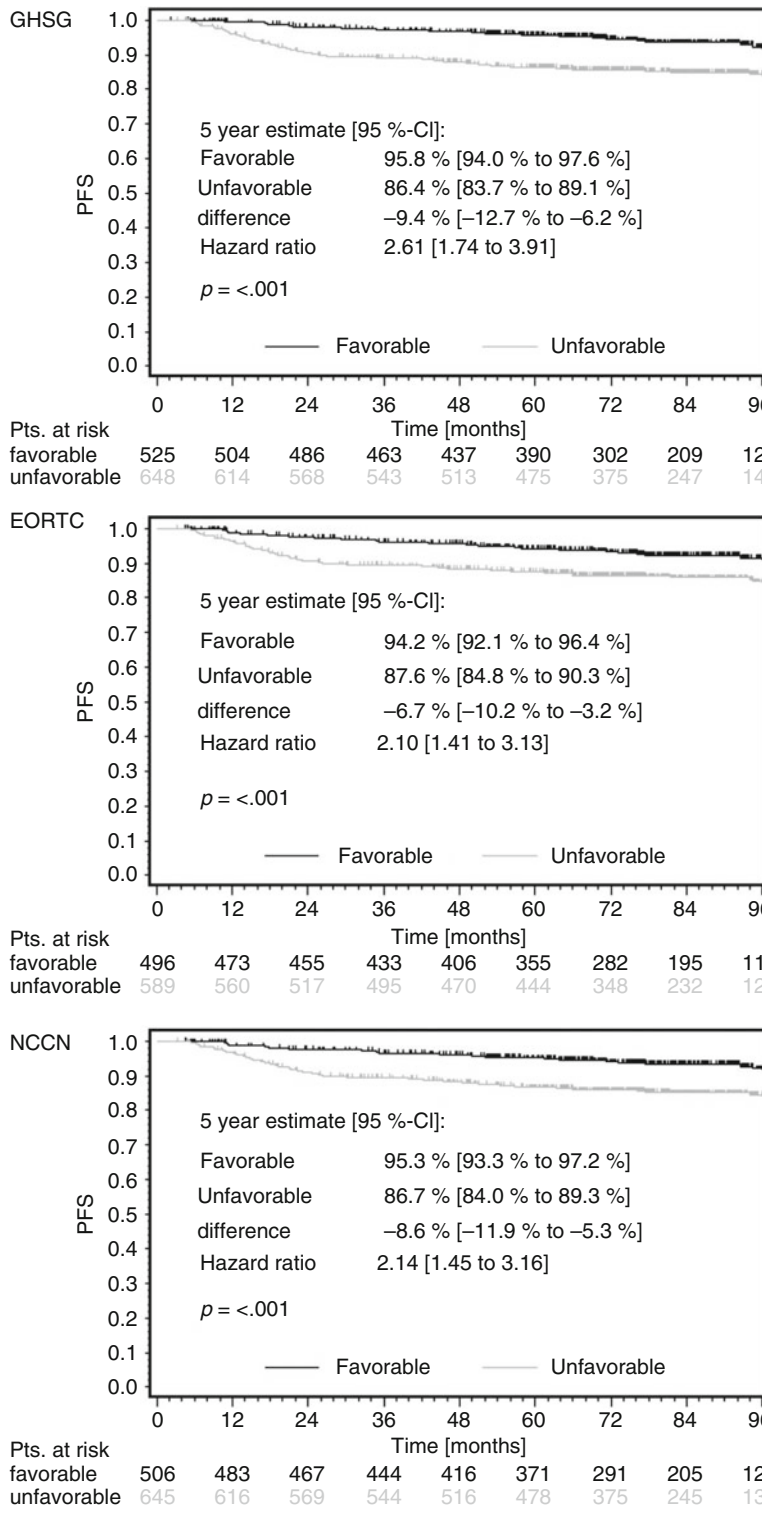

Fig. 12.2 Estimated progression-free survival using staging definitions of the German Hodgkin Study Group, the European Organisation for Research and Treatment of Cancer (*EORTC*), or National Comprehensive Cancer Network (*NCCN*) [9]

Table 12.2 Randomized clinical trials in unfavorable CS I/II disease on ABVD vs. alternative chemotherapy regimens

Trial (ref)	Treatment	Number of patients included	PFS (years)	OS (years)	Remarks
EORTC/GELA	ABVDx6 + IF-RT 30–36 Gy	276	91 % (4)	95 % (4)	Not final analysis
H9U [14]	ABVDx4 + IF-RT 30–36 Gy	277	87 % (4)	94 % (4)	EFS instead of PFS
	BEACOPPx4 + IF-RT 30–36 Gy	255	90 % (4)	93 % (4)	n.s.
GHSG HD11 [15]	ABVDx4 + IF-RT 30 Gy	356	87 % (5)	94 % (5)	Final analysis
	ABVDx4 + IF-RT 20 Gy	347	82 % (5)	94 % (5)	n.s.
	BEACOPPx4 + IF-RT 30 Gy	341	88 % (5)	95 % (5)	
	BEACOPPx4 + IF-RT 20 Gy	351	87 % (5)	95 % (5)	
GHSG HD14 [16, 17]	ABVDx4 + IF-RT 30 Gy	757	89 % (5)	97 % (5)	$p<0.001$ (PFS)
	BEACOPPesc.x2 + ABVD	744	95 % (5)	96 % (5)	$p=0.7$ (OS)
	x2 + IF-RT 30 Gy				
Intergroup USA [18]	ABVDx6 + IF-RT 36 Gy	395	74 % (5)	88 % (5)	n.s.
	Stanford V + IF-RT 36 Gy	399	71 % (5)	88 % (5)	70 % CSIII/IV

ref reference, *PFS* progression-free survival, *OS* overall survival, *EORTC* European Organisation for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *EFS* event-free survival, *IF-RT* involved-field radiotherapy, *n.s.* statistically not significant, *GHSG* German Hodgkin Study Group

Leucémies et Autres Maladies du Sang) included both early favorable and unfavorable patients in their H90-NM study [13]. A total of 386 patients were randomized between ABVDm (ABVD plus methylprednisolone) and the potentially less toxic EBVMm, followed by extended-field RT in responding patients. The ABVDm arm proved to be superior to the EBVMm treatment in terms of complete remission rates and FFS. Very similar to the conclusions of the EORTC H7 trial, these results highlight the need for sufficiently effective chemotherapy. Notwithstanding concerns on toxicity of chemotherapy and a reluctance to apply more intense treatment in CS I/II disease, one could argue that a 10–15 % failure rate in the unfavorable subset of patients is too high and warrants improvement. In this respect, the trials summarized in Table 12.2 are important. Both the EORTC H9U and the GHSG HD11 studies failed to show a significant PFS advantage for more intensive treatment comparing four cycles of BEACOPP baseline with four cycles of conventional ABVD [14, 15]. The GHSG follow-up trial for early unfavorable patients, HD14, compared four cycles of ABVD with two cycles of BEACOPP escalated followed by two cycles of ABVD ("2+2"). The decision for this combination was in part based on the higher effective dose (ED) model calculations [8, 19]. Here, four cycles of ABVD given over 16 weeks have an ED of 15 as compared with 15.2 for four cycles of BEACOPP baseline given over 12 weeks. In contrast, the "2+2" variant has an ED of 17.3. In both treatment arms of the HD14 study, additional IF-RT with 30 Gy was given. The final analysis demonstrated a significantly better PFS for the more intensive "2+2" arm: PFS at 5 years was 95.4 % with "2+2" treatment compared with 89.1 % after ABVD ($p<0.001$) [20]. While an absolute improvement in PFS of 6 % appears rather modest at first glance and one can argue about clinical relevance, the results show that even an up-front intensification with only two cycles of BEACOPP escalated indeed improves outcome in this group of patients. It corroborates the claim for a start of treatment with the most effective regimen to prevent the development of early chemoresistance, but it remains to be seen whether this gain in PFS outbalances the putative increased toxicity, for example, infertility and secondary malignancies. Whether the 12-week intense chemotherapy regimen Stanford V, with

its mainly alkylating-agent-induced toxicity, could improve treatment outcome as compared with ABVD was addressed in the US intergroup study [16]. In this trial only 30 % of patients had stage I/II disease; the remaining were in stage III/IV. No benefit for the Stanford V over ABVD was observed. Intensification from ABVD to BEACOPP escalated dependent of persistent FDG-PET scan positivity after two cycles of ABVD is being addressed in EORTC/LYSA/FIL randomized H10 trial. Final results are not yet available (vide infra). So, the more intense BEACOPP escalated based "2×2" design reports a superior PFS suggesting that it is indeed possible to improve efficacy in this group of patients albeit at the cost of increased toxicity.

12.5 Number of Cycles of Chemotherapy

Only a few randomized trials have addressed the issue of number of cycles required. These studies show that four cycles of conventional chemotherapy are sufficient in a combined modality setting. In the EORTC/GELA H8U study, MOPP/ABV hybrid was used as standard chemotherapy regimen; four or six cycles followed by IF-RT were compared [21]. The EFS at 7 years did not differ significantly with rates of 86 and 84 %, respectively (Fig. 12.3). In the EORTC/GELA H9U trial, 533 patients were randomized between four and six cycles of ABVD followed by IF-RT [14]. The interim analysis showed an EFS of 87 and 91 % at 4 years, which was not significantly different. While some cooperative groups consider early unfavorable CS I/II disease as advanced stage and treat accordingly with six cycles of chemotherapy, a number of four cycles in a combined modality setting are currently considered standard treatment.

12.6 Extent and Dose of RT

A number of randomized trials focused on the comparison of extended- and IF-RT in combined modality approaches (Table 12.3) [22, 24]. The important general conclusion from these trials was that extended-field RT was not needed in combined modality treatment and was associated with more long-term adverse effects. Thus, IF-RT became the standard of care in this setting. Meanwhile, the concept of involved-node irradiation (IN-RT) was introduced by the EORTC as part of the combined modality approach. The irradiated volume is further reduced to involved nodes instead of a complete lymphoid region and consequently less late adverse effects are anticipated [18]. The concept has been applied already in the EORTC/LYSA/FIL H10 trial (vide infra), but it has not yet been tested in a randomized trial.

In the era of extended-field RT as single modality, the standard dose of RT was 36 Gy, often followed by a boost of 4–6 Gy to residual disease and/or initial bulky sites. When combined with chemotherapy, both the field size and the RT dose could be reduced. In the GHSG HD11 trial, four cycles of ABVD or four cycles of BEACOPP baseline were followed by IF-RT, either 30 or 20 Gy dose. The final analysis showed no significant difference in PFS between the 30 and 20 Gy treatment arms for those patients receiving BEACOPP baseline. In contrast, those treated with four cycles of ABVD and 20 Gy IF-RT had a poorer tumor control as compared to those receiving 30 Gy IF-RT ($p=0.048$) [15]. In the EORTC/GELA H9F trial randomizing between a dose of 36 and 20 Gy of IF-RT after EBVP chemotherapy, no differences in PFS were seen in the interim analysis, but this trial included only favorable stage I/II disease [14]. Thus, the dose of IF-RT needed in the combined modality treatment of early unfavorable HL depends on the efficacy of the preceding chemotherapy. To conclude, the extent and dose of RT can be reduced only in the appropriate combined modality treatment setting: adequate chemotherapy is the first prerequisite, then IF-RT can be given at a reduced dose of 20 Gy, or alternatively IN-RT can be preferred but—at least for the moment—at the higher dose of 30–36 Gy.

12.7 Chemotherapy Alone

Several randomized trials performed in patients with advanced stages indicated that RT can be omitted without compromising outcome, providing a robust CR was achieved with six to eight

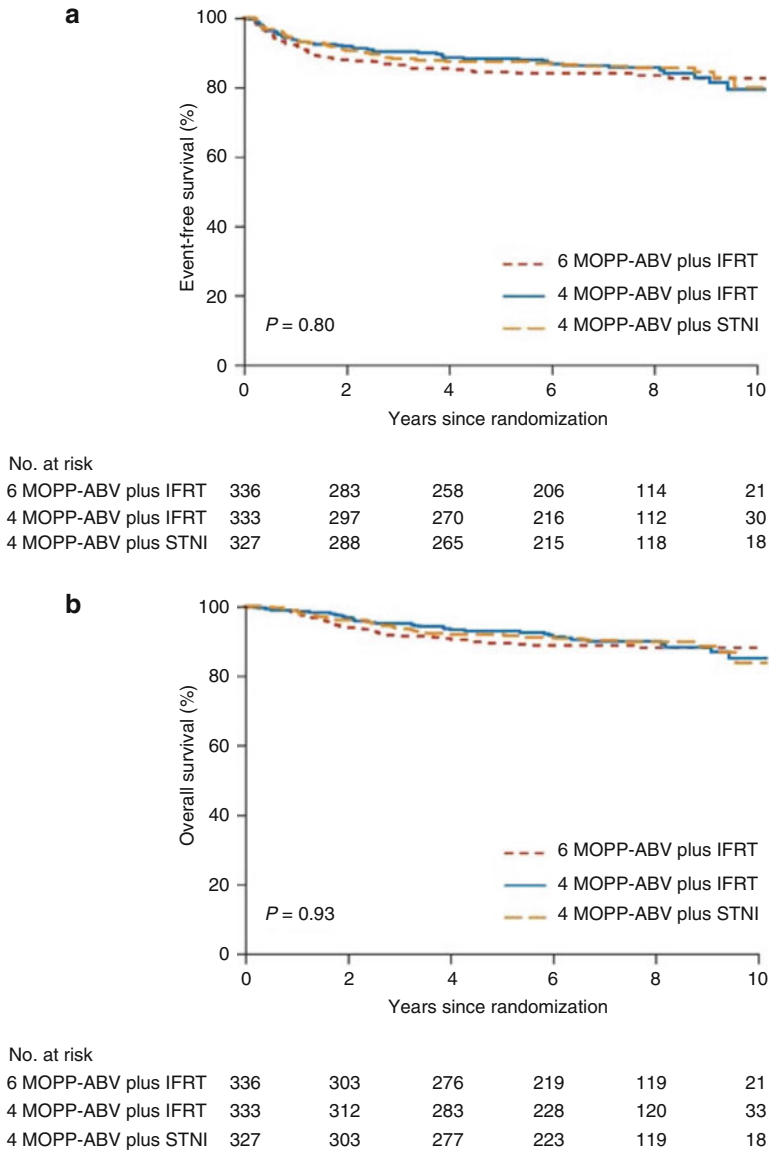

Fig. 12.3 Estimated event-free (a) and overall survival (b) of the unfavorable cohort of patients enrolled in the European Organisation for Research and Treatment of Cancer (EORTC) and Groupe d'Etude des Lymphomes de l'Adulte (GELA) randomized H8 trial comparing different numbers of cycles of chemotherapy combined with different radiation fields [21]

cycles of chemotherapy such as MOP/BAP, MOPP/ABV hybrid, or BEACOPP escalated [25, 26]. Positron emission tomography (PET) holds the promise of predicting more accurately which remission is robust and if residual masses will benefit from additional RT [27]. Conflicting data came out of a study from India [28]. Here, six cycles of ABVD were followed for patients in CR by IF-RT or no RT in a randomized fashion. Though patients who received RT had a significantly better PFS than those who did not, this study included many early stages, pediatric patients, and used suboptimal imaging methods. These data suggest that after an adequate number of cycles of effective chemotherapy and good response, additional RT will not further improve the outcome in patients with advanced-stage disease. The question therefore arose whether RT can also be omitted in unfavorable early stages. Table 12.4 summarizes the results of the most relevant trials, all having their limitations. In the GATLA study [29], a nonstandard chemotherapy was used; other studies included pediatric patients or all stages of disease, used divergent definitions

Table 12.3 Randomized trials on extent and dose of RT, combined with ABVD(-like) chemotherapy

Trial (ref)	Treatment	Number of patients included	PFS (years)	OS (years)	Remarks
Extent of RT					
GHSG HD8 [22]	COPP/ABVDx2 + EF-RT 30–40 Gy	532	85 % (5)	90 % (5)	n.s.
	COPP/ABVDx2 + IF-RT 30–40 Gy	532	84 % (5)	92 % (5)	
Milan [23]	ABVDx4 + EF-RT	65	96 %	100 %	n.s.
	ABVDx4 + IF-RT	68	93 %	96 %	
EORTC/GELA	MOPP/ABVx6 + IF-RT 36–40 Gy	336	84 % (7)	89 % (7)	EFS instead of PFS
H8U [21]	MOPP/ABVx4 + IF-RT 36–40 Gy	333	86 % (7)	90 % (7)	n.s.
	MOPP/ABVx4 + STNI 36–40 Gy	327	86 % (7)	90 % (7)	
Anselmo et al. [24]	ABVDx4 + EF-RT	102	94 % (5)	97 % (5)	n.s.
	ABVDx4 + IF-RT	107	91 % (5)	96 % (5)	
Dose of RT					
GHSG HD11 [15]	ABVDx4 + IF-RT 30 Gy	343	88 % (5)	95 % (5)	Final analysis
	ABVDx4 + IF-RT 20 Gy	339	83 % (5)	95 % (5)	PFS $p=0.03$, OS n.s.
	BEACOPPx4 + IF-RT 30 Gy	332	89 % (5)	96 % (5)	
	BEACOPPx4 + IF-RT 20 Gy	337	89 % (5)	97 % (5)	

ref reference, *PFS* progression-free survival, *OS* overall survival, *GHSG* German Hodgkin Study Group, *EF-RT* extended-field radiotherapy, *IF-RT* involved-field radiotherapy, *n.s.* statistically not significant, *EORTC* European Organisation for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *STNI* subtotal nodal irradiation, *EFS* event-free survival

of unfavorable prognostic features, or had not enough statistical power to detect clinically significant differences in PFS between RT and no-RT arms. The NCIC/ECOG study on early stages had 12-year overall survival as primary endpoint; patients with bulky disease were excluded from entry. This study showed a significant 11 % survival benefit for treatment with ABVD alone as compared to ABVD+STNI, notwithstanding a significant 8 % advantage in PFS for those who received combined modality approach [33]. The remarkable conversion of an inferior PFS to a superior long-term OS for the ABVD alone treatment arm was mainly due to an excess of late toxic deaths in the combined modality treatment: 23 vs. 11 in the former. These deaths were mainly due to second cancers. Admittedly, STNI is outdated now, but the results corroborate the difficulties in interpreting different treatment approaches with divergent short-term (control of disease) and long-term (toxicity) effects.

This dilemma was also encountered in the EORTC/LYSA/FIL randomized H10 trial. Based on the prognostic significance of an early FDG-PET scan, investigators hypothesized that patients who attain a negative FDG-PET scan after two cycles of ABVD would not need additional RT. Therefore, patients in the standard arm received standard combined modality treatment (ABVDx4+IN-RT) irrespective of the result of the early FDG-PET scan, whereas those in the experimental arm in case of a negative early FDG-PET scan had no IN-RT but instead a total of six cycles of ABVD. In this non-inferiority trial, a decrease of maximally 10 % in 3-year EFS was accepted as non-inferiority margin in an attempt to compensate for the presumed long-term benefit of omitting RT. The preplanned interim

Table 12.4 Randomized clinical trials in unfavorable CS I/II disease on combined modality treatment vs. chemotherapy alone

Trial (ref)	Treatment	Number of patients included	PFS (years)	OS	Remarks
GATLA [29]	CVPPx3 + IF-RT	44	75 % (7)	84 %	PFS $p=0.001$; OS n.s.
	30 Gy + CVPPx3	66	34 % (7)	66 %	
	CVPPx6				
Aviles [30]	ABVDx6 + IF-RT 30 Gy		76 % (11)	88 %	PFS and OS $p<0.01$; only
	ABVDx6		48 % (11)	59 %	bulky IA and IIA
CCG children [31]	COPP/ABVx4-6+ IF-RT 21 Gy	501	93 % (3)	n.s.	PFS $p=0.02$; all stages
	COPP/ABVx4-6 (only CR randomized for RT or no RT)		85 % (3)		(68 % CS I/II); only children
Tata Memorial Hospital [28]	ABVDx6 + IF-RT 30 Gy	179	88 % (8)	100 %	PFS $p=0.01$; OS $p=0.002$; all stages (55 % CS I/II) and children (50 %) included
	ABVDx6 (only CR randomized for RT or no RT)		76 % (8)	89 %	
MSKCC [32]	ABVDx6 + IF-RT or EF-RT	76	86 % (5)	97 %	n.s.; non-bulky CS IB, IIB, IIIA; only powered for differences in PFS >20 %
	ABVDx6	76	81 % (5)	90 %	
NCIC/ECOG [33, 34]	ABVDx2 + STNI 35 Gy	139	94 % (12)	81 % (12)	PFS $p=0.006$
	ABVDx4-6, no RT	137	86 % (12)	92 % (12)	OS 0.04.; B symptoms and bulky disease excluded
EORTC/LYSA/FIL H10 [35]	ABVDx4 + IN-RT, irrespective of early FDG-PET scan	251	97.2 (1)	Too early	*Preplanned futility interim analysis* $p=0.026$
	ABVDx2, if early-FDG-PET scan negative: ABVDx4, no RT	268	94.7 (1)	Too early	

ref reference, *PFS* progression-free survival, *OS* overall survival, *GATLA* Grupo Argentino Tratamiento de la Leucemia Aguda, *IF-RT* involved-field radiotherapy, *n.s.* statistically not significant, *CCG* Children's Cancer Study Group, *MSKCC* Memorial Sloan Kettering Cancer Center, *EF-RT* extended-field radiotherapy, *NCIC* National Cancer Institute of Canada, *ECOG* Eastern Cooperative Oncology Group, *STNI* subtotal nodal irradiation, *EORTC* European Organisation for Research and Treatment of Cancer, *LYSA* Lymphoma Study Association, *FIL* Fondazione Italiana Linfomi, *IN-RT* involved-node radiotherapy

analysis after 22 events revealed a 74 % rate of early FDG-PET scan negativity [35]. The median follow-up at the time of analysis was 1.1 years. In the standard arm, less events occurred than in the experimental no-RT arm: 7 events out of 251 patients in the standard arm against 16 out of 268 in the no-RT arm ($p=0.026$). Based on these results, it was unlikely that the trial would show

non-inferiority for the experimental arm when continuing accrual to the originally planned total numbers and randomization was stopped. Thus, although overall outcome was excellent in both arms, omitting radiotherapy in early FDG-PET-negative patients with unfavorable stage I/II disease resulted in more early progressions than combined modality treatment. An individual patient-data comparison of combined modality and ABVD alone, including also early favorable stages, performed on the GHSG HD10 and HD11 and the NCIC HD trial confirmed the better short-term disease control for combined modality treatment over chemotherapy alone [36]. Until there is generally accepted evidence that RT can really be omitted in—subsets of identifiable—unfavorable stage I/II patients without jeopardizing the long-term outcome, combined modality treatment remains the preferred treatment approach.

12.8 Special Situations

12.8.1 Bulky Mediastinal Tumor

The presence of a bulky mediastinal tumor, defined as a mediastinum/thorax ratio of ≥0.35, is one of the most prominent negative prognostic factors in HL patients with CS I/II disease. Some groups treat these patients according to protocols for advanced disease. Upon treatment, the nodular sclerosing histology is associated with inherent slow regression particularly of bulky mediastinal tumors. When evaluated by conventional CT scans, a reliable and reproducible interpretation of response after chemotherapy is often difficult. In case of post-chemotherapy residual masses with uncertain dignity, investigators may easily conclude a partial remission and advocate additional RT. That would possibly not be wrong from a tumor control point of view; however, mediastinal radiation fields are typically associated with severe adverse long-term effects such as secondary malignancies (e.g., breast and bronchus carcinoma) and early cardiovascular events (see Chaps. 22 and 23 for more details). There are no randomized data specifically addressing the need for RT in patients with bulky mediastinal disease based on modern imaging techniques. Although being a single-arm study on a fixed combined modality approach, the experience with Stanford V chemotherapy followed by IF-RT provides the most appropriate data in this respect, including response evaluation with FDG-PET [37]. Patients with a persistent positive FDG-PET scan after Stanford V had a significantly higher relapse rate even after additional IF-RT when compared to those patients with a negative FDG-PET scan post-chemotherapy who also received RT as planned.

In future studies, patients who really need additional RT and those who will not benefit might be better identified by FDG-PET-based response evaluation. This would hopefully secure optimal tumor control and spare subgroups of patients already cured by chemotherapy alone from long-term RT-induced toxicity. For the time being, however, combined modality treatment remains the standard treatment for patients with CS I/II disease with bulky mediastinal disease.

12.8.2 Concomitant Disease

For patients who cannot tolerate chemotherapy or for whom chemotherapy is contraindicated due to concomitant disease, large-field RT at doses of 36–40 Gy is still an alternative treatment option. However, patients with unfavorable CS I/II disease have a relapse rate of more than 40 % after RT alone and will probably also experience considerable toxicity from large-field RT. Thus, a balance on an individual basis between tumor control and avoidance of serious toxicity has to be found.

12.9 Future

The most important challenge is the identification of patients who are adequately treated with ABVD alone, those who need combined modality treatment, and those who need intensified chemotherapy such as BEACOPP escalated. The results from the GHSG HD14 study show that more intense chemotherapy significantly improves tumor control. On the other hand, in these patients with localized

disease, we also aim at minimizing early and late toxicity of treatment. New clinical prognostic factors are unlikely to allow for selecting patients needing more or less intensive treatment. Biomarkers could become useful, but at present no individual marker or set of markers has been sufficiently reliable. New functional imaging techniques will very likely become valid tools to identify subsets of patients requiring different treatment approaches early in the course of treatment (see Chap. 7). The EORTC/LYSA/FIL H10 trial on early treatment adaptation in early FDG-PET scan-negative patients was prematurely closed because of more events in the no-RT arm as compared to the combined modality approach [35].

In the meantime, new RT techniques will further evolve, and especially the reduction of the involved-field to the involved-node principle in the combined modality treatment setting will reduce toxicity while—probably—maintaining the high efficacy [18] (see Chap. 9). It remains to be seen whether refinement in the use of FDG-PET scanning, for example, by incorporating SUV values, will increase its predictive power for early treatment optimization. Ultimately, an individualized approach taking into account the risk factors and perspectives of the individual patient will define the most appropriate treatment out of a choice of treatments [38, 39].

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Treatment of Advanced-Stage Hodgkin Lymphoma

13

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13.1 From MOPP to MOPP/ABVD to ABVD

Before the introduction of combination chemotherapy, more than 95 % of patients with advanced HL succumbed to their disease within 5 years. Thus, remission rates in excess of 50 % achieved with MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) were a major breakthrough in oncology [1, 2]. MOPP was successfully introduced almost 40 years ago and used for many years for advanced-stage disease, resulting in long-term remission of nearly 50 % [1, 3]. It was then replaced by ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), after a series of large multicenter trials had compared ABVD with alternating MOPP/ABVD or MOPP alone [3–5] (Table 13.1).

Bonadonna et al. were the first to report on the substantial relevance of anthracyclines in ABVD for the treatment of advanced-stage HL [3].

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_13,

Table 13.1 MOPP/ABVD in randomized trials

Trial (Ref.)	Publ.	Therapy regimen	# Pts.	Outcome	FU and comments
Bonadonna [3]	1986	A. MOPP/ABVD altern.	43	64.6 % (FFP); 83.9 % (OS)	FU 8 years;
		B. MOPP	45	35.9 % (FFP); 63.9 % (OS)	
Santoro [5]	1987	A. 3xMOPP-RT-3xMOPP	114	62.8 % (FFP); 77.4 % (OS)	FU 7 years; (sub)total nodal irradiation in all patients
		B. 3xABVD-RT-3xABVD	118	80.8 % (FFP); 67.9 % (OS)	
US Intergroup [4]	2003	C. ABVD (6 cycles)	433	63 % (FFS); 82 % (OS)	FU 5 years; MDS and sAML only in MOPP-treated patients
		D. MOPP/ABV hybrid (6 cycles)	419	66 % (EFS); 81 % (OS)	
Viviani [6]	1996	A. MOPP/ABVD alternating	211	67 % (FFP); 74 % (OS)	FU 10 years
		B. MOPP/ABVD hybrid	204	69 % (FFP); 72 % (OS)	
Connors [7]	1997	A. MOPP/ABVD hybrid (8 cycles)	252	71 % (FFS); 81 % (OS)	FU 5 years
		B. MOPP/ABVD altern. (8 cycles) radiotherapy after cycle 6 for PR	248	67 % (FFS); 83 % (OS)	
GHSG HD6 [8]	2003	A. COPP/ABV/IMEP (hybrid 4x)	223	54 % (FFTF); 73 % (OS)	FU 7 years
		B. COPP/ABVD (altern. 4x)	245	56 % (FFTF); 73 % (OS)	

Abbreviations: *SWOG* Southwest Oncology Group, *EORTC* European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *ECOG* Eastern Cooperative Oncology Group, *EF/IFRT* extended-/involved-field radiotherapy, *STNI* subtotal nodal irradiation, *FFS* failure-free survival, *FFP* freedom from progression, *FFTF* freedom from treatment failure, *EFS* event-free survival, *PFS* progression-free survival, *OS* overall survival, *FU* follow-up

Patients were randomly assigned to receive either MOPP or MOPP alternated with ABVD. All 88 evaluable patients had not received prior chemotherapy, and 25 had relapsed after primary radiotherapy. The complete remission (CR) rate with MOPP/ABVD was 88.9 and 74.4 % with MOPP alone. The 8-year results showed that MOPP/ABVD was superior to MOPP in terms of freedom from progression (64.6 % vs. 35.9 %; $p<0.005$), relapse-free survival (72.6 % vs. 45.1 %; $p<0.01$), and overall survival (83.9 % vs. 63.9 %; $p<0.06$). This study impressively demonstrated the benefit of ABVD in terms of efficacy when added to MOPP.

When compared to MOPP, ABVD was more effective: Santoro et al. investigated 3xMOPP+RT+3xMOPP versus 3xABVD+RT+3xABVD. In this trial, the 7-year results indicated that ABVD was better than MOPP in terms of freedom from progression (80.8 % vs. 62.8 %; $p<0.002$), relapse-free survival (RFS, 87.7 % vs. 77.2 %; $p=0.06$), and most importantly overall survival (OS, 77.4 % vs. 67.9 %; $p=0.03$) [5]. An important US trial tested 6–8 cycles of ABVD against 6–8 cycles of MOPP or MOPP alternating with ABVD for 12 cycles [9]. Of 361 eligible patients, 123 received MOPP, 123 received MOPP alternating with ABVD, and 115 received ABVD alone. The overall response rate was 93 %, with a CR rate of 77 %: MOPP 67 %, ABVD 82 %, and MOPP-ABVD 83 % ($p=0.006$ for the comparison of MOPP with the doxorubicin-containing regimens). The rates of failure-free survival at 5 years were 50 % for MOPP, 61 % for ABVD, and 65 % for MOPP-ABVD. OS at 5 years was 66 % for MOPP, 73 % for ABVD,

and 75 % for MOPP-ABVD ($p=0.28$ for the comparison of MOPP with the doxorubicin-based regimens). MOPP was associated with more severe hematologic toxicity. Since ABVD was equally effective and less toxic than MOPP-ABVD, this trial supported the use of ABVD alone as first-line therapy for advanced-stage HL.

Finally, a large American intergroup trial ($N=856$) tested ABVD versus MOPP/ABV hybrid. The rates of complete remission (76 % vs. 80 %, $p=0.16$), failure-free survival at 5 years (63 % vs. 66 %, $p=0.42$), and OS at 5 years (82 % vs. 81 %, $p=0.82$) were similar for ABVD and MOPP/ABV, respectively [4]. However, clinically significant acute pulmonary and hematologic toxicity was more common with MOPP/ABV ($p=0.06$ and 0.001, respectively). More therapy-associated fatal outcomes were reported for the hybrid regimen (ABVD = 9, MOPP/ABV = 15, $p=0.057$). Furthermore, secondary malignancies occurred more often with MOPP/ABV, without reaching statistical significance. Out of 13 patients developing MDS or acute leukemia, 11 were initially treated with MOPP/ABV, and only 2 with ABVD. Both subsequently received MOPP-containing regimens and radiotherapy before developing leukemia ($p=0.011$) [4]. Therefore, it was concluded from this study that ABVD and MOPP/ABV hybrid are equally effective in HL, but due to significant less toxicity, ABVD should become the standard regimen for advanced-stage HL.

This conclusion is supported by the fact that the alkylating agents within the MOPP regimen lead to more severe toxicity in most studies. The comparative iatrogenic morbidity showed that irreversible gonadal dysfunction as well as acute leukemia occurred only in patients treated with MOPP [5]. Since the use of MOPP was also associated with a higher incidence of secondary acute leukemia and infertility, ABVD subsequently became standard of care.

Finally, the evaluation of rapidly alternating and non-cross-resistant regimens was not successful. Alternating MOPP/ABVD was tested against the MOPP/ABV hybrid regimen, alternating COPP/ABV/IMEP against COPP/ABVD hybrid, and alternating MOPP/ABVD against MOPP/ABVD hybrid, all without improving patient outcome [6–8].

Taken together, ABVD has become widely accepted as standard regimen for advanced-stage HL. A major advantage of this regimen is its tolerability. ABVD is a safe outpatient treatment without the need for close white blood cell monitoring and can be administered also in developing countries [10]. One has to keep in mind, though, that a long-term follow-up report of 123 patients treated with ABVD for advanced HL revealed a failure-free survival of only 47 % and an OS of 59 % after 14.1 years [11]. Since 40 % mortality among young patients suffering from a curable malignancy is unacceptably high, alternative approaches were developed to improve on these results.

13.2 Fourth-Generation Regimens

13.2.1 Hybrid and Alternating Regimens

Up-front ABVD was further tested against the Stanford V regimen (see below) and the MOPP/EBV/CAD program in an Italian cooperative study; it was also compared with alternating or hybrid multidrug regimens such as ChlVPP/PABlOE and ChlVPP/EVA in the UK [12, 13] (Table 13.2).

The Italian cooperative study was a multicenter, prospective, randomized clinical trial investigating two chemotherapy regimens (i.e., Stanford V, doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone, and MOPPEBVCAD, mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine), which were compared to ABVD [12]. Radiotherapy was limited to ≤ two sites of either previous bulky or partially remitting disease. The CR rates for ABVD, Stanford V, and MOPPEBVCAD were 89, 76, and 94 %, respectively; the 5-year failure-free survival and progression-free survival rates were 78, 54, and 81 % and 85, 73, and 94 %, respectively ($p<0.01$ for

Table 13.2 Fourth-generation trials

Trial (Ref.)	Publ.	Therapy regimen	# Pts.	Outcome	FU and comments
Intergroup Italy [12]	2005	A. ABVD (6 cycles)	98	83 % (FFS); 91 % (OS)	FU 5 years; patients in stage IIB without additional risk factors included
		B. Stanford V (12 weeks)	89	67 % (FFS); 89 % (OS)	
		C. MEC hybrid (6 cycles) (+ RT initial bulk/residual mass)	88	85 % (FFS); 87 % (OS)	
UK Lymphoma Group [13]	2005	A. ABVD (6 cycles)	391	77 % (EFS); 86 % (FFP); 90 % (OS)	FU 3 years; stages I and II included; stages III and IV at FU 5 years: 65 % (EFS); 81 % (OS)
		B. ChlVPP/EVA (6 cycles)	109	77 % (EFS); 76 % (FFP); 83 % (OS)	
		C. ChlVPP/PABlOE (3x altern.)	275	74 % (EFS); 93 % (FFP); 90 % (OS)	
Intergroup GB and Italy [14]	2002	A. ChlVPP/EVA hybrid (6 cycles)	144	82 % (FFP); 78 % (EFS); 89 % (OS)	FU 5 years
		B. VAPEC-B (11 weeks) (±RT initial bulk/residual mass)	138	62 % (FFP); 58 % (EFS); 79 % (OS)	
Stanford V [15]	2002	Single-arm phase II Stanford V	142	89 % (FFP); 96 % (OS)	FU 5 years; patients with stages I or II with risk factor LMM included; 129 of 152 patients (91 %) received additional radiotherapy
		36-Gy RT to initial sites of bulky (> or =5 cm) or macroscopic splenic disease		In patients IPS ≥3: 75 % (FFP)	
UKNCRI [16]	2009	A. ABVD (6–8 cycles)	252	76 % (PFS); 90 % (OS)	FU 5 years;
		B. Stanford V 36-Gy RT to initial sites of bulky (> or =5 cm) or splenic deposits	248	74 % (PFS); 92 % (OS)	Patients in stages I and II with bulky disease included; 20 % more patients irradiated after S V (73 %)
GHSG HD9 [17]	2003	A. COPP/ABVD (4 cycles)	260	69 % (FFTF); 83 % (OS)	FU 5 years
		B. BEACOPP baseline (8 cycles)	469	76 % (FFTF); 88 % (OS)	
		C. BEACOPP escalated (8 cycles)	466	87 % (FFTF); 91 % (OS)	
GHSG HD9 [18]	2009	A. COPP/ABVD (4 cycles)	260	64 % (FFTF); 75 % (OS)	FU 10 years
		B. BEACOPP baseline (8 cycles)	469	70 % (FFTF); 80 % (OS)	
		C. BEACOPP escalated (8 cycles)	466	82 % (FFTF); 86 % (OS)	

Table 13.2 (continued)

Trial (Ref.)	Publ.	Therapy regimen	# Pts.	Outcome	FU and comments
GHSG HD12 [19]		A. 8 BEA escalated	887	A + B: 88 % (PFS); 92 % (OS)	FU 5 years
		B. 8 BEA escalated	887	C + D: 85 % (PFS); 90 % (OS)	
		C. 4 BEA esc. + 4 BEA baseline			
		D. 4 BEA esc. + 4 BEA baseline			
		(A. + C.: +RT bulk/ residual mass)			
GHSG HD15 [20]	2012	A. 8 BEA escalated	2,126	84 % (FFTF); 91.9 % (OS)	
		B. 6 BEA escalated		89 % (FFTF); 95.3 % (OS)	
		C. 8 BEA baseline-14		85 % (FFTF); 94.5 % (OS)	

Abbreviations: *SWOG* Southwest Oncology Group, *EORTC* European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *ECOG* Eastern Cooperative Oncology Group, *EF/IFRT* extended-/involved-field radiotherapy, *STNI* subtotal nodal irradiation, *FFS* failure-free survival, *FFP* freedom from progression, *FFTF* freedom from treatment failure, *EFS* event-free survival, *PFS* progression-free survival, *OS* overall survival, *FU* follow-up

comparison of Stanford V with the other two regimens). Corresponding 5-year OS rates were 90, 82, and 89 % for ABVD, Stanford V, and MOPPEBVCAD, respectively. Stanford V was more myelotoxic than ABVD but less myelotoxic compared with MOPPEBVCAD. The authors concluded that ABVD was still the treatment choice when combined with optional limited irradiation. The reported failure-free survival for ABVD, however, was higher compared to other studies. This might in part be explained by the fact that stage IIB patients without additional risk factors were enrolled into this study, resulting in a relatively high percentage of good-prognosis patients according to the International Prognostic Score (35 %).

The UK study compared ABVD with two multidrug regimens, i.e., alternating chlorambucil, vinblastine, procarbazine, and prednisolone (ChlVPP) with prednisolone, doxorubicin, bleomycin, vincristine, and etoposide (PABIOE), or hybrid ChlVPP/etoposide, vincristine, and doxorubicin (EVA) [13]. Radiotherapy was planned for incomplete response or initial bulky disease. At 52-month median follow-up, the primary objective EFS at 3 years was 75 % (95 % CI, 71–79 %) for ABVD and 75 % (95 % CI, 70–79 %) for multidrug regimens (hazard ratio [HR] = 1.05; 95 % CI, 0.8–1.37). The 3-year OS rates were 90 % (95 % CI, 87–93 %) in patients allocated to ABVD and 88 % (95 % CI, 84–91 %) in patients allocated to multidrug regimens (HR = 1.22; 95 % CI, 0.84–1.77). Patients receiving multidrug regimen experienced more grade 3/4 side effects including infection, mucositis, and neuropathy. To conclude, in the absence of significant differences in EFS or OS between ABVD and multidrug regimen, ABVD remained the standard for treatment of advanced HL. It should be mentioned that this study reported a better EFS and OS for ABVD than other trials. This might be due to the inclusion of patients

with stage I/II disease who had systemic symptoms, multiple sites of involvement, or bulky disease. Looking at stage III and IV patients only, the 5-year EFS and OS were 65 % and 82 %, respectively.

Taken together, hybrid regimens did not show superiority over ABVD in both trials. This regimen therefore remained the treatment of choice for advanced-stage HL based on equivalent efficacy and lower toxicity in the last 40 years.

The Manchester group followed a different approach. They developed the hybrid ChlVPP/EVA to improve the outcome of MOPP [21]. Patients in the hybrid arm of this trial had a higher CR rate (68.1 % vs. 55.3 %) and a lower failure rate (2.4 % vs. 12.5 %). With a median follow-up period for survivors of 4.5 years (range 0–9), actuarial 5-year progression-free survival (PFS) for all cases was 80 % in the hybrid arm and 66 % in the MOPP arm ($p=0.005$) with a trend toward better OS. ChlVPP/EVA was therefore adopted as standard first-line therapy in this group. This regimen was then tested against VAPEC-B, an abbreviated 11-week chemotherapy program. After 5 years, event-free survival and OS were significantly better with ChlVPP/EVA than with VAPEC-B (EFS, 78 vs. 58 %; OS, 89 vs. 79 %) [14]. Thereafter, ChlVPP/EVA was tested against ABVD and did not show superiority, so that ABVD remained the gold standard [13].

13.2.2 Stanford V

Stanford V was developed as a short-duration, reduced-toxicity program and was applied weekly over 12 weeks. Consolidating radiotherapy to sites of initial disease was employed [15]. Data were initially generated in a single-center setting with a limited number of patients. One hundred forty-two patients with stage III or IV or locally extensive mediastinal stage I or II HL received Stanford V chemotherapy for 12 weeks followed by 36 Gy RT to initial sites of bulky (≥5 cm) or macroscopic splenic disease. With a median follow-up of 5.4 years, the 5-year freedom from progression (FFP) was 89 % and the OS 96 %. However, FFP was significantly worse among patients having an International Prognostic Score of 3 and higher (94 % vs. 75 %, $p=0.0001$). One hundred twenty-nine of 152 patients (91 %) received additional radiotherapy. A prospectively randomized multicenter comparison of Stanford V with MOPPEBVCAD and ABVD showed that Stanford V was inferior in terms of response rate (76 % vs. 89 % and 94 %) and PFS (73 % vs. 85 % and 94 %) in a multicenter setting [12]. These conflicting results might be partially explained by the use of less radiotherapy in the randomized setting and the better treatment quality in single-center studies. Furthermore, in a large intergroup trial including all US cooperative study groups, Stanford V was compared to ABVD ± RT [16]. In this multicenter, prospective, controlled trial, weekly alternating Stanford V was randomized against the standard twice-weekly ABVD regimen. Patients had stage IIB, III, or IV disease, or stage I to IIA disease with bulky disease or other adverse features. Radiotherapy was administered in both arms to sites of previous bulk (>5 cm) and to splenic deposits, although this was omitted in the latter part of the trial for patients achieving CR in the ABVD arm. Five hundred patients received protocol treatment, and radiotherapy was administered to 73 % in the Stanford V arm and 53 % in the ABVD arm. The overall response rate after completion of all treatment was 91 % for Stanford V and 92 % for ABVD. During a median follow-up of 4.3 years, there was no difference in the projected 5-year PFS and overall survival (OS) rates (76 and 90 %, respectively, for ABVD; 74 and 92 %, respectively, for Stanford V). Thus, in this large, randomized trial, Stanford V was not better than standard ABVD when given in combination with radiotherapy. However, 20 % more patients had to be irradiated in the Stanford V arm, and the 5-year PFS was about 15 % lower than reported in the single-center setting. This inferiority in terms of PFS is seen in this magnitude also in the Intergruppo Italiano Linfomi trial [12]. Finally, a large US intergroup (E2496) study was compared to Stanford V and ABVD. The primary endpoint was failure-free survival (FFS), defined as the time from random assignment to progression, relapse, or death.

Overall survival (OS), a secondary endpoint, was measured from random assignment to death as a result of any cause. There was no significant difference in the overall response rate between the two arms, with complete remission and clinical complete remission rates of 73 % for ABVD and 69 % for Stanford V. At a median follow-up of 6.4 years, there was no difference in FFS: 74 % for ABVD and 71 % for Stanford V at 5 years. Seventy-three percent of patients had RT after Stanford V, and 40 % of patients had RT on ABVD. Tolerability of the regimens was comparable; however, more grade 3 sensory neuropathy was observed with Stanford V (10 % vs. 3 %, $p<0.001$). Since the number of very low-risk patients with stage I or II disease was high in this trial, the authors reported the outcome for stage III and IV patients separately. In this cohort, the 5-year FFS was 66 % and OS 85 % only without differences between the treatment groups.

To summarize, the compelling single-center phase II data for Stanford V could not be confirmed in multicenter randomized trials, and this regimen has thus been abandoned in current clinical trials.

13.2.3 BEACOPP Escalated

The German Hodgkin Study Group (GHSG) developed the BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), which is characterized by an increased dose density and dose intensity compared to ABVD and hybrid regimens. Although some indications for a role of dose intensity were available in the early 1990s, no prospective randomized trial had been undertaken. Hasenclever and coworkers analyzed a set of data in which dose variations had been used and developed a novel statistical model of dose-response characteristics. The model took tumor growth and chemotherapy effects into account and was applied to correlate tumor control in relation to treatment intensity. It was fitted to the data of 706 patients who had received COPP/ABVD-like regimens and revealed considerable heterogeneity in chemosensitivity for the single drugs, but showed a positive slope for dose-response relationship. The model was used to simulate the effect of dose escalation, changes of schedule, and architecture of the COPP-ABVD regimen. On the basis of such simulations, the model predicted that shortening cycle intervals from 4 to 3 weeks should lead to small benefits (about 3 % in 5-year tumor control rates), but a moderate average-dose escalation by 30 % of a standard chemotherapy would lead to a potential benefit in the range of 10–15 % in tumor control at 5 years. Based on this model, the BEACOPP regimen was designed. G-CSF was mandatory to compensate for the myelotoxic effects. In a phase II study, the optimal dose of the BEACOPP baseline and BEACOPP escalated regimen were determined [22]. The subsequent HD9 trial of the GHSG found the predicted dose-response curve to be correct. The GHSG HD9 trial then compared COPP/ABVD, BEACOPP baseline, and BEACOPP escalated. Results from 1,195 randomized patients showed a clear superiority of BEACOPP escalated over BEACOPP baseline and COPP/ABVD at 5 years [17]. The follow-up data at 10 years confirmed these results: with a median follow-up of 112 months, the FFTF and OS rates were 64 and 75 % in the COPP/ABVD group, 70 and 80 % in the BEACOPP baseline group, and 82 and 86 % in the BEACOPP escalated group [18]. The 10-year update of the HD9 study did not only confirm a significant improvement in long-term FFTF and OS for BEACOPP escalated but also showed that this advantage is particularly evident in the subset of intermediate-prognosis patients, as defined by the International Prognostic Score (IPS 2–3). Importantly, this is the largest subset of patients (IPS 0–1, 28 %; IPS 2–3, 38 %; IPS 4–7, 13 %) [18].

However, toxicity of this more aggressive approach remained a concern. The subsequent GHSG HD12 trial thus aimed at de-escalating chemo- and radiotherapy by comparing four courses of BEACOPP escalated with four courses of escalated and four courses of baseline BEACOPP ("4+4") [19]. Furthermore, in the HD12 trial, the role of radiotherapy was tested by a second randomization between consolidating radiation to initial bulky and residual disease and

no radiotherapy. At 5 years, OS was 91 %, FFTF 85.5 %, and PFS 86.2 %. However, there was no statistical difference between 8xBEACOPP escalated and the 4+4 arm in all outcome parameters. There was also no significant difference between the RT or no-RT arms in this study, with the caveat that a number of high-risk patients received RT based on the blinded panel decision. Surprisingly, there was no relevant benefit in terms of toxicity in the 4+4 treated patients, and BEACOPP escalated remained standard for advanced-stage HL patients in the GHSG.

In the subsequent HD15 study, de-escalation of chemotherapy was investigated with a reduction in the number of escalated cycles from 8 to 6 and the introduction of a dose-dense BEACOPP baseline regimen (BEACOPP-14) [20]. The study was designed to show non-inferiority of the experimental treatment groups. In addition, PET-guided radiotherapy of residual disease ≥2.5 cm was investigated. Only PET-positive patients received consolidating radiotherapy. A total of 2,182 patients were randomized among the three study arms. Surprisingly, when comparing six cycles of BEACOPP escalated with eight cycles, both PFS (90.3 % vs. 85.6 %) and OS (95.3 % vs. 91.9 %) were significantly better with the reduced number of cycles. With regard to radiotherapy, the negative predictive value for PET at 12 months was 94.1 % (95 % CI 92.1–96.1 %) and only 11 % of all patients received additional RT without compromising the tumor control [23]. In summary, HD15 established six cycles of BEACOPP escalated as a new standard of care based on a significantly improved PFS and OS. So far, these are the best results that have been reported for advanced-stage HL patients.

13.3 What Is the Standard Treatment Today?

The academic community has intensively discussed two different strategies for the treatment of advanced-stage HL: The first strategy claimed a superior outcome when high-dose chemotherapy (HDCT) and autologous stem cell transplantation were included for patients relapsing on ABVD. With this strategy, the majority of patients could be cured with ABVD only without exposing them to the toxicity of first-line treatment with BEACOPP [4, 9]. The second strategy, followed by those using BEACOPP escalated as first-line treatment, claimed a superior outcome by curing as many patients as possible with first-line therapy accepting more toxicity for those patients who could have been cured with a less intensive therapy [18]. These opposing strategies have been discussed very intensively in the past based on indirect comparisons. This situation has changed dramatically during the last few years. Not only study results from direct comparisons have become available, but also a large meta-analysis provided evidence on this important question.

13.3.1 ABVD Versus BEACOPP in Direct Comparisons

Four studies have been conducted so far comparing these two approaches in a prospective randomized setting. The HD2000 trial enrolled 307 patients in three different treatment arms showing a significant superiority of BEACOPP over ABVD in terms of FFP but not for OS [24]. At 5 years, the freedom from progression was 68 % for ABVD and 81 % for BEACOPP (4 escalated+2 baseline, "4+2"); OS was 84 % for ABVD and 92 % for BEACOPP, respectively (Table 13.3).

In the IIL-GITIL-Michelangelo study, ABVD (6–8 courses) or BEACOPP given in 4+4 fashion plus preplanned high-dose salvage produced a comparable 3-year outcome [28]. The final analysis showed a freedom from first progression of 85 % at a median observation time of 61 months among patients who had received initial treatment with BEACOPP and 73 % among those who had received initial treatment with ABVD ($p=0.004$). A total of 65 patients (20 in the BEACOPP group, and 45 in the ABVD group) needed high-dose chemotherapy salvage treatment. However, only 15 patients (33 %) failing first-line ABVD could be rescued. After completion of the overall planned treatment includ-

Table 13.3 ABVD versus BEACOPP in direct comparisons

Study	Treatment	*n*	5-year PFS	Difference (%)	*p*	5-year OS	Difference (%)
HD 2000 [24]	ABVD	99	68	13	0.038	84	8
	BEACOPP (4 esc. +2 baseline)	98	81			92	
IIL[a] [25]	ABVD	168	73	12	0.004	84	5
	BEACOPP (4 esc. +4 baseline)	163	85			89	
IG 20012[b] [26] IPS 3–7	ABVD	275	69	15	0.0003	86.7	4
	BEACOPP (4 esc. +4 baseline)	274	84			90.3	
LYSA H34 [27] IPS 0–2	ABVD	77	75	18	0.008	92	7
	BEACOPP (4 esc. +4 baseline)	68	93			99	

Abbreviations: *SWOG* Southwest Oncology Group, *EORTC* European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *ECOG* Eastern Cooperative Oncology Group, *EF/IFRT* extended-/involved-field radiotherapy, *STNI* subtotal nodal irradiation, *FFS* failure-free survival, *FFP* freedom from progression, *FFTF* freedom from treatment failure, *EFS* event-free survival, *PFS* progression-free survival, *OS* overall survival, *FU* follow-up

[a]7-year PFS

[b]4-year PFS

ing salvage therapy, the 7-year rate of overall survival was 89 and 84 %, respectively ($p=0.39$) [25]. This trial was not powered to detect differences in OS and suffered from additional shortcomings [29]. Nonetheless, the authors concluded from the absence of evidence on the evidence of absence, although the secondary endpoint OS was well in line with the primary endpoint FFP.

The results were similar in a larger intergroup trial organized by the EORTC, which has been published so far only as abstract [26]. In this trial, ABVD was compared to BEACOPP 4+4. Only advanced-stage patients were included (Ann Arbor stage III or IV) suffering from high-risk disease as defined by an IPS ≥3. In the interim analysis, PFS was significantly different with 69 % for ABVD and 84 % for BEACOPP 4+4 with an OS of 86.7 and 90.3 %, respectively. However, there was no difference in the primary endpoint, EFS, and between ABVD and BEACOPP 4+4 so far.

Patients with low-risk advanced-stage disease (IPS 0–2) were enrolled in the H34 trial conducted by the LYSA [27]. With 150 patients randomized in this trial, the complete remission rate was 85 % for ABVD and 90 % for BEACOPP. Progression or relapse was more frequent in patients treated with ABVD than in those treated with BEACOPP (17 vs. 5 patients). With a median follow-up of 5.5 years, seven patients died: six treated with ABVD and one with BEACOPP. The EFS at 5 years was estimated at 62 % for ABVD and 77 % for BEACOPP, respectively (HR=0.6, $p=0.07$). The PFS at 5 years was 75 and 93 % (HR=0.3, $p=0.007$) and the OS 92 and 99 % (HR=0.18, $p=0.06$). Although the number of patients recruited in this trial was rather small, these results suggest that BEACOPP is more effective than ABVD in lower-risk advanced-stage patients.

13.3.2 ABVD Versus BEACOPP in a Network Meta-analysis

All trials in this analysis compared ABVD and BEACOPP directly using BEACOPP variants (4+4 or 4+2, escalated and baseline, respectively). In addition, the former standard of eight cycles BEACOPP escalated was replaced by six cycles as

established in the GHSG HD15 study. Since there was uncertainty regarding the difference in OS between ABVD and BEACOPP, a network meta-analysis was performed to indirectly compare these regimens. The analysis included more than 10,000 patients and had 47,033 patient-years of follow-up; there were 1,189 deaths, with an average median follow-up of 5.9 years. Compared to ABVD, the survival benefit for six cycles of BEACOPP escalated was 7 % (95 % CI 3–10 %). Reconstructed individual survival data indicated that BEACOPP escalated has a 10 % advantage over ABVD in terms of OS at 5 years (95 % confidence interval 3–15 %). Kaplan-Meier curves showed increasing hazard ratios over time indicating more OS differences with longer follow-up. This finding is in line with the 10-year follow-up data from the HD9 study, which also showed increasing differences over time [18]. Interestingly, event rates were too low to allow testing for second cancer or treatment-related mortality. Thus, six cycles of BEACOPP escalated offer advanced-stage HL patients the highest chance of cure.

It should be mentioned though that treatment with BEACOPP escalated is associated with more hematological toxicity. BEACOPP escalated should only be used in patients younger than 60 years; older patients should be treated with less aggressive treatment approaches. In addition, also advanced-stage patients aged >40 years have an increased treatment-related mortality when treated with BEACOPP escalated, in particular if they also suffer from a poor performance status [30].

13.4 Outcome Prediction

13.4.1 The International Prognostic Score

Overall, it would be preferable to treat each advanced-stage HL patient according to the individual risk profile in order to better balance efficacy and toxicity. In line with this, some current concepts base the treatment plan on prognostic factors by using the international prognostic score (IPS) for risk stratification [31].

The score was derived from 5,141 patients who had been treated with C(M)OPP/ABVD-like regimen with or without radiotherapy. The endpoint was freedom from progression of disease. Seven factors had similar independent prognostic effects: serum albumin of less than 4 g per deciliter, hemoglobin level of less than 10.5 g per deciliter, male sex, age of 45 years or older, stage IV disease (according to the Ann Arbor classification), leukocytosis (white cell count of at least 15,000/mm [3]), and lymphocytopenia (lymphocyte count of less than 600/mm [3], or less than 8 % of the white cell count, or both). The IPS is currently being used for a risk-adapted therapy in an Israeli phase II study (NCT00392314). Patients in lower-risk advanced stages (IPS 0–2) are treated with ABVD, and patients with an IPS ≥3 receive BEACOPP escalated induction therapy. This strategy might be questionable after the publication of the French H34 study results. However, a distinct group of patients at very high risk cannot be identified on the basis of routinely documented demographics and clinical characteristics as used in the IPS. With BEACOPP escalated, the IPS has lost most of its discriminative power since treatment failures are more rare.

13.4.2 Positron Emission Tomography (PET)

The IPS is increasingly being challenged by response-adapted risk evaluation. It has been demonstrated for HL patients that response to chemotherapy has an impact on the final treatment outcome [32, 33]. However, response as measured by computed tomography (CT) scan might occur with some delay in advanced HL. This is likely due to the fibrotic tissue infiltrating lymph nodes in this disease, which often results in residual masses remaining several months after treatment, especially in cases of bulky disease. For example, in the GHSG HD15 trial, 311 of 817 patients (38 %) showed residual disease >2.5 cm as determined by CT after the completion of chemotherapy [23]. However, 79 % ($n=245$) of these patients at the same time had a negative FDG-PET scan. These patients did not

receive any additional radiotherapy, and, with a rather short median observation time of 18 months, their outcome was not inferior compared to patients reaching a complete remission after chemotherapy. These data indicate that in this setting the biologic response determined by FDG-PET is better than the morphologic response in terms of the negative predictive value. PET is discussed in detail elsewhere in this book (see Chap. 21); nevertheless, the work by Gallamini, Hutchings, and their coworkers must be mentioned in this context. They were able to show that the early PET response (after two cycles of ABVD) overshadows the prognostic value of the IPS and thus is an important tool for planning risk-adapted treatment in advanced HL [34, 35].

Therefore, current concepts include early response evaluation, guided by FDG-PET, into treatment strategies and will hopefully help to define a new standard of care in which each patient receives as much therapy as needed.

13.5 Current Concepts: Response-Adapted Therapy

13.5.1 De-escalating BEACOPP Escalated

The HD15 trial of the GHSG was the first large trial to investigate the negative predictive value of PET in advanced HL, which was used to guide therapy after completion of chemotherapy. Patients were randomized between eight courses of BEACOPP escalated, six courses of BEACOPP escalated, or eight courses of BEACOPP-14 (a time-dense variant of BEACOPP baseline) [36]. As described above, additional radiotherapy was applied only to residual lesions >2.5 cm positive by PET, and a high negative predictive value for progression or early relapse was found (NPV = 94 %). Encouraged by these results and by reports from other studies, the GHSG decided to test a PET-guided strategy in the current HD18 trial [35, 37]. In this study, PET is used to assess the early response after two cycles of BEACOPP escalated, and, in case of negativity, therapy is reduced to a total of four cycles and compared to the standard of eight cycles. This is a de-escalating approach based on the excellent negative predictive value of PET in HL. First results from the Israeli group have recently been published and support this approach [38]. Patients with advanced-stage HL and an IPS ≥3 received two initial cycles of BEACOPP escalated and were then evaluated by PET/computed tomography scan. In case of PET negativity, they were treated with four cycles of ABVD. After a median follow-up of 48 months, progression-free survival (PFS) and overall survival at 4 years were 78 and 95 %, respectively. Though the PFS of 78 % in this trial published by Avigdor and coworkers looks a little disappointing at the first glance, this is within the expected range. In the HD9 trial, FFTF for patients in the unfavorable risk group (IPS 4–7) was 82 % at 5 years. However, looking at the PET results, the 4-year PFS for early PET-negative patients ($n = 31$) and early PET-positive patients ($n = 13$) was 87 and 53 %, respectively ($p = 0.01$).

Though the absolute patient number is small, these data suggest that a de-escalating approach in early PET-negative patients after two cycles of BEACOPP escalated might be feasible.

13.5.2 Escalating Treatment After ABVD Failure

Several groups follow the alternative approach of escalating treatment in patients not responding to two cycles of ABVD as defined by PET positivity. These patients have a very poor outcome with ABVD or ABVD-like therapy. The 2-year PFS is reported as low as 6 % [39]. So far, only very preliminary data are available from ongoing trials. First results of the GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) trial were published in 2009 [40]. In this trial, PET-positive patients received two cycles of ABVD followed by eight cycles of BEACOPP (4+4). Of 164 enrolled patients, 24 (15 %) were PET-2 positive and 136 PET-2 negative, respectively. The two cohorts of patients were well matched in terms of prognostic factors, and the IPS ≥3 was equally frequent in both arms (29 and 28 %, $p = 0.95$). Of

the 24 PET-positive patients, 15 (62 %) were in continuous CR (CCR) after BEACOPP and nine progressed; the mean duration of CR for the responding patients was 18 months (11–37). 127/136 PET-negative patients (93.5 %) were in CCR after standard ABVD and nine progressed or relapsed. The 2-year PFS of PET-positive patients was 56 % only and 93 % for the PET-negative patients, respectively.

These data can be compared with those published by Dann et al. who used two cycles of BEACOPP baseline as induction and increased the dose to BEACOPP escalated in PET-positive cases. In this study, the 5-year PFS was 85 % for these high-risk patients, accounting for a difference of almost 30 % as compared to the induction with ABVD. A possible explanation for this observation is the longer duration (8 vs. 6 weeks for 2x ABVD vs. 2x BEACOPP) and lower-dose intensity in the first 2 months. The initial dose infinity might be most relevant for long-term outcome, since Hodgkin and Reed-Sternberg cells develop chemoresistance. This hypothesis developed many years ago and was termed "Kairos Principle," referring to the ancient Greek mythology. Another observation supports this hypothesis: the most relevant improvement when using BEACOPP escalated occurs in the early treatment phase with the reduction of the number of patients suffering from progressive disease compared to ABVD (difference around 8 %) [24]. There are many other study groups studying the ABVD escalation approach, and mature results are eagerly awaited.

The SWOG currently conducts a study (NCT00822120) in which treatment intensification using six cycles of BEACOPP escalated is being evaluated in PET-positive patients after two cycles of ABVD. The design of a cooperative trial including UKNCRI, Italian, and Nordic centers is very similar. In this study, PET-positive patients receive two cycles of ABVD followed by four to six cycles of dose-dense BACOPP-14 or four to six cycles of BEACOPP escalated. The FIL (Fondazione Italiana Linfomi) increased chemotherapy intensity in patients who were PET+ after two cycles of ABVD using IGEV (ifosfamide, gemcitabine, vinorelbine) followed by high-dose chemotherapy and ASCT (NCT00784537). A similar approach in the "pre-PET era" randomized patients with unfavorable HL (defined as the presence of two poor risk factors consisting of high serum LDH, large mediastinal mass, > one extranodal site, low hematocrit, or inguinal involvement) who achieved CR or PR after four courses of ABVD to either ASCT or four cycles of conventional chemotherapy [41]. ASCT was not better than conventional-dose therapy in terms of PFS or OS. However, early PET-positive patients represent a very poor-prognosis group and might benefit more from this aggressive strategy than a patient population selected by two baseline risk factors.

In summary, the early PET-guided escalation approach after ABVD induction is currently being investigated in several clinical trials. Only one of which has been presented as interim analysis so far. In this analysis, the PFS at 2 years was poor with only 56 %. Though this is better than a historical control with patients treated with ABVD only, it is much worse than the PFS for PET-positive patients after two cycles BEACOPP baseline induction [37, 40]. So far, this data supports the Kairos hypothesis, favoring an early escalation and thus a more aggressive induction therapy. However, more mature results of the ongoing trials must consolidate this hypothesis before final conclusions can be drawn.

13.5.3 Introduction of Brentuximab Vedotin into First-Line Treatment

With the approval of brentuximab vedotin (BV) for relapsed and refractory patients (see Chap. 21), a targeted drug has been introduced into the treatment of HL. This new drug has shown an outstanding balance of efficacy and tolerability. BV is therefore currently being used to improve both the ABVD and the BEACOPP regimen.

BV was initially combined with ABVD in a phase I study; however, life-threatening pulmonary toxicity in this bleomycin-containing combination was observed [42]. BV at a fixed dose (1.2 mg/kg body weight) was then added to the

bleomycin-deleted AVD variant, and 26 patients were treated. Data on safety suggest a high incidence of peripheral neuropathy with the combination of vinblastine and MMAE, two tubulin inhibitors (72 %, mainly grades 1 and 2). The outcome of this or other toxicities has not been reported so far. Concerning efficacy, response rates were very high (96 %). PFS has been reported for 12 months only, which is obviously too short to allow any conclusions. The new regimen AVD-A (Adcetris) is currently being investigated in an international phase III trial (NCT01712490). This trial aims at improving the PFS at 3 years from 75 % with ABVD to 82.5 % with AVD-A. The final analysis of this trial will show if the new regimen adds substantial efficacy to the well-established ABVD regimen without increasing toxicity. From a clinical point of view, tolerability and safety will be critically important since a better PFS has been reported for conventional chemotherapy already.

The GHSG has modified BEACOPP in order to improve tolerability while maintaining the high efficacy. The phase II targeted BEACOPP study (NCT01569204) is fully recruited. Results of 100 evaluable patients will be available in early 2015. Two BEACOPP variants have been randomized in this study. In a more conservative approach, vincristine was replaced by BV and bleomycin omitted. A more experimental regimen additionally introduced dacarbazine for procarbazine and short-term dexamethasone instead of long-term prednisone. An interim analysis showed promising results in terms of safety, feasibility, and efficacy; however, longer follow-up is needed to judge on these new regimens [43].

13.6 The Role of Radiotherapy

The role of consolidating radiotherapy for advanced HL depends on the efficacy of the prior chemotherapy. After MOPP or MOPP-like regimen, there might be a potential advantage of IFRT as detected by a meta-analysis of 16 randomized studies, whereas this advantage is not evident after ABVD or ABVD-like regimens [44, 45]. The randomized EORTC study demonstrated that consolidation with IFRT did not improve the outcome in CR patients after six to eight courses of alternating MOPP and ABV, but potentially improved the outcome of PR patients [46]. A randomized GELA trial showed that consolidation with IFRT after doxorubicin-induced CR was not superior to two additional cycles of chemotherapy [47]. The GHSG HD12 study randomized consolidating radiotherapy to residual disease versus observation only and showed a non-inferiority of the observation arm [19]. Unfortunately, the study was biased by the central review. Experts in this panel were blinded to the randomization result and recommend radiotherapy independent of the randomization status in patients deemed at very high risk of relapse. Based on this expert panel recommendation, almost 10 % of patients who had been randomized into the observation group were irradiated. This bias might have affected outcome; thus, no definite conclusions on the role of radiotherapy can be drawn from this study.

Thus, patients achieving a CR with chemotherapy might not need consolidating radiotherapy to improve the overall outcome. On the other hand, patients with residual disease or PR only might benefit from consolidating radiotherapy. However, FDG-PET scan might be more helpful to identify patients with active residual disease and the need for consolidating therapy. This has been shown to be the case after treatment with BEACOPP regimen [23]. Similar data for the less active ABVD regimen from large studies are not yet available and are eagerly warranted.

13.7 Summary

Advanced-stage HL has become a curable disease for the majority of patients. First-line treatment with six to eight cycles of ABVD is still widely being used. However, the dose-intensified BEACOPP escalated regimen induces a clinically relevant better PFS, which translated into a superior OS in a large network meta-analysis, prospectively randomized studies, and indirect comparisons to ABVD. Thus, six cycles of BEACOPP escalated meanwhile represent the

standard for the treatment of advanced-stage HL patients for many groups. Accordingly, cooperative groups such as the EORTC or LYSA have implemented BEACOPP escalated as standard arm in their ongoing prospective trials. Scientific interest is currently focusing on the questions whether (1) two cycles of the less toxic ABVD regimen should be escalated to the dose-intensified BEACOPP regimen in case of PET-2 positivity or (2) if after a more aggressive induction therapy with two cycles of BEACOPP escalated, further treatment can be de-escalated (GHSG HD18). Both approaches promise to find the best balance between toxicity and efficacy for the benefit of each individual patient. Apart from these more personalized treatment strategies, the targeted drug brentuximab vedotin is currently being used to improve both regimens, ABVD in terms of efficacy and BEACOPP in terms of tolerability. After decades of substantial but slow advances in the treatment of advanced-stage HL, personalized or targeted treatment strategies will hopefully result in better treatment options for our patients in the near future.

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Part III

Special Clinical Situations

Pediatric Hodgkin Lymphoma

14

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14.1 Introduction

14.1.1 Comparison of Pediatric/Adolescent Versus Adult HL

Pediatric/young adult HL is one of the few childhood malignancies that shares aspects of its biology and natural history with an adult cancer. Historically, children were thought to have a worse prognosis than adults due to antiquated treatment approaches that were initially designed to mitigate toxicities in children. It is now clear that effective therapy provides similar or even superior outcomes in children/young adults. A comparison of the demographics of clinical presentations of pediatric/adolescent HL compared with adult HL is presented in Table 14.1. The first of the bimodal incidence peaks in Hodgkin lymphoma (HL) occurs in teenagers and young adults (15–25-year age group). HL represents less than 5 % of malignancies in children under the age of 15 years. In contrast, it represents 16–20 % of malignancies in adolescents making it the most common malignancy of this age group.

Childhood HL is biologically indistinguishable from HL of young and middle-aged adults other than the relative incidence of specific disease histologies (Table 14.1). Mixed cellularity (MC) and nodular lymphocyte-predominant (NLP) HL are the common types of HL in the preadolescent child; adolescents and young adults are most frequently (85 %) afflicted with nodular sclerosing (NS) HL [1]. Only a third of children

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_14, © Springer International Publishing 2015

Table 14.1 Demographic and clinical characteristics at presentation of pediatric HL

	Childhood HL	AYA HL	Adult HL
Age range (years)	≤14	15–35	≥35
Prevalence of HL cases (%)	10–12	50	
Gender			
Male:female	2–3:1	1:1–1.3:1	
Histology			
Nodular sclerosis (%)	40–45	65–80	
Mixed cellularity (%)	30–45	10–25	
Lymphocyte depleted (%)	0–3	1–5	
NLPHL (%)	8–20	2–8	
EBV associated	27–54 % Risk factors: male, younger age, mixed cellularity histology, economically disadvantaged countries	20–25 %	34–40 %
Other risk factors	Lower SES, increasing family size	Higher SES, smaller family size, early birth order	
Stage at presentation	30–35 % with stage III or IV disease, 25 % with B symptoms	40 % with stage III or IV disease, 30–40 % with B symptoms	
Relative survival rates at 5 years	94 % (<20 years)	90 % (<50 years)	

Modified from Refs. [84, 85]
AYA adolescents and young adults, *IPS* International Prognostic Score, *SES* socioeconomic status

will have advanced disease; approximately 25 % will have B symptoms. The incidence of HL with adverse features increases with age. Although there were no discernable differences in clinical presentation, response to therapy, or long-term outcome noted for adolescents (16–21 years) vs. young adults (22–45 years) treated similarly for HL [2], the treatment of children/adolescents and adults has diverged over the years primarily due to concerns about the late adverse effects of therapy.

14.1.2 Classical Pediatric Hodgkin Lymphoma (PHL)

14.1.2.1 Overall Strategies

The adverse consequences of therapy have driven the pediatric treatment paradigm of care. Clinical trials for pediatric and adolescent HL have been designed both to reduce long-term organ injury and to increase efficacy. Pediatric oncologists responded first to developmental issues in the young child and later to the long-term treatment consequences in all young survivors in the design of treatment approaches. Recognition of musculoskeletal hypoplasia in young children with HL treated with high-dose radiation such as shortened sitting height, thin necks, and narrow shoulders and chest [3–6] precipitated the development of pediatric-specific regimens for HL. Combined-modality treatments, even for low-stage disease, allowed for the reduction of radiation dose [7] and field size, thus sparing normal structures (Fig. 14.1). This strategy for care was extended to older children and adolescents when hypothyroidism [8, 9], secondary cancers, and valvular and atherosclerotic heart disease [10, 11] were also found to be attributable to high-dose radiation.

Low-dose radiation of 15–25 Gy has been the standard in childhood and adolescent HL for decades. This reduced the potential for long-term risk without adversely impacting event-free survival. A convergence of treatment approaches may be emerging as recent adult trials have begun to address these issues and reduce radiation doses. With overall survival over 90 %, the quality of survival becomes paramount.

Early response to therapy was recognized [12, 13] as highly predictive of outcome.

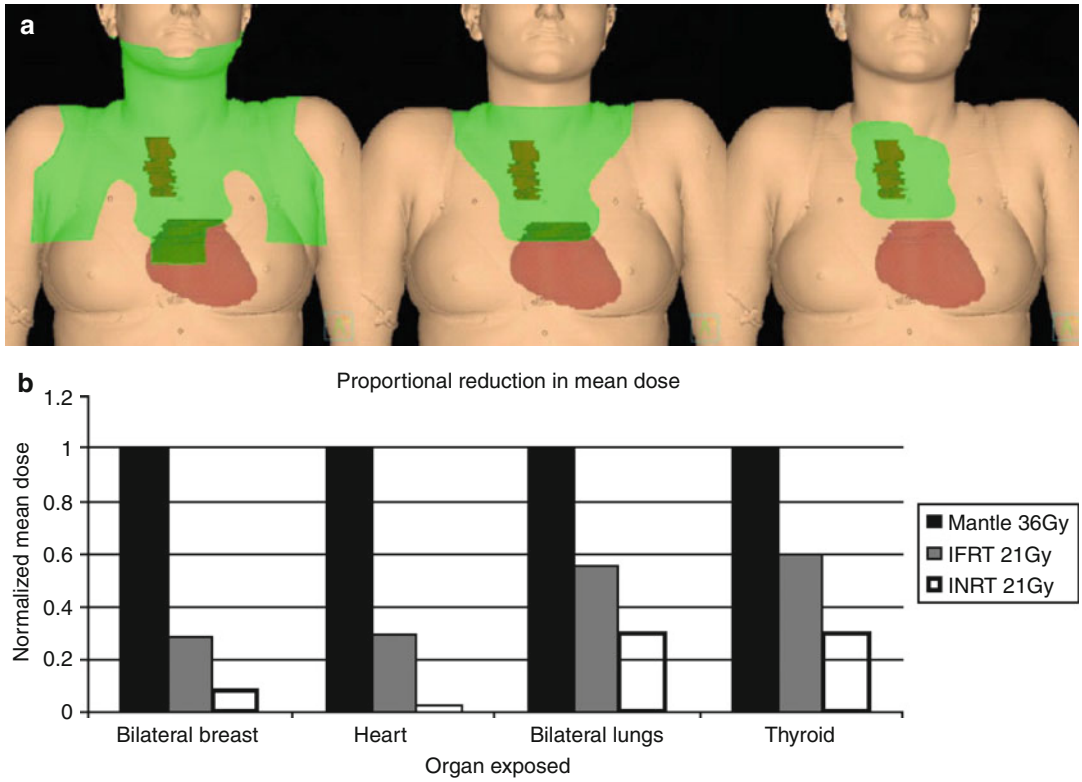

Fig. 14.1 CT-based planning images depicting a historic mantle RT, compared to standard involved-field radiation treatment (IFRT), and involved node RT (INRT) for a patient with stage I disease involving the mediastinum. The postchemotherapy volume of initially involved paratracheal nodes is depicted in *dark red* and the cardiac silhouette is also evident. (**b**) Demonstration of the reduction in dose to breast, lung, heart, and thyroid for the female patient shown in (**a**) (From Hodgson et al. [83])

In Europe and the USA, response-based, risk-adapted approach to treating HL [14] allows therapy to be tailored to each individual, within the context of clinical trials. Dose-dense regimens [14] used are similar to those used by adult groups [15, 16], but the pediatric algorithms use the enhanced efficacy to support reduction of therapy.

14.1.2.2 Low-Risk (Early Favorable) Disease

Although there have been differing definitions of low-risk disease (Table 14.2), risk-adapted approaches aim to define a cohort of patients that is curable with minimal therapy. Treatment group allocation, risk stratification, and response assessment vary according to each study group (Table 14.2), but all treatment groups define low risk based on stage and bulky disease. Patients with NLPHL are increasingly being treated on specific low-dose regimens separate from those used for the treatment of classical HL.

In the decade following the introduction of MOPP, secondary leukemia and sterility emerged as significant concerns [17–20]. During the 1980s, alkylator exposure and leukemia risk were reduced by alternating MOPP and ABVD [21, 22]. The goal was to avoid reaching thresholds of toxicity for any specific agent. The Pediatric Oncology Group (POG) compared four cycles of MOPP/ABVD plus 25.5 Gy to six cycles of chemotherapy alone without detecting differences in efficacy [12]. However, the profound sensitivity of testes to procarbazine continued to cause sterility in boys, even with only two cycles of procarbazine-containing chemotherapy [23]. Although early attempts to avoid procarbazine

Table 14.2 Risk groups employed by selected pediatric study groups

Study group	Risk features (RF)	Low risk	Intermediate/early unfavorable risk	High risk
Pediatric				
Children's Oncology Group [14]		IA/IIA no bulk or extranodal extension	IA bulk or "E" extension IB IIA bulk or "E" extension IIB IIIA IVA	IIIB, IVB
German Multicenter Studies (Pediatric) [87]		IA/B IIA	IIB IIIEA IIIB	IIEB IIIEA/B IIIB IVA/B
St. Jude/Stanford/Dana-Farber [28, 88]	Categorized as favorable or unfavorable risk by IPS	IA/IIA no bulk	IA bulk IB IIIA bulk IIIB IIII IIV	
Children's Cancer Group [32]	Hilar lymphadenopathy, >4 sites nodal disease, bulky disease	IA/B without RFs IIA without RFs	IA/B with RFs IIA with RFs IIB IIIA/B	V

Modified from Refs. [84, 85]
RF refractory fever

were unsuccessful [24], more recent regimens have achieved this goal [14].

ABVD is used routinely in adults [25] but is not the standard of care in children with early favorable HL. Successful regimens have been devised by the German Paediatric Oncology Hodgkin's Group (GPOH) [26] using OEPA (vincristine, etoposide, prednisone, and doxorubicin) in males (see Table 14.3), by the French Society of Pediatric Oncology [27] using EBVP (etoposide, bleomycin, vincristine, prednisone), by Donaldson et al. [28] using VAMP (vincristine, doxorubicin, methotrexate, and prednisone), and by the Pediatric Oncology Group (POG) using ABVE (doxorubicin, bleomycin, vincristine, etoposide) [29] all avoiding the use of procarbazine. With these approaches, EFS of 88–92 % can be achieved without significant radiation or alkylator toxicity. Patients treated on these newer regimens receive less than 200 mg/m^2 of doxorubicin plus or minus 20–25 Gy of involved field radiation.

The traditional approach of most pediatric HL treatment groups has been to use combined-modality therapy. Currently, these study groups are involved in evaluating methods to define low-risk patients who may be cured without radiotherapy, i.e., with chemotherapy alone. However, patients with early stage HL treated with chemotherapy alone most frequently relapse in the initially involved lymph node(s) [30]. Therefore, an effort has also been made to reduce further the size of the radiation field by including only the initially involved lymph node(s) – the so-called involved node radiation (INRT) [31]. The complexity of defining the field for INRT has led to the development of an alternative approach termed "involved site radiation therapy" (ISRT) [32, 33]. This is a "modernized" version of IFRT, recommended for patients who do not have adequate imaging for INRT treatment planning but who may nonetheless receive more limited radiation fields on the basis of modern treatment planning methodologies.

Table 14.3 Treatment results for early, favorable pediatric HL

Group or institution	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy) field	Survival (%)		Follow-up interval (years)	References
					Overall	DFS, EFS, or RFS		
Combined-modality trials								
POG 8625 (2006)	81	CS I–IIIA	4 MOPP/ABVD	25.5 IF	97	91	8	[12]
US CCG (2002)	294	CS IA/B, IIA	4 COPP/ABV	21, IF	100	97	3	[34]
(2012)							10	[35]
SFOP MDH-90 (2000)	171	I–II	4 VBVP, good responders	20, IF	97.5	91	5	[27]
	27	I–II	4 VBVP 1–2 OPPA, poor responders	20, IF		78	5	
Germany–Austria HD-95 (2001)	326	I, IIA	2 OEPA/OPPA	20–35, IF for PR	97	91	3	[87]
(2013)							10	[47]
	224	IIB, IIIA	2 OEPA/OPPA + 2 COPP	No RT if CR	97	94	3	
Germany–Austria	275	IA/IB–IIA	2 OEPA/OPPA	25, IF	99	94/95	5	[91]
HD-90 (1996)	124	IIB–IIIA	2 OEPA/OPPA, 2 COPP	25, IF	97	90/96	5	
Royal Marsden (1997)	125	II	6–10 ChlVPP	35, IF	92	85	10	[92]
Chemotherapy alone								
US CCG (2002)	106	CS IA/B, IIA	4 COPP/ABV	None	100	91	3	[34]
POG 8625 (2006)	78	CS I–IIIA	6 MOPP/ABVD	None	94	83	8	[12]
Response-based RT	278	IA, IIA	4 AV-PC	21 IF/none if CR	99	80	4	[38]
AHOD0431 [D,E]								
St. Jude consortium [C]	88	IA, IIA	4 VAMP	25.5 IF/none if early CR	100	89	5	

ABVD Adriamycin, bleomycin, vinblastine, and dacarbazine; *AEIOP* Italian Association of Hematology and Pediatric Oncology; *CCG* Children's Cancer Group, *ChlVPP* chlorambucil, vinblastine, procarbazine, and prednisolone; *COPP* cyclophosphamide, vincristine (Oncovin), prednisone, and procarbazine; *COPP/ABV* cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone, Adriamycin, bleomycin, and vinblastine, *CR* complete response; *CS* clinical stage; *EF* extended field; *EFS* event-free survival; *HD* Hodgkin disease; *IF* involved field; *MDH* multicenter trial; *MH* Multicentre Hodgkin Trial; *MOPP* nitrogen mustard, vincristine (Oncovin), procarbazine, and prednisone; *M/T* mediastinal/thoracic ratio; *OEPA* vincristine (Oncovin), etoposide, prednisone, and Adriamycin; *OPA* vincristine (Oncovin), prednisone, and Adriamycin; *OPPA* vincristine (Oncovin), procarbazine, prednisolone, and Adriamycin; *PR* partial response; *PS* pathologic stage; *R* regional; *RFS* relapse-free survival; *RT* radiotherapy; *SFOP* French Society of Pediatric Oncology; *VAMP* vinblastine, Adriamycin, methotrexate, and prednisone; *VBVP* vinblastine, bleomycin, etoposide (VP-16), and prednisone; *AVPC* doxorubicin, vincristine, prednisone, and etoposide

Mediastinal thoracic ratio <0.33. Lymph node <6 cm

Some patients were clinically staged

Nachman et al. showed an increased relapse rate in patients who did not receive radiation despite achieving CR at the end of chemotherapy [34, 35]. Late-response evaluation may not have identified the optimal cohort for reduction of radiation. Early response may better define the profoundly chemotherapy-sensitive patient who does not need radiation. Based on the excellent outcomes of low-risk HL patients achieving CR after two cycles of chemotherapy [12], recent trials in the COG, the St. Jude/DFCI/Stanford consortium, and the EuroNet PHL group [36, 37] have examined early response to determine who does or does not require radiation postchemotherapy.

The prognostic importance of early chemotherapy response rather than end-of-chemotherapy response has led to the use of early response assessment (after 6–9 weeks) to titrate individual therapy and dense regimens to maximize the early response rates. The St. Jude/DFCI/Stanford consortium has reported 2-year EFS of 90.8 % in early responding, low-risk patients with either classical or lymphocyte-predominant HL treated with four cycles of VAMP without radiation [37]. The most recent COG study (AHOD0431) found that early assessment by PET after one cycle is a predictor of recurrence [38, 39]. The current EuroNet PHL-C1 classical HL trial is evaluating PET activity after two intensive cycles of OEPA (cumulative dose of anthracycline is 160 mg/m^2) to predict who does not require radiotherapy [40]. All such reductions in treatment may increase the risk of relapse; hence, adverse outcomes such as the need for high-dose salvage therapy (e.g., stem cell transplant or high-dose radiation) must be closely monitored.

14.1.2.3 High-Risk (Advanced, Unfavorable) Disease

For children with advanced stage disease, improving efficacy while limiting long-term toxicity is even more challenging. The approach in pediatric HL has been to increase the number of agents so as to limit cumulative doses of individual agents. Regimens used in the 1980–1990s alternated MOPP/ABVD [22, 41] or used the hybrid COPP/ABV [34] to avoid the cumulative doses of doxorubicin (300–400 mg/m^2) and bleomycin (120–160 mg/m^2) associated with six to eight cycles of the four-drug ABVD regimen [21, 25].

Minimalistic dose regimens in combined-modality protocols, such as VEPA (Table 14.4) that eliminated traditional alkylating agents, were not successful and resulted in a 70 and 49 % 5-year EFS for stage III and IV HD, respectively [42].

It has been known for decades that outcome in HL is optimized by dose intensity. Only recently has this knowledge been considered a clue to improving outcome [43–45]. ABVE-PC was developed by the COG (by adding prednisolone and cyclophosphamide to ABVE) for the treatment of advanced HL, and dose density was increased by the use of 3-week cycles [14]. This regimen is similar to dose-dense regimens such as Stanford V and BEACOPP, developed simultaneously in the adult groups [15, 16]. BEACOPP and escalated BEACOPP are dose-intensive regimens with improved efficacy compared to COPP/ABVD. Instead of further cumulative dose escalation, the COG and EuroNet PHL take advantage of dose-dense delivery to limit cumulative cytotoxic therapy. Such dose-intensive regimens also limit the cumulative dose of agents delivered to the early responders.

ABVE-PC is the backbone for all new COG trials. This dose-dense approach allows for the elimination of procarbazine and the limitation of the doxorubicin and etoposide dose. The first such study (POG 9425) resulted in 5-year EFS of 84 % and 5-year overall survival (OS) of 95 % for advanced HL. Early responders (after three cycles of ABVE-PC) on this study proceeded directly to receive 21-Gy regional RT. Others received two more cycles (total five ABVE-PC in 15 weeks) prior to 21-Gy RT. The GPOH-HD group have substituted dacarbazine for procarbazine in boys with HL, resulting in excellent long-term results [46].

Low-dose, involved field radiation remains a significant modality of therapy in high-risk disease. The multicenter trial GPOH-HD-95 used OPPA/COPP for girls and OEPA/COPP for boys with radiation dose determined by end-of-chemotherapy response. For the intermediate- and higher-risk groups (TG2 and TG4), outcome was significantly better for those

Table 14.4 Treatment results for advanced, unfavorable pediatric Hodgkin lymphoma

Group of institution	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy) field	Survival, %		Follow-up interval (years)	Reference
					Overall	DFS, EFS, or RFS		
Combined-modality trials								
Germany–Austria HD-90 (1996)	179	II_EB, III_EA/B, IIIB, IVA/B	2 OEPA/OPPA + 4 COPP	20, IF	98/89	83/91	5	[91]
Germany–Austria HD-95 (2001) (2013)	280	II_EB, III_EA/B, IIIB, IVA/B	2 OEPA/OPPA + 4 COPP	PR, 20–35; IF CR, no RT	97	84	3 10	[87] [47]
Gustave-Roussy (1985)	60	I–IV	3–6 MOPP	40, IF	93	86	5	[89]
SFOP MDH-82 (1992)	40 21	CS III CS IV	3 MOPP/3 ABVD 3 MOPP/3 ABVD	20–40, EF 20–40, EF		82 62	6 6	[90]
AEIOP MH-83 (1993)	49 24	Group 3 IIIB–IV I–IV	Group 3 5 MOPP/5 ABVD CCOPP/CAPTe	 20–40, EF 30–40, IF	 60 	 83	7 5	[93]
Royal Marsden (1997)	80 27	III IV	6–10 ChlVPP 6–10 ChlVPP	35, IF 35, IF	84 71	73 38	10 10	[92]
US POG (1997)	80	CS/PS IIB, $IIIA_2$, IIIB, IV	4 MOPP/4 ABVD	21, EF	87	80	5	[13]
Stanford, St. Jude, Dana-Farber (2002)	56	CS I/II bulky ($n=26$), CS III/IV ($n=30$)	6 VEPA	15–25.5, IF	81.9	67.8	5	[42]
US CCG (2002) (2012)	394	CS I/II[a], CS IIB, CS III	6 COPP/ABV	21, IF	95	87	3 10	[34] [35]
	141	CS IV	COPP/ABV+CHOP + AraC/VP-16	21, IF	100	90	3	
St. Jude, Stanford, DFCI (2004)		CS IB/IIB or bulky >6 cm	6 VAMP/COP	15 IF if CR	93	76	5	[88]
159		CS III/IV		25.5 IF if PR				
COG – P9425 (2009)	216	CS IB, IIB, $IIIA_2$, IIIB, IV	RER, 3 ABVE-PC; SER, 5 ABVE-PC	21 IF	95	86	5	[14]
		IIA/IIIA1 “bulk”		21 IF		84		

(continued)

Table 14.4 (continued)

Group of institution	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy) field	Survival, %		Follow-up interval (years)	Reference
					Overall	DFS, EFS, or RFS		
Chemotherapy alone								
UKCCSG (2002)	67	CS IV	6–8 ChlVPP	None[b]	80.8	55.2	5	[94]
US CCG (2002)	394	CS I/II[a], CS IIB, CS III	6 COPP/ABV	None	100	83	3	[34]
	141	CS IV	COPP/ABV, CHOP, AraC/VP-16	None	94	81	3	
US POG (1997)	81	CS IIB, III2A, IIIB, IV	4 MOPP/4 ABVD	None	96	79	5	
Response-based RT AHOD0031 (2010)	1,712	All except: IA, IIA non-bulk IIIB, IVB	Standard arm; 21 IF/4 ABVE-PC	Randomized: RER, ± RT	98	85	4	[13]
				SER, ± 2 DECA				

ABVD Adriamycin, bleomycin, vinblastine, and dacarbazine; *ABVE-PC* Adriamycin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; *AEIOP* Italian Association of Hematology and Pediatric Oncology; *AraC* cytosine arabinoside; *CAPTe* cyclophosphamide, Adriamycin, prednisone, and teniposide; *CCG* Children's Cancer Group; *CCOPP* vincristine (Oncovin), procarbazine, and prednisone; *ChlVPP* chlorambucil, vinblastine, procarbazine, and prednisolone; *CHOP* cyclophosphamide, hydroxydaunomycin, vincristine (Oncovin), and prednisone; *COMP* cyclophosphamide, vincristine (Oncovin), methotrexate, and prednisolone; *COPP* cyclophosphamide, vincristine (Oncovin), prednisone, and procarbazine; *COPP/ABV* cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone, Adriamycin, bleomycin, and vinblastine; *CR* complete response; *CS* clinical stage; *CVPP* cyclophosphamide, vinblastine, procarbazine, and prednisone; *DFS* disease-free survival; *EF* extended field; *EFS* event-free survival; *HD* Hodgkin disease; *IF* involved field; *MDH* multicenter trial; *MH* Multicentre Hodgkin Trial; *MOPP* nitrogen mustard, vincristine (Oncovin), procarbazine, and prednisone; *NR* no response; *OEPA* vincristine (Oncovin), etoposide, prednisone, and Adriamycin; *OPA* vincristine (Oncovin), prednisone, and Adriamycin; *OPPA* vincristine (Oncovin), procarbazine, prednisolone, and Adriamycin; *POG* Pediatric Oncology Group; *PR* partial response; *PS* pathologic stage; *R* regional; *RFS* relapse-free survival; *RT* radiotherapy; *SFOP* French Society of Pediatric Oncology; *TLI* total lymphoid irradiation; *UKCCSG* United Kingdom Children's Cancer Study Group; *VAMP* vinblastine, doxorubicin, methotrexate, and prednisone; *VEEP* vincristine, etoposide, epirubicin, and prednisolone; *VEPA* vinblastine, etoposide, prednisone, and Adriamycin; *DECA* dexamethasone, etoposide, cisplatin, cytarabine

[a]12 patients received 20–35 Gy, IF; 2 received whole-lung irradiation

[b]Only 12 patients had IFRT of 20-35 Gy to sites of residual or initial bulk disease

receiving radiation therapy (TG2, 0.78 vs. 0.92; TG2+3, 0.79 vs. 0.91) [26, 47]. The Children's Cancer Group also noted improved outcome for patients treated with radiation, despite CR at the end of chemotherapy [34, 35]. Kelly et al. [48] reported excellent results using a modified approach to BEACOPP that reduced the doses of chemotherapy for girls and for boys with a rapid response. Nonetheless, this regimen is not being used currently because cumulative doses of chemotherapy remain high.

Recent trials both in the COG and in Europe addressed early response-directed approaches to limit the need for radiation. AHOD0031 for intermediate-risk HL used the dose-dense ABVE-PC regimen to support and evaluate the concept of an early response-based algorithm [49]. This study showed that rapid early response (RER) could identify a cohort comprising 45 % of patients who did not benefit from radiation. Similarly, those with slow early response (SER) may benefit from augmented chemotherapy. The high-risk study (AHOD-0831) limited the radiation field for rapid early responders while augmenting the therapy for slow early responders; outcomes were similar to POG9425 but used less radiation for RER and less doxorubicin for SER [E].

14.1.2.4 Future Considerations in Classical Pediatric and Adolescent HL

Progress has been made in the treatment of children with HL with all stages of disease and risk factors, but several issues remain to be resolved. Response to chemotherapy may define both the total amount of chemotherapy required and the need for radiotherapy (RT). For early stage patients, the balance between chemotherapy dose and radiation exposure continues to be explored. Restriction of RT to initially involved lymph nodes (involved node irradiation or involved site irradiation) rather than chains (or regions) of nodes may affect the balance of risk. For high-risk disease, dose-dense chemotherapy improves efficacy and supports tailoring of therapy to the patient's response. RT is clearly effective in enhancing the local control of PHL but has a dose-dependent toxicity profile favoring a limited volume/dose approach. Ongoing studies are needed to assess the role of RT for initial bulky disease, to residual postchemotherapy disease (particularly if it is PET negative), and to involved organs. Carefully designed and sequential evidence-based studies are needed to continue to improve efficacy while limiting toxicity.

14.1.3 Nodular Lymphocyte-Predominant HL (NLPHL)

An indolent, peripheral, NHL-like disease, NLPHL was recognized in the early 1990s as a clinicopathologically distinct form of HL [50]. Unlike classical HL, NLPHL is a CD20-positive, CD30- and CD15-negative, B-cell lymphoma that is not associated with EBV genomic integration. There is a distinct male predominance (ratio 2–3:1) with nearly 90 % of pediatric patients having early stage disease (IA/IIA). A higher percentage (10–20 %) of children have NLPHL [1] compared to adults (3–8 %) [51], and although >50 % of pediatric and adolescent cases are under the age of 14 years [52], the incidence peaks between 14 and 18 years. Peripheral lymphadenopathy is the most common presentation involving the axilla, cervical, and inguinal regions, often present for months or years. Rarely is advanced or central disease seen.

Adults with early stage NLPHL are treated with involved field radiotherapy, standard cHL therapy, or combined-modality therapy. Children have until 2005, and the start of NLPHL-specific clinical trials received standard pediatric cHL therapy with combined-modality chemoradiotherapy [53] which is excessively toxic.

Morbidity, even mortality, secondary to repeated courses of intensive therapy to eradicate this indolent, usually nonfatal disease has resulted in a drive to reduce the intensity of therapy to avoid late effects [52].

Children with fully resected early stage NLPHD have been cured without the need for any chemoradiotherapy [54–57], but the specific situations in which this strategy is appropriate are currently under investigation. Understanding more about the natural history, risk categories,

variant histologies, and transformation rates can only be achieved with clinical trials. Two nonrandomized studies, EuroNetPHL-LP1 and COG (NCT00107198), have looked at reducing the toxicity of therapy using surgical resection alone or low-dose chemotherapy (+/– radiotherapy) for early stage disease (stages I and II) [54, 55]. As salvage therapy is effective for late or even multiple relapses especially as most recur at the original site of disease with no upgrade, OS is expected to remain near to 100 % [58].

Because of transformation rates of approx 5 % to aggressive B-NHL [59] in adults, usually diffuse large B-cell lymphoma [60], concerns regarding reduced therapy, potentially allowing persistence of the CD20 clone and increased transformation rates, remain. However, transformation rates in children are not known but appear extremely low.

Rituximab has been studied in adults for use in this CD20-positive tumor [61]. The pediatric community have traditionally been wary about using rituximab in young children because of the impact on immune status/memory. As early stage NLPHL is viewed as a highly curable disease with minimal chemotherapy or surgery alone, rituximab tends to be reserved for treating more aggressive, advanced, or relapsed disease. Addressing the impact of adjuvant rituximab therapy on EFS and transformation rates in children within a clinical trial has been the aim of clinicians for over a decade. However, without international collaboration, funding from drug companies, and inclusion of young adults, a randomized controlled trial into the management of NLPHL remains an unattainable goal.

14.1.4 Recurrence, Relapse, and Salvage in PHL

14.1.4.1 Introduction

Relapsed and refractory classical Hodgkin lymphoma (HL) remains a clinical and therapeutic challenge. Approximately 10 % of patients with early stage, and up to 30 % with advanced stage disease, relapse after first-line chemotherapy.

Cure can still be achieved in a substantial proportion of patients with recurrent disease, but there is no uniform approach to salvage therapy. There are several different salvage treatment options. Standard-dose chemotherapy forms the basis of salvage in almost all situations, and this is followed by consolidation treatment. The choice of consolidation treatment is guided by prognostic factors and risk stratification and may include consolidation radiotherapy only, high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT), and HDCT and allogeneic transplantation or novel agent approach.

No pediatric trials have compared standard-dose chemotherapy regimens to high-dose chemotherapy followed by autologous stem cell transplantation. Radiotherapy has an important role in salvage but must be individualized based on previous radiation exposure, in- or outfield recurrence, stage at recurrence, and the toxicities of total treatment burden.

14.1.4.2 Standard-Dose Salvage Chemotherapy Regimens

After recurrence is noted, the first step is reinduction with a salvage regimen. There is no "best" chemotherapy regimen at salvage, and there are no randomized studies comparing standard-dose chemotherapy regimens. The choice of regimen should take account of primary therapy, use of non-cross-resistant drugs, and cumulative drug toxicities. The aim of salvage therapy is to obtain cytoreduction and to demonstrate chemosensitivity. It also facilitates collection of peripheral stem cells for ASCT. Salvage regimes can be divided into intensive conventional regimens[1] (mini-BEAM), cisplatin-based regimens[2] (ESHAP, DHAP (ESHAP, DHAP, APPE, DECAL)), ifosfamide-based regimens[3](EPIC, IEP, ICE, IV), or others[4] (GV, IGEV). The COG uses IV as its

[1] Mini-BEAM; BCNU, etoposide, cytarabine, melphalan.

[2] *ESHAP* etoposide, methylprednisolone, cytarabine, cisplatin; *DHAP* dexamethasone, cytarabine, cisplatin; *APPE* cytarabine, cisplatin, prednisone, etoposide; *DECAL* cytarabine, cisplatin, prednisone, etoposide, asparaginase.

[3] *EPIC* etoposide, vincristine, epirubicin, prednisolone; *IEP* ifosfamide, etoposide, prednisolone; *ICE* ifosfamide, carboplatin, etoposide; *IV* ifosfamide, vinorelbine.

[4] *GV* gemcitabine, vinorelbine; *IGEV* ifosfamide, gemcitabine, vinorelbine, prednisolone.

standard regimen because of efficacy and with the intent of avoiding etoposide-induced secondary malignancy after stem cell transplantation [62]. The decision to continue salvage therapy with RT for consolidation vs. use of high-dose chemotherapy and stem cell transplantation is based on the assessment of predictive factors.

14.1.4.3 Prognostic Factors at Relapse in Pediatric HL: Standard-Dose Chemoradiotherapy Versus High-Dose Chemotherapy/Stem Cell Transplantation

Prognostic factors at relapse may be used to allocate patients to a risk stratified salvage approach. This is in contrast to adult practice where consolidation with HDCT/ASCT is considered standard of care. In children, low-risk patients may be salvaged without HDCT. Patients with limited stage, late relapse, and chemotherapy-responsive disease are usually salvaged with standard-dose chemotherapy plus RT particularly if first-line treatment was chemotherapy only. Response to retrieval chemotherapy is particularly relevant in determining likelihood of curative intent. FDG-PET/CT is increasingly used for response assessment.

Early relapse and primary progressive disease is associated with lower OS and EFS in pediatric studies [63–65]. Chemosensitivity to standard-dose chemotherapy and disease status at transplantation are also predictive of outcome. In one study, 5-year FFS was 35 % for patients with chemosensitive disease vs. 9 % with chemoresistant disease [63]. Another group found 68 % OS and 59 % FFS at 5 years in chemosensitive patients vs. 18 and 0 % in chemoresistant patients [64]. Several particularly adverse factors have been noted. Chemoresistant patients had 5-year FFS of 0 % with HDCT/ASCT [53]. Adolescents with B symptoms at recurrence had poor OS even after HDCT/ASCT (11-year OS 27 % with B symptoms vs. 60 % without) [66]. No difference in OS or FFS between age subgroups or in comparison with adult cohorts has been reported by several studies [63, 64, 67].

The largest pediatric review of outcome after recurrent/refractory HL defined the prognostic factors [68] in 176 pediatric patients diagnosed with HL and treated on the DAL/GPOH studies over a 17-year period. HDCT/ASCT was used only in a subgroup (30 %) with an unfavorable prognosis. The 10-year DFS and OS were 62 and 75 %, respectively. Length of time between primary therapy and disease recurrence was the strongest prognostic factor with DFS of 41, 55, and 86 % for those with refractory disease, early relapse, and late relapse, respectively. Stage IV, extranodal disease, and female gender were associated with lower OS. This study showed that salvage can be risk adapted. A recent French experience [69] found the only relevant prognostic factors to be time to relapse and chemoresistance. In this study of 70 relapsed patients, those with primary progression had an EFS <40 % compared with approximately 80 % in late relapse, and chemosensitivity (CR or PR >70 %) to salvage was associated with a DFS of 77 % versus 10 % with poor response ($p < 0.0001$).

14.1.4.4 High-Dose Chemotherapy and Autologous Stem Cell Transplant

COG protocols have studied HDCT/ASCT and immunomodulatory therapy in all patients except the lowest-risk group (late relapse without bulky disease or B symptom in those initially treated for IA/IIA disease with minimal systemic therapy) [70]. In Europe, HDCT/ASCT has a recognized role in salvage for those with higher-risk features, primary progressive HL, and poor response to reinduction. Intermediate-risk patients who achieve a complete FDG-PET-defined response after two cycles of SDCT receive more chemotherapy plus RT.

There are no studies that define the most effective HDCT; BEAM and CVB (cyclophosphamide, etoposide, carmustine) are commonly used. TBI-containing regimens confer no benefit and are associated with increased toxicity and late effects. Transplant-related mortality is down to 0–2 % in some series. A higher TRM rate has been associated with history of atopy, thoracic irradiation, multiple chemotherapy regimens, and multiple relapses.

Series with HDCT/ASCT in pediatric and adolescent patients are small and report EFS

rates of 31–67 % [63, 64, 67, 71]; outcome for children is similar to adults with HDCT/ASCT [63, 67]. Studies that evaluate survival benefit rather than event-free survival after disease recurrence often rely on transplant after second or later recurrence to achieve good OS [64, 72]. Patients with primary progressive disease and those resistant to salvage regimens remain a huge challenge. SDCT with radiotherapy will not afford a chance of cure, but even HDCT/ASCT is an inadequate therapy for most such patients. New approaches to such patients such as the use of allogeneic SCT or immunomodulatory therapy may prove beneficial [70].

Long-term follow-up is required post-HDCT for the detection of late relapse and development of second cancers, which have been reported at a rate of 5–10 % at 5 years and substantially higher at 20 years or more in some series. Thirty-eight percent of deaths occurred 4–12 years after ASCT; 85 % of relapses occur within 2 years of ASCT [65].

14.1.4.5 High-Dose Chemotherapy and Allogeneic Stem Cell Transplantation

The role of allogeneic transplant in relapsed HL remains unknown. The poor outcome with HDCT/ASCT in chemotherapy poor responders to salvage and those who remain FDG-PET positive after salvage has resulted in exploration of alloSCT. Allogeneic transplantation is not recommended as the initial transplant approach outside of a clinical trial setting [73] due to high nonrelapse mortality (NRM) rate, mainly caused by graft vs. host disease and infection. Reduced intensity conditioning (RIC) ameliorates the NRM while maintaining theoretical graft vs. lymphoma effect. Allogeneic SCT may be an option for relapse post-HDCT/post-ASCT and for patients with refractory advanced stage HL and chemoresistant disease at salvage.

Children and adolescents allografted for HL had an OS of 45 % and PFS of 30 % at 5 years [74]. All were heavily pretreated, almost half with HDCT/ASCT. Those with chemosensitive disease and good performance status achieved 3-year OS of 83 % and PFS of 60 %. NRM was 21 ± 4 % in both the RIC and myeloablative conditioning groups. RIC was associated with a significantly higher relapse risk compared to myeloablative conditioning. Graft vs. host disease did not affect relapse rate.

Although studies based on registry data are useful, prospective trials are required to gain a better understanding of the role of allogeneic transplantation. The indications, optimal time point, conditioning regimen, and GVHD prophylaxis still need to be better defined.

14.1.4.6 Brentuximab Vedotin

There is very limited data in pediatric patients. A single phase I/II study [75] of brentuximab vedotin in relapsed and refractory HL defined the recommended dose as 1.8 mg/kg every 3 weeks and observed an overall response rate of 64 % with 21 % achieving a CR and 43 % PR. Responses are typically observed early by cycle 2, and the drug is generally well tolerated. As in adults, there is interest in the use of brentuximab vedotin in achieving CR prior to HDCT/ASCT and as a bridge to alloSCT.

14.1.5 Late Effects

Long-term adverse sequelae of greatest concern in children treated for HL (particularly with regimens including high-dose radiation) include impairment of muscle and bone development [3] and injury to the lungs [76], heart [10, 77], thyroid gland [8, 9], and reproductive organs [78]. Cardiovascular dysfunction, pulmonary fibrosis, and secondary malignancies significantly compromise the quality and length of life in survivors [79].

14.1.5.1 Cardiac Toxicities

High-dose (>30 Gy) radiation to the mediastinum has been associated with significant long-term effects in patients with HL. Stanford investigators reported that the actuarial risk of developing cardiac disease necessitating pericardiectomy was 4 % at 17 years in a series of long-term survivors of childhood HL who had received high-dose radiation [11]. Screening echocardiogram,

exercise stress test, and resting and 24-h ECG identified numerous clinically significant cardiac abnormalities in HL patients who had mediastinal irradiation at a median age of 16.5 years (range, 6.4–25 years). Significant valvular defects were detected in 42 %, autonomic dysfunction in 57 %, persistent tachycardia in 31 %, and reduced hemodynamic response to exercise in 27 % of patients [80]. With the introduction of techniques that reduce the radiation dosage to the heart, the rates of radiation-associated cardiac injury have declined dramatically.

Mediastinal irradiation given for HL may further predispose patients with PHL to anthracycline-related myocardiopathy [11, 81]. Cardiac dysfunction after anthracycline therapy itself can be noted, with the highest risk in those receiving high cumulative doses or in [11, 81] young children who may be affected by an adverse effect on cardiac myocyte growth. Fortunately, most pHL patients are adolescents, and current pHL regimen doses are significantly lower than those used in adult ABVD regimens.

14.1.5.2 Pulmonary Toxicities

Chronic pneumonitis and pulmonary fibrosis should be rare in the current era of treatment for primary HL (Fig. 14.1). Predisposing therapies include thoracic radiation and bleomycin chemotherapy [76, 77]. The bleomycin in ABVD can cause both acute pulmonary compromise and late pulmonary fibrosis and can be augmented by the fibrosis that can be associated with pulmonary radiation. Asymptomatic pulmonary dysfunction that improves over time has been observed after contemporary combined-modality treatment.

14.1.5.3 Thyroid Toxicities

Thyroid sequelae are common after RT for PHL. Hypothyroidism, hyperthyroidism, thyroid nodules, and thyroid cancer have been observed in long-term survivors [8, 9]. Of these, hypothyroidism, particularly compensated hypothyroidism, defined as thyroid-stimulating hormone (TSH) elevation in the presence of a normal thyroxine (T4) level, is the most common thyroid abnormality. The primary risk factor for hypothyroidism is higher cumulative radiation dosage; the influence of age remains controversial [8, 9]. As many as 78 % of patients treated with radiation dosages greater than 26 Gy demonstrate thyroid dysfunction, as indicated by elevated TSH levels [8].

14.1.5.4 Secondary Malignancies

The overall cumulative risk of developing a subsequent malignancy after treatment for PHL has been reported to range from 7 to 10 % at 15 years from diagnosis and rises to 16–28 % by 20 years (Table 14.5) [82]; these data are based on patients treated in earlier decades. The most common secondary malignancies historically included both secondary acute myeloid leukemia (MDS/secondary AML) and solid tumors. However, leukemias are now infrequent due to changes in chemotherapy. Female breast cancer is a particular concern but is likely to be less common with

Table 14.5 Secondary cancers after childhood HL

Reference	Cohort size	Time period studied	Number of secondary cancers	Cumulative incidence (%) (years)	Standardized incidence ratio
Stanford [95]	694	1960–1995	59	Males: 9.7 % (20 years) Females: 16.8 % (20 years)	Males: 10.6 Females: 15.4
LESG [86]	1,641	1940s–1991	62	18 % (30 year)	7.7
Roswell [96]	182	1960–1989	28	26.7 % (30 year)	9.4
LESG [97]	1,380	1955–1986	135	31.2 % (30 year)	17.9
USA/European [98]	5,925	1935–1994	195	Solid tumors: 11.7 % (25 year)	7.7
University of Rochester/Johns Hopkins/University of Florida/St. Jude/Dana-Farber [82]	930	1960–1990	102	19 % (25 year)	Males: 8.41 Females: 19.93

current radiation doses and techniques, since it is associated with RT fields that include breast tissue (especially mantle fields) and higher radiation doses (Fig. 14.1).

14.1.6 Summary/Future Directions

Tremendous strides have been made in treating children with HL, both in terms of cure and reduction of toxicity. Devising new strategies to treat children with HL is problematic because of the overall success of current treatment regimens. However, grouping patients into different risk categories, using response-based therapy and newer imaging techniques, allows investigators to construct protocols intended to diminish therapy-induced toxicity for patients with favorable prognoses. These protocols also aim to improve efficacy of treatment for patients with intermediate and unfavorable prognoses. Unfortunately, the ability to conduct clinical trials, where the difference in survival between treatment arms is likely to be small, is compromised by the large patient numbers required to detect such differences. If a reduction in treatment toxicity is the intended goal of a new regimen, then many years of follow-up are necessary to prove efficacy. For patients with refractory or multiply relapsed disease, phase II studies investigating the use of monoclonal anti-CD30 antibodies, HDAC, and mTOR inhibitors in children are being planned internationally. The importance of investigators working together throughout the world to share data, and new treatment approaches, in order to cure children with HL safely, is clear.

Acknowledgment Thanks to Ann Muhs, Rochester, for her help with the manuscript, particularly the references.

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The Management of Older Patients with Hodgkin Lymphoma

15

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15.1 Introduction

Survival rates for Hodgkin lymphoma (HL) have substantially improved during the past several decades. Using stage-adapted polychemotherapy regimens and innovative radiation techniques, 5-year progression-free survival (PFS) has reached almost 90 % in young patients [1–3]. Since the median age at diagnosis is approximately 32 years, these excellent results account for the majority of patients. Unfortunately, this progress has not translated into a similar benefit for older patients, especially for advanced-stage disease [4–8]. Survival rates for HL patients aged ≥60 years remain significantly and disproportionately inferior compared with younger patient populations.

"Older age" is most often defined as age over 60 years, in part due to the poor tolerability of aggressive chemotherapy regimens above the age of 60 years. Accordingly, these patients are often not included in randomized controlled trials (RCTs). Thus, the percentage of older patients is underestimated using data from RCTs [9]. On the other hand, population studies estimate that patients over 60 years account for a substantial proportion of patients in clinical practice, i.e., about 20 % of the total HL population [10]. In part because older patients are under represented within clinical trials, a "standard of care" for this patient cohort has not been well defined [11]. The lack of improvement in outcome for these patients will become magnified as the most rapidly growing segment of the US population is persons aged

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_15,

>65 years, especially the age group ≥80 years; the latter has increased >250 % between 1960 and 2000, and it is expected that the population aged >75 will triple by year 2030 [12]. Malignant disorders in the elderly will become one of the most important topics in oncology, and also the absolute number of older HL patients will increase. There is an important and continued unmet medical need to improve outcomes for older HL patients, especially in advanced stages and for patients with comorbidity. In this chapter, we summarize the currently available data on the management of older patients with HL and address the particular issues that should be incorporated into prospective studies in order to improve future outcomes for patients [13].

15.2 Epidemiology

In contrast to non-Hodgkin lymphomas (NHLs), the incidence of HL seems to be constant at two to three cases per 100,000 people in recent decades [14, 15]. The previously described bimodal age distribution with a first incidence peak around 30 years and a second around 70 years is less apparent, but still present in recent analyses. This might be due to an improved hematopathologic workup including immunohistochemistry and the close cooperation with reference pathologists in most study groups. As a result, many HL cases were reclassified as NHL (e.g., T-cell anaplastic large cell lymphoma, Ki-1 anaplastic lymphoma, or T-cell-rich B-cell lymphoma) [16]. In addition, there are notable race differences in HL based in part on age. In an analysis of the US Surveillance, Epidemiology, and End Results (SEER) data, there were distinct age-related incidence patterns based on race [17]. Incidence rates for older HL patients (i.e., aged >64 years) were highest among Hispanics, followed by Whites and Blacks (see Fig. 15.1).

Many prospective studies and RCTs have excluded older patients on the basis of age or performance status. Only 5–10 % of patients included in HL RCTs have been older than 60 years [5, 18, 19]. The most accurate assessments have come from population-based studies. Two Swedish studies covering from 1979 to 1988 and 1973 to 1994 showed a proportion of 31 and 26 % of HL patients older than 60 years, respectively, in the population [7, 20]. The Scotland and Newcastle Lymphoma Group (SNLG) data demonstrated that from 1979 to 2003, 624 (20 %) of 3,373 patients registered on the population registry were over 60 years [21]. For the registry period 1994–2003, 399 of 1,701 patients were >60 years (23 %). This is a percentage confirmed in the Northern UK regional survey of elderly HL, where the age-specific incidence was 1.97/100,000 for patients aged 60–69 and 2.18/100,000 for patients aged 70 or older [10, 11]. The incidence is somewhat higher than that reported by trial study groups since the SNLG data is population based and, therefore, likely to have fewer exclusions. An analysis of the British National Lymphoma Investigation (BNLI) group found about 15 % of all HL patients older than 65 years, but only 5 % had been included in BNLI studies [19], while another study confirmed the proportion of about 20 % of older HL patients [10].

15.3 Pathology

With regard to histology, there are several differences between older and younger HL patient populations. The German Hodgkin Study Group (GHSG) published a prior comprehensive retrospective review of elderly patients [5]. Mixed cellularity was more common in older patients (35 %) as compared with younger (19 %) ($p<0.001$). By contrast, nodular sclerosis was less frequent among older patients with 41 vs. 66 % in younger patients ($p<0.001$). However, this subtype still remains the most common in both groups. The remaining rare subtypes, lymphocyte predominant and lymphocyte depleted, were represented with the same frequency in elderly and younger patients.

Comparable results have been obtained in other studies. A higher frequency of the mixed cellularity subtype was reported by the Nebraska Study Group, CALGB (the Cancer and Leukemia Group B), ECOG (Eastern Cooperative Oncology Group), and a recent Chicago series [6, 8, 18, 22, 23].

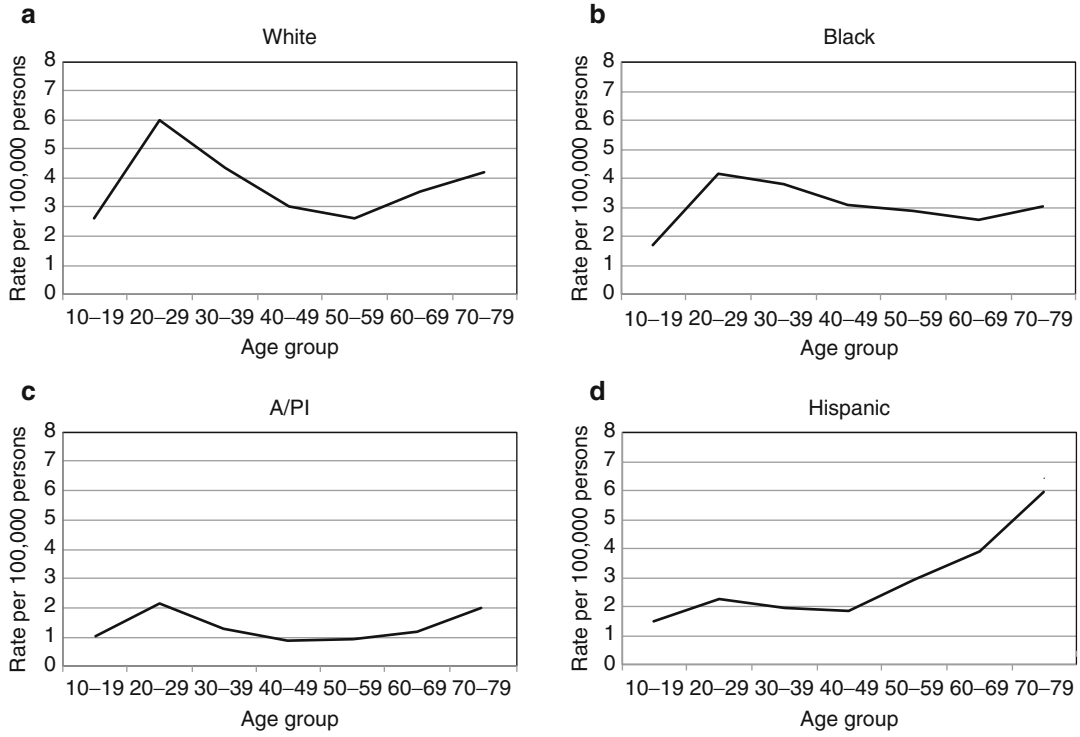

Fig. 15.1 Age-specific incidence of Hodgkin lymphoma by race. Data shown are age-specific incidence rates for 10-year age groups ranging from ages 10 to 79 years for each race (non-Hispanics Whites (referred to as: Whites), Hispanic Whites (referred to as: Hispanics), Blacks, and A/PIs). Rates are presented in terms of cases per 100,000 population. (**a**) Whites showed a continued bimodal age-incidence pattern, while (**b**) Blacks had a much less clear bimodal distribution. (**c**) A/PIs exhibited a bimodal pattern and have the lowest incidence rates of any race/ethnic group. (**d**) Age-specific incidence in Hispanics was distinctly not bimodal with a small increase at ages 20–29 followed by an exponential-like rise in incidence. Abbreviation: *A/PI* Asian/Pacific Islander (Reprinted with permission Evens et al. [17])

Jarrett et al. have drawn attention to the issue of Epstein–Barr virus (EBV) positivity in the Hodgkin and Reed–Sternberg (H-RS) cells at diagnosis [24]. EBV-associated disease was more often present in patients aged 50 years and older as compared to patients aged 15–34 years and 35–49 years. Importantly, EBV positivity was recognized as a poor prognostic factor for clinical outcome in patients over 50 years, but not in the other groups [24]. Stark et al. also recognized EBV-associated disease as a negative prognostic factor [10]. The EBV-positive status was also associated with advanced-stage disease. It is speculated that such patients have failure of immune response to EBV and present with an enhanced state of immunodeficiency and hence higher risk disease [10].

15.4 Clinical Presentation

There have been several population-based publications on the clinical presentation of older HL patients [7, 8]. In a study by Erdkamp et al., there were significantly more patients in stage II among younger patients ($p<0.001$) [8]. Enblad et al. reported in their study more patients with advanced stages among elderly patients ($p=0.02$) [7]. A comprehensive analysis of elderly HL patients treated within clinical trials of the GHSG among 372 patients aged ≥60 years also found a significant difference in clinical stage with more pronounced incidence of advanced stage in the elderly population [5].

With regard to clinical symptoms, Erdkamp et al. report a trend for a higher number of patients

over 50 years presenting with B symptoms [8]. The GHSG analysis showed statistically significant more female patients and more patients presenting with B symptoms, elevated erythrocyte sedimentation rate, and worse ECOG performance status. Furthermore, there were less patients with large mediastinal mass and bulky disease as compared with 3,879 patients aged <60 years [5]. A recent subgroup analysis from the E2496 phase III study that randomized advanced-stage HL patients to ABVD versus Stanford V showed that older patients significantly more often had poor performance status, and B symptoms at diagnosis, but less often presented with bulky mediastinal disease compared with younger patients [25].

To summarize, compared with younger patients, older HL patients present more often with B symptoms, in a poorer performance status, but with less bulky (mediastinal) disease. The stage distribution is also different with older patients presenting more often in advanced-stage disease.

15.5 Age Issues Affecting Treatment and Outcome

15.5.1 Comorbidity

Several analyses have documented the prognostic importance of comorbidities in older HL patients. Van Spronsen et al. analyzed 194 HL patients and 904 NHL patients registered between 1993 and 1996 with regard to their age-specific comorbidities and the potential impact on the outcome. The most frequent comorbidity in the HL patient cohort was cardiovascular disease (18 %), followed by chronic obstructive lung disease (13 %), diabetes mellitus (10 %), and hypertension (3 %). Taken together, 56 % of HL patients aged over 60 years had severe comorbidity. Patients with severe comorbidity received systemic chemotherapy less frequently and had a poorer overall survival (OS) especially within the first 4 months after first diagnosis of the HL. This indicates that comorbidities likely have an impact on survival [26]. Levis et al. reported similar findings noting comorbidities in 35 % of 105 older HL patients treated with VEPEMB. A multivariate analysis of this cohort identified comorbidity as an independent prognostic factor for poorer survival [27]. A recent retrospective analysis of older HL patients across several Chicago medical centers was completed [23]. Among 95 older patients with untreated HL, 61 % of patients had at least one severe comorbidity, 26 % were classified as "unfit," 17 % had presence of a geriatric syndrome, and 13 % had loss of activities of daily living (ADLs) at diagnosis [23]. The presence of loss of ADLs at diagnosis was a strong prognostic factor for survival in this data set (see Fig. 15.2).

Guinee et al. compared the outcome of patients aged 60–70 years and 40–59 years, respectively. They investigated the time period between 1977 and 1983. As compared with younger patients, older HL patients had a twofold increased risk of dying due to HL but even a fourfold increased risk of dying due to other reasons. Surprisingly, the response rates (RR) were not different between the two cohorts with an overall RR of 84 % for the older patients and 88 % for the younger patients [28]. The strongest prognostic factor in the aforementioned Chicago series was loss of ADLs at initial diagnosis. On multivariate regression, ages ≥70 years and loss of ADLs were the strongest prognostic factors that predicted survival; moreover, patients with both factors present at diagnosis had 3-year OS of 0 % [23].

To summarize available data, presence of comorbidities and compromised functional status are common, and they represent prognostic factors predicting outcome of older patients with HL. There remains a clear need for development of an age-specific prognostic tool for older HL patients that incorporates comorbidity, frailty, and functional and biological parameters.

15.5.2 Therapy-Associated Toxicity

Therapy-associated toxicities have a major impact on the treatment of older HL patients. The reduced tolerability of conventional chemotherapy results in more toxicities overall and more severe toxicities (including fatal outcomes), the inability to maintain the scheduled dose density, and a shorter survival for relapsing or progressing patients [6–8, 20, 29–31]. This was shown in the GHSG analysis, in which the reduced dose

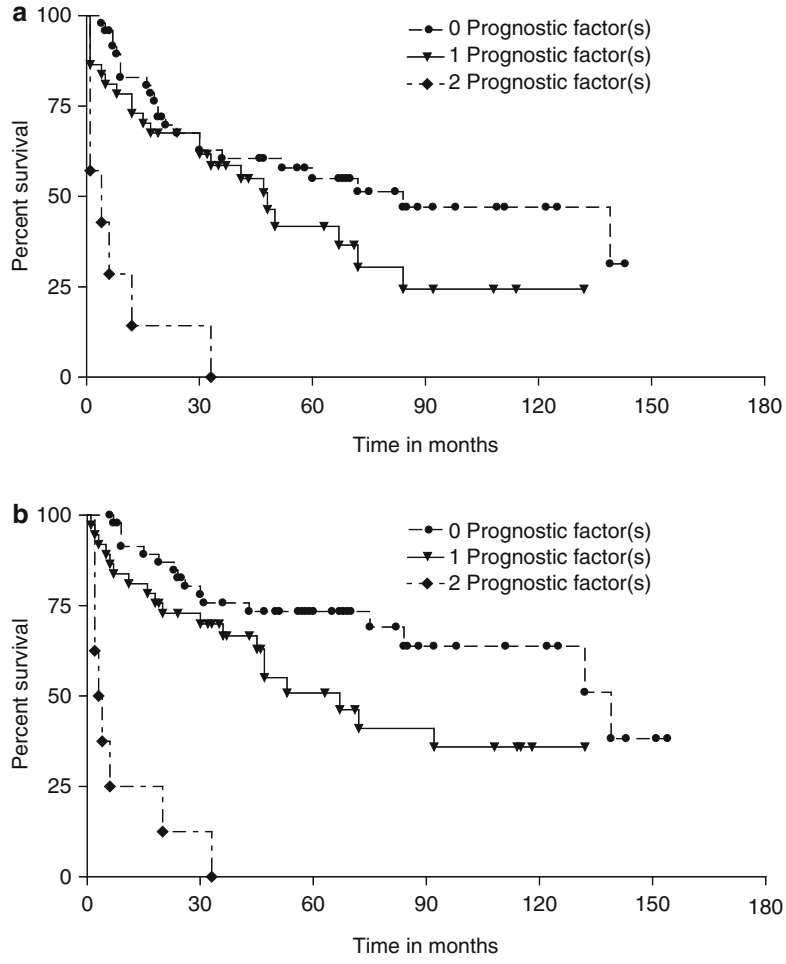

Fig. 15.2 Survival model for older Hodgkin lymphoma patients. (**a**) Progression-free survival and (**b**) overall survival for older HL patients based on the number of adverse prognostic factors present (age ≥70 years and loss of ADLs). The numbers of patients with 0, 1, or 2 factors at diagnosis were 48, 38, and 9, respectively; the increasing number of risk factors portended an increasingly poor survival. A Classification and Regression Trees (CART) survival model based on the number of adverse factors present (0, 1, or 2) was formed: 2-year PFS of 68, 68, and 13 %, respectively ($p<0.001$); 2-year OS of 83, 70, and 13 %, respectively ($p<0.001$); 5-year PFS of 55, 39, and 0 %, respectively ($p<0.0001$); and 5-year OS of 73, 51, and 0 %, respectively ($p<0.0001$) (This research was originally published in Blood. Evens et al. [23]. © the American Society of Hematology)

density and the increased mortality during therapy were identified as the major determinants for an inferior outcome of older patients [5]. Landgren et al. reported that older HL patients who received ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine)-based chemotherapy with a relative dose intensity (RDI) >65 % had significantly improved OS versus RDI ≤65 % ($p=0.001$) [20]. However, a significant fraction of older patients are unable to tolerate ABVD with RDI of >65 % [20].

As in younger patients, the GHSG and other studies identified the most prominent toxicities as leukopenia, infectious and cardiopulmonary events [5, 29, 32, 33]. Early termination of the scheduled therapy in older patients had a negative impact on survival [5, 20]. The incidence of severe therapy-associated toxicities varies in the literature for commonly used polychemotherapy regimens ranging between 8 and 20 % [6–8, 28, 32, 33]. Using COPP/ABVD, a toxic death rate of 19% has been reported [34]; this number was 18 % for

MOPP/ABVD. In the randomized study comparing baseline BEACOPP regimen with COPP/ABVD ($HD9_{elderly}$), the treatment-related mortality rates (TRM) among 75 newly diagnosed advanced-stage HL patients aged 66–75 years were 21 and 8 %, respectively [32]. Other modified chemotherapeutic regimens designed specifically for older HL patients had a low toxicity but also a low efficacy [34–36].

There had been a lack of data examining the tolerability with ABVD for older HL patients in the contemporary era; however, two recent papers addressed this question. Severe hematologic toxicities were significantly more frequent in older versus younger HL patients treated on the randomized E2496 study [25]. Additionally, the incidence of bleomycin lung toxicity (BLT) among older HL patients was 24 % with an associated BLT death rate of 18 %. The vast majority of BLT cases occurred with ABVD. The incidence of BLT in the Chicago series was 32 %, which was associated with a mortality rate of 25 % [23]. Furthermore, the incidence of BLT was 38 % versus 0 % among patients who received granulocyte-colony stimulating factor (G-CSF) versus those who did not, respectively ($P<0.0001$). Retrospective analyses and preclinical data have suggested that the risk of BLT is increased when G-CSF is given concurrently with bleomycin [37–40]. Overall, the TRM rates for older versus younger HL patients treated on E2496 were 9 % versus 0.3 % (<0.001). Similar results were reported from a recent GHSG analysis on older early stage HL patients receiving four cycles of ABVD [41]. WHO grade 3 and 4 toxicities were observed in 68 % of the 117 older patients compared to 50 % in the reference population of 1,182 younger patients [41].

15.6 Therapy

15.6.1 Early Stages

In Europe, early stage is comprised of "early favorable" and "early unfavorable" subsets. In young patients, the standard of care is a combined modality treatment using two to six cycles of ABVD plus involved-field radiotherapy. Recent studies in younger early stage HL have evaluated the use of PET-guided response-adapted radiotherapy reporting conflicting results. Moreover, these trials included only few, if any, older patients (Table 15.1). In the GHSG HD8 trial, patients in early unfavorable stage were randomized to four courses of chemotherapy (COPP/ABVD – cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, dacarbazine) and either involved-field or extended-field radiotherapy [42]. The analysis of the older subgroup of patients in this study demonstrated lower 5-year freedom from treatment failure (FFTF) and OS in older patients (FFTF 64 vs. 87 %, $p<0.001$ and OS 70 vs. 94 %, $p<0.001$). Furthermore, older patients had a poorer outcome when treated with extended-field radiation compared with involved-field radiotherapy, lower 5-year FFTF (58 vs. 70 %; $p=0.034$), and lower OS (59 vs. 81 %; $p=0.008$), suggesting that EF radiotherapy should be avoided in older patients.

A recent analysis focusing on older patients treated within the GHSG HD10 and HD11 trials included 117 older early stage HL patients treated with two to four cycles of ABVD followed by IFRT [41]. Mean delay of treatment was twice as high in the older patients (2.2 vs. 1.2 weeks) and WHO grade 3 and 4 toxicities were also more frequent in this group (68 vs. 50 %) as compared to younger patients. This resulted in higher treatment-related mortality in older patients. Despite lower dose intensity and higher toxicity, complete response was achieved in 89 % of older patients; however, 3 % had progressive disease, 11 % relapsed, and 28 % died within the median observation time of 92 months resulting in a low 5-year progression-free survival of 75 % (see Fig. 15.3). Regarding older early favorable HL patients who received two cycles of ABVD only followed by involved-field radiotherapy, feasibility was higher, and toxicity during chemotherapy was considerably lower with only 38 % of patients experiencing WHO grade 2–4 toxicities. Overall, 96 % of the patients receiving two cycles of ABVD achieved CR as final treatment outcome. However, rates of progression or relapse (10 %) and death (23 %)

Table 15.1 Selected studies for elderly HL patients in advanced stages

Author, year	*N*	Therapy	Outcome	Study comments
Kim, 2003 [30]	52	RT alone ($n=37$), chemotherapy alone ($n=9$), combined modality ($n=6$)	10-year FFTF 71 %, 5-year OS 55 %, 10-year OS 31 %	No significant difference noted among different treatment modalities; 8.6 % second malignancy rate
Levis, 2004 [27]	48	3 cycles VEPEMB followed by IFRT	CR 98 %, 5-year RFS 95 %, DSS 97 %, FFS 79 %, and OS 94 %	Dose intensity 85 %; 5 % infection rate, transfusion needed in 2 %, hospitalization rate 8 %
Landgren, 2006 [43]	68	RT alone – median dose 40 Gy (IF $n=28$; MF $n=20$; TNI $n=10$; others $n=10$)	CR 82 %; RR 42 %	Lower CR rate vs. younger pts 82 % vs. 90 % ($p=0.05$); 16 % developed second malignancy
Klimm, 2007 [42]	89	4 cycles COPP/ABVD followed by EFRT or IFRT (both 40 Gy)	5-year FFTF, EFRT 58 % vs. IFRT 70 %; 5-year OS, EFRT 59 % vs. IFRT 81 %	Toxicity increased with EF vs. IF (WHO grades 3 and 4: 27 % vs. 9 %)
Böll, 2013 [41]	117	4 cycles ABVD followed by 20–30 Gy IFRT	5-year OS and PFS for older patients 81 and 75 %, respectively	Mean treatment delay 2.2 weeks in older vs. 1.2 weeks in younger patients; WHO grades 3 and 4 toxicity 68 % older patients; TRM 6 %

RT radiation, *FFTF* freedom from treatment failure, *OS* overall survival, *CR* complete remission, *RFS* relapse-free survival, *DSS* disease-specific survival, *FFS* freedom from treatment failure, *RR* relapse rate, *TNI* total nodal irradiation, *MF* mantle field, *RT* radiation therapy, *IFRT* involved-field radiation therapy, *EFRT* extended-field radiation therapy, *TRM* treatment-related mortality

were comparable in both treatment groups, and the 5-year estimates for overall survival (84 %) and progression-free survival (79 %) did not differ [41].

Levis et al. reported results of the VEPEMB schedule specifically designed for elderly patients treating 48 patients in stages IA–IIA matching the early favorable risk group [27]. The therapeutic approach was to administer three courses of VEPEMB chemotherapy plus involved-field radiotherapy. The CR rate was 98 % and 5-year FFS and OS were 79 and 94 %, respectively. However, this FFS would be unacceptably low for early favorable HL in younger patients. A retrospective study by a Norwegian group investigated CHOP (cyclophosphamide, vincristine, prednisone, and Adriamycin) in elderly HL patients [44]. Among 29 patients, 11 were stages I–IIA and 18 were stages IIB–IV. Patients in early stages received two or four cycles of CHOP (depending on presence of risk factors) followed by involved-field radiotherapy. The CR rate for early stages was 91 %; 3-year OS and PFS were 91 and 82 %, respectively. Obviously, the number of patients is too small to allow a fair judgment of this regimen in the treatment of HL.

Based on currently available data, the GHSG recommends two cycles of ABVD followed by 20 Gy involved-field radiotherapy for both young and elderly HL patients. Accordingly, four cycles of ABVD plus 30 Gy IF radiotherapy is recommended for early unfavorable stage HL. VEPEMB or CHOP may be considered as secondary therapeutic options. Due to potential severe toxicity, the use of bleomycin should be considered cautiously in older patients. In the case of preexisting pulmonary comorbidity, omitting bleomycin in this group of patients a priori is justifiable (i.e., AVD). If bleomycin is used, patients should be followed closely clinically with low threshold to discontinue it with the development of any clinical symptoms or sequelae suggestive of bleomycin lung toxicity.

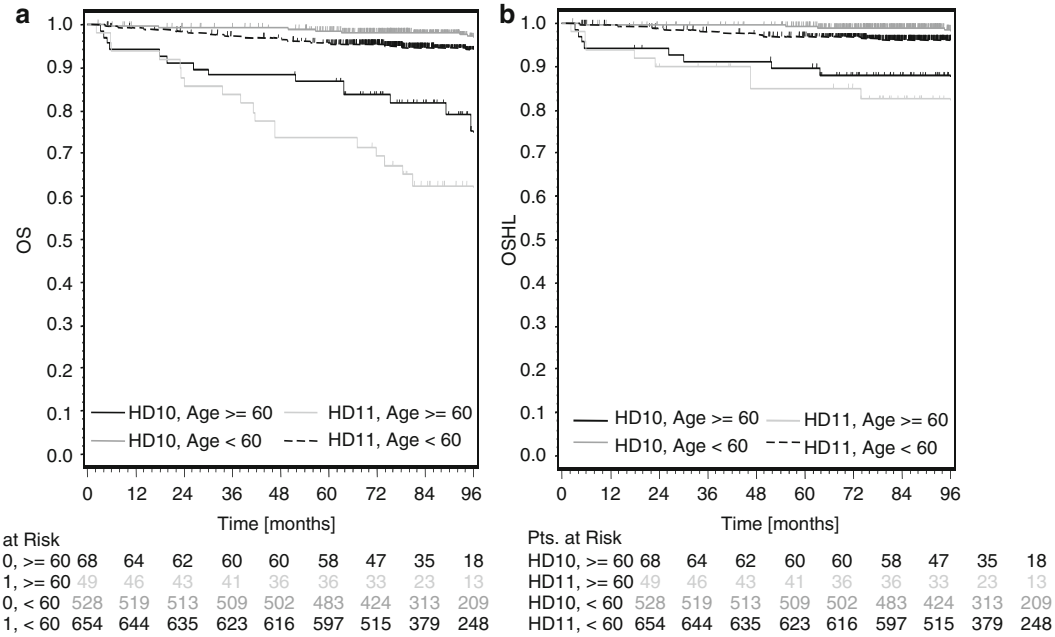

Fig. 15.3 Survival in older HL patients treated with ABVD. (**a**) Overall survival and (**b**) progression-free survival in 117 older (>60) and younger (<60) early stage HL patients treated with four cycles of ABVD within the German Hodgkin Study Group (GHSG) HD10 and HD11 trials. HD10, early favorable stage patients; HD11, early unfavorable stage patients. The OS and PFS estimates for all older patients at 5 years were 81 % (95 % CI, 73–87 %) and 75 % (95 % CI, 66–82 %), respectively. OS and PFS of younger patients were significantly superior compared with those of older patients (all log-rank $P<0.001$) (Modified from original figure; reprinted with permission (Ref.: Böll et al. [41]))

15.6.2 Advanced Stages

15.6.2.1 Earlier Data

Although a superior outcome of younger HL patients can be reached by intensification of chemotherapy, ABVD can be regarded as possible for advanced-stage HL [45, 46]. However, when ABVD is given with curative intent to patients over 60–65 years, chemotherapy-related toxicities may be prohibitive [5, 18, 29, 37]. This is often due to bleomycin. The 5-year OS for older patients treated on the ABVD-based randomized CALGB 8251 trial was 31 % compared with 79 % for patients aged less than 40 years ($p<0.0001$) in the late 1980s. Levis et al. analyzed the outcome of 65 patients aged ≥65 years receiving a registry-recommended protocol of ABVD, MOPP (mechlorethamine, vincristine, procarbazine, prednisone), or ABVD/MOPP 30. Eight-year event-free survival (EFS) and OS in these patients were 41 and 46 %, respectively, both significantly inferior compared with patients aged <65 years [29]. Toxicity was prohibitive in this study with a TRM rate of 23 %.

Anthracycline is likely an important component of therapy for older HL patients. The Nebraska Group compared ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisone) with the hybrid ChlVPP/ABV (added Adriamycin, bleomycin, and vincristine) in a non-randomized study including 262 previously untreated HL patients (see Table 15.2) [47]. Among patients aged ≥60 years, the 5-year EFS was 31 % and 5-year OS at 5 years was 39 %, compared with 75 % EFS and 87 % OS for younger patients. In addition, older patients treated with ChlVPP had a poorer outcome as those treated with ChlVPP/ABV. The 5-year EFS were 24 % versus 52 %, respectively ($p=0.011$), and 5-year OS 30 % versus 67 %, respectively ($p=0.0086$).

The Vancouver Group attempted to intensify treatment for older patients [36]. They used a five-drug chemotherapy regimen called ODBEP (vincristine, doxorubicin, bleomycin, etoposide, and prednisone) from 1986 to 1995. This regimen

Table 15.2 Selected studies for elderly HL patients in advanced stages

Author, year	*N*	Therapy	Outcome	Therapy-associated death rate
Levis, 1994 [29]	26	ABVD, MOPP/ABVD	CR rate = 61 %	23 %
			8-year OS = 48 %	
			8-year RFS = 75 %	
			8-year EFS = 36 %	
Levis, 1996 [34]	25	CVP/CEB	CR rate = 73 %	4 %
			5-year OS = 65 %	
			5-year RFS = 47 %	
Weekes, 2002 [6]	31	ChlVPP	5-year OS = 30 %	13 %
			5-year EFS = 24 %	
	25	ChlVPP/ABV	5-year OS = 67 %	16 %
			5-year EFS = 52 %	
Macpherson, 2002 [36]	38	ODBEP	5-year OS = 42 %	0
			5-year DFS = 49 %	
Levis, 2004 [27]	57	VEPEMB	CR rate = 58 %	3 %
			5-year OS = 32 %	
			5-year RFS = 66 %	
Ballova, 2005 [32]	26	COPP/ABVD	CR rate = 77 %	8 %
			5-year OS = 50 %	
			5-year HD-FFTF = 55 %	
	42	BEACOPP baseline	CR rate = 76 %	21 %
			5-year OS = 50 %	
			5-year HD-FFTF = 74 %	
Kolstad, 2007 [44]	18	CHOP	CR rate = 72 %	7 %
			3-year OS = 67 %	
			3-year PFS = 72 %	
Halbsguth, 2010 [48]	60	BACOPP	CR rate = 85 %	12 %
			2-year OS = 76 %	
			2-year PFS = 71 %	
Böll, 2011 [49]	59	PVAG	CR rate = 78 %	2 %
			3-year OS = 66 %	
			3-year PFS = 58 %	
Evens, 2012 [23]	61	ABVD most common (75 %)	5-year OS = 46 %	NR[a]
			5-year PFS = 36 %	
Proctor, 2012 [50]	72	VEPEMB	CR rate 61 %	4 %
			3-year OS = 62 %	
			3-year PFS = 52 %	
Evens, 2013 [25]	45	ABVD and Stanford V	CR rate = 64 %	9 %
			5-year OS = 58 %	
			5-year PFS = 48 %	

Prospective clinical studies denoted in italics

OS overall survival, *RFS* relapse-free survival, *EFS* event-free survival, *DFS* disease-free survival, *FFTF* freedom from treatment failure, *PFS* progression-free survival, *ODBEP* vincristine, doxorubicin, bleomycin, etoposide, and prednisolone, *VEPEMB* vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone, and bleomycin, *ChlVPP* chlorambucil, vinblastine, procarbazine, and prednisone, *COPP* cyclophosphamide, vincristine, procarbazine, and prednisone, *ABVD* doxorubicin, bleomycin, vinblastine, and dacarbazine, *BEACOPP* bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone, *BACOPP* bleomycin, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone, *PVAG* prednisone, vinblastine, doxorubicin, and gemcitabine, *NR* not reported

[a]Incidence of bleomycin lung toxicity 32 %, which had an associated mortality rate of 25 %

tested the increase of dose intensity by delivery of treatment without delays. In addition, the number of non-cross-resistant cytostatic drugs that were selected for minimal cumulative myelotoxicity was increased (see Table 15.1). Comparison was made with a similar group of patients treated from 1981 to 1986 with a MOPP/ABV-variant chemotherapy. The 5-year DFS and OS were higher in patients treated with ODBEP as compared to patients treated with MOPP/ABV; however, the differences were not significant (DFS, 49 vs. 37 %, and OS, 42 vs. 32 %, respectively); generally, outcome in this trial was poor.

The Italian group followed another strategy by developing less-intensive polychemotherapy regimens specifically for older patients (see Table 15.1). They started in the early 1990s with the CVP/CEB regimen (chlorambucil, vinblastine, procarbazine, prednisone, cyclophosphamide, etoposide, bleomycin) and subsequently used VEPEMB [51]. CVP/CEB, a low-toxicity regimen, was administered to 25 patients and well tolerated. The CR rate at the end of treatment was 73 %. However, the 5-year EFS and OS were disappointing with 32 and 55 %, respectively.

The subsequent study investigated the VEPEMB regimen (see Table 15.1). Among 105 patients, 57 were in advanced stages of disease receiving six cycles of this regimen with additional radiotherapy to bulky disease or residual mass. VEPEMB was well tolerated and could be administrated to most patients, and only one patient died during treatment. After the end of treatment, 58 % of patients were in CR; the 5-year FFS was 34 % and OS 32 % [27]. In an interim analysis of a prospectively randomized phase III study comparing this regimen with ABVD, the final CR rate was slightly better with ABVD than in the VEPEMB arm (86 vs. 77 %), although this difference was not statistically significant. The 3-year relapse-free survival rates were 57 and 50 % (p = ns) for the ABVD and VEPEMB arms, respectively. The 3-year OS and the EFS rates for ABVD and VEPEMB were 79 vs. 60 % (p = ns) and 52 vs. 24 % (p=0.08), respectively [51]. Though this is not the final analysis, the data do not support the routine use of VEPEMB outside clinical studies, since superiority to ABVD cannot be seen so far and only a minority of patients with advanced-stage disease might be cured using this schedule.

15.6.2.2 Contemporary Data

The GHSG more recently reported results of two phase II studies for untreated, older HL patients, using BACOPP (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and PVAG (prednisone, vinblastine, doxorubicin, gemcitabine) [48, 49]. The CR rate with BACOPP was 85 % with associated 3-year PFS and OS rates of 60 and 71 %, respectively. However, this regimen was associated with significant toxicity with 87 % of patients experiencing grade 3–4 adverse events, 30 % early termination, and 12 %TRM [48]. PVAG was developed in part to eliminate the need for bleomycin or dacarbazine by substituting prednisone and gemcitabine [49]. The CR rate of this new regimen in elderly HL patients was 78 %, and the 3-year PFS and OS rates were 58 and 66 %, respectively. Therapy was overal well tolerated and the TRM rate was 2 %.

Kolstad et al. used CHOP (cyclophosphamide, Adriamycin, oncovin, prednisone) for older HL patients [44]. They treated 29 patients with CHOP using two to four cycles and involved-field radiotherapy (IFRT) for early stage and six to eight cycles +/− IFRT for advanced-stage disease. The CR rate was 93 % and the 3-year PFS and OS rates for advanced-stage patients were 67 and 72 %, respectively. Proctor et al. reported results from the largest prospective study conducted to date for older HL patients – known as the Study of Hodgkin lymphoma In the Elderly/Lymphoma Database (SHIELD) project (http://www.shieldstudy.co.uk) [50]. They treated 103 older HL patients with VEPEMB, of which 72 patients had advanced-stage disease. Comorbidities and frailty were objectively assessed; only non-frail patients were eligible for this prospective study. For advanced-stage patients, the CR rate was 61 % and 3-year PFS and OS rates were 58 and 66 %, respectively. Therapy was generally well tolerated with a TRM rate of 3 %. In prognostic factor analyses, achievement of CR strongly predicted survival. Factors associated with CR were comorbidity score (by modified ACE 27) and activities of daily living (ADLs). In the same report, there was an additional observational group of older HL patients (frail and non-frail) treated according to physician discretion. Among 13 frail HL

patients in this sub-study, all died (12 from HL) with median OS of 7 months [50].

Findings on elderly HL patients from a subgroup analysis of the North American Intergroup Trial E2496 were reported [25]. E2496 was a phase III study that randomized advanced-stage HL patients to ABVD or Stanford V; 45 patients were ≥60 years. There were no survival differences between ABVD and Stanford V for older HL patients. Toxicities were rather similar to other chemotherapy regimens used for older patients; however, the incidence of BLT was 24 % with 91 % of cases occurring with ABVD. Furthermore, there was an associated BLT death rate of 18 %. Altogether, the TRM was significantly higher for older versus younger HL patients (i.e., 9 % vs. 0.3 %, $p<0.001$). Moreover, outcomes were markedly inferior for older patients with 5-year FFS rates of 48 % vs. 74 %, respectively ($p=0.002$), and 5-year OS rates of 58 and 90 %, respectively, when compared to younger patients treated in this trial ($p<0.0001$) (see Fig. 15.4) [25].

Interestingly, TTP was not significantly different between age groups in E2496 (i.e., 5-year TTP: 68 % vs. 78 %, respectively). The latter finding was partly due to the higher cumulative incidence of death without progression in older HL patients (i.e., 22 % vs. 9 %, respectively, $p<0.0001$, at 5 years). A "competing risk" survival analysis was performed, which is important since Kaplan–Meier analyses may result in incorrect and biased estimates of risk of progression. Bias occurs because the Kaplan–Meier method assumes that all events are independent and all events other than the event of interest are censored. Progression and death without progression are not independent since patients who experience death before progression cannot be at further risk of progression of disease. The incidence of progression for older HL patients in E2496 with competing risks was 19 and 30 % at 2 and 5 years, respectively, versus 19 and 23 %, respectively, for younger patients ($p=0.30$). The incidence of death without progression for older patients was 13 and 22 % at 2 and 5 years, respectively, versus 2 and 9 %, respectively, for younger patients ($p=<0.0001$) (see Fig. 15.5). These data support the finding that a significant component of the age-dependent survival difference in HL is due to non-progression events.

In conclusion, the use of anthracycline-based chemotherapy in the treatment of elderly patients with advanced HL appears to be important. Though no randomized studies for this special cohort of elderly patients are available, six to eight cycles of ABVD followed by radiotherapy to residual disease can still be regarded as the

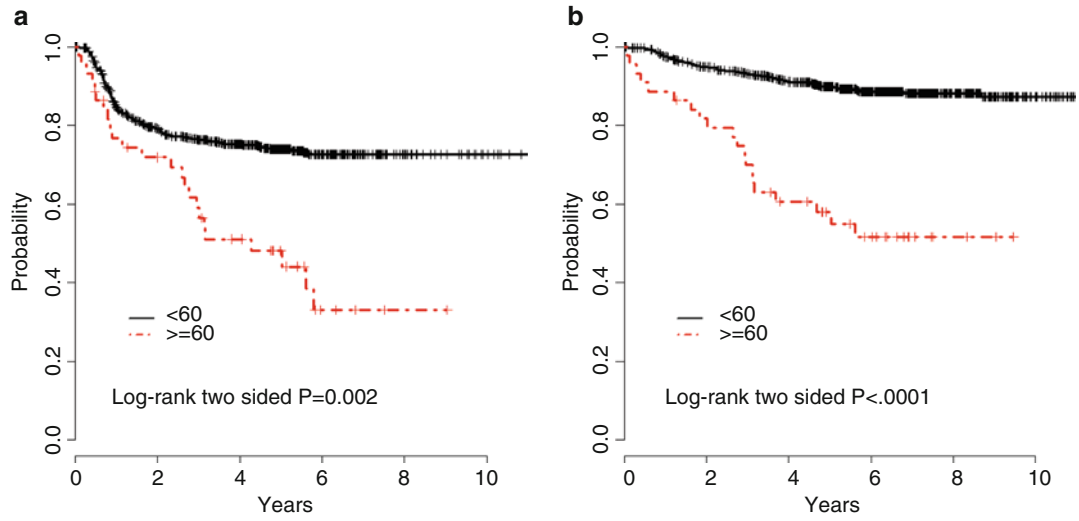

Fig. 15.4 Outcomes comparing older HL with younger patients. The (**a**) 3- and 5-year FFS for patients aged ≥60 years were 56 and 48 %, respectively, compared with 76 and 74 %, respectively, for patients aged <60 years ($p=0.002$), while (**b**) the 3- and 5-year OS for patients aged ≥60 years were 70 and 58 %, respectively, compared with 93 and 90 %, respectively, for patients aged <60 years ($p<0.0001$) (Modified from original figure; reprinted with permission Radford et al. [3])

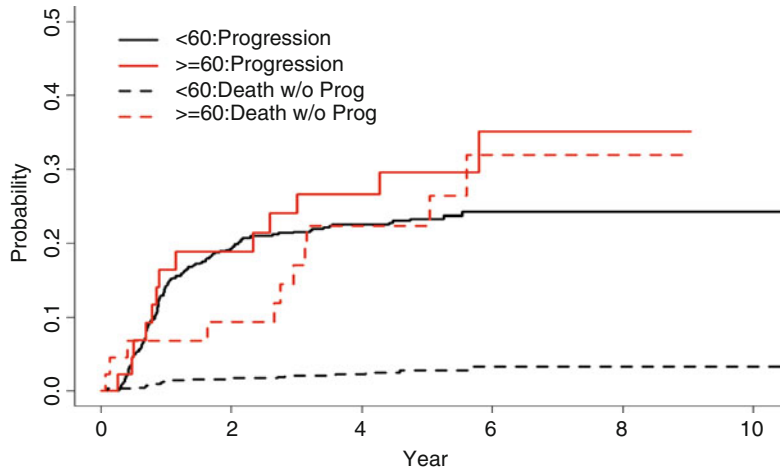

Fig. 15.5 Competing risk survival analysis for older versus younger Hodgkin lymphoma patients. The rates of progression were determined with competing risk analysis since death without progression is a competing risk for disease progression. The incidence rates of progression including competing risks for patients aged ≥60 years at 2 and 5 years were 19 and 30 %, respectively, compared with 19 and 23 %, respectively, for patients aged <60 years ($p = 0.30$); however, the incidence rates of death without progression for patients aged ≥60 years at 2 and 5 years were 13 and 22 %, respectively, compared with 2 and 9 %, respectively, for patients aged <60 years ($p \leq 0.0001$) (Modified from original figure; reprinted with permission Radford et al. [3])

standard of care [9, 11]. As noted before, impact of bleomycin in the ABVD regimen has been demonstrated in the HD13 trial. In elderly patients, omission of bleomycin from ABVD can be considered [52]. If bleomycin is utilized in older patients, there should be caution with the concurrent use of G-CSF. Dose-intensification approaches, including BEACOPP variants, have not been successful, mainly due to an unacceptable increase in toxicity including high rates of TRM. The major problem in older HL patients is finding the right balance between intensity of chemotherapy and acceptable tolerability.

This gap may be potentially addressed by the incorporation of novel therapeutic agents into future treatment paradigms. There are ongoing prospective clinical studies that are incorporating the antibody–drug conjugate brentuximab vedotin (e.g., NCT01476410 and NCT01716806) and lenalidomide (e.g., NCT01056679) in lieu of or in combination (or sequence) with standard chemotherapy for older patients with newly diagnosed HL. Data from these studies are eagerly awaited. Additionally, response-adapted therapeutic approaches should also be examined in older HL patients. Early PET response (after two cycles of ABVD) has been shown to be a strong prognostic factor in newly diagnosed HL; however, most published data are in younger patients [53, 54].

15.6.3 Relapsed Patients

Prospective randomized studies have not specifically evaluated the treatment of relapsed older HL patients. Therefore, treatment recommendations in this setting are largely based on personal experience and retrospective single-center analyses. Treatment options for relapsed or refractory HL in older patients include intensified treatment, polychemotherapy, radiotherapy in selected patients, single-agent (palliative) chemotherapy, and best supportive care.

With the development of novel drugs with impressive single-agent activity such as brentuximab vedotin, potentially less toxic alternative treatments are available for older patients in whom conventional treatment is not an option due to comorbidity [55–57].

The use of different treatment strategies is guided by patient preference, comorbidity/functional status, and the duration of response to first-line therapy. In patients with long-lasting remission after first-line treatment, polychemotherapy regimens such as PVAG, ABVD, CHOP,

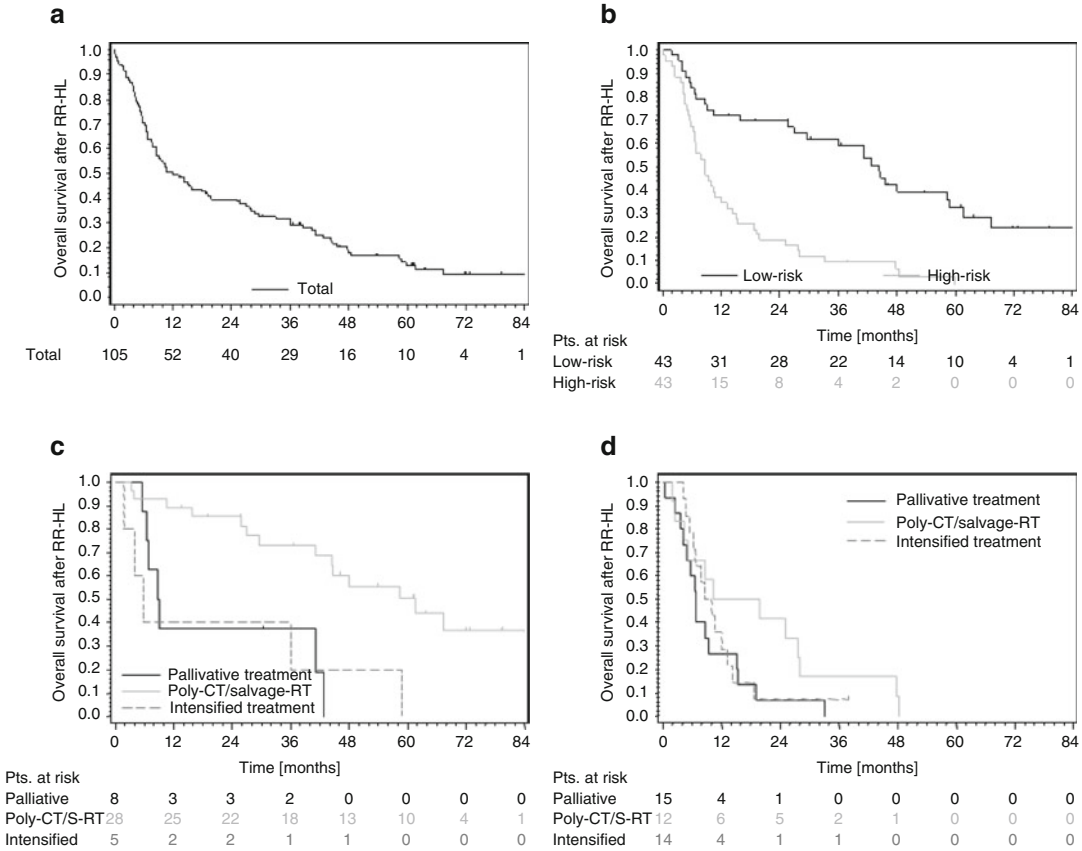

Fig. 15.6 Overall survival of older HL patients after relapse/progression. Kaplan–Meier plots of overall survival (OS) in (**a**) all evaluable patients (median OS, 12 months; 95 % CI, 8–19 months; 3-year OS, 31 %; 95 % CI, 22–40 %), (**b**) all evaluable patients according to risk group (high-risk patients, 3-year OS, 11 %; 95 % CI, 1–22 %; low-risk patients, 3-year OS, 57 %; 95 % CI, 40–73 %), (**c**) low-risk patients according to treatment (intensified treatment, 3-year OS, 20 %; 95 % CI, 0–55 %; polychemotherapy [poly-CT]/salvage radiotherapy [RT], 3-year OS, 71 %; 95 % CI, 53–89 %, could not be estimated for patients receiving palliative treatment), and (**d**) high-risk patients according to treatment. RR-HL, relapsed/refractory Hodgkin lymphoma (Modified from original figure; reprinted with permission (Ref.: Böll et al. [59]))

or the oral PECC regimen (prednisolone, etoposide, chlorambucil, and CCNU) are valid options [58]. Drugs with known single-agent activity in HL include alkylating agents (e.g., ifosfamide, trofosfamide, and procarbazine), gemcitabine, vinca alkaloids, and platinum derivates.

Smaller retrospective single-center studies have suggested that high-dose chemotherapy followed by autologous stem-cell support might be an effective treatment for selected patients with relapsed HL [59]. A recent, larger GHSG analysis examined 105 patients with a median age of 66 years [59]. Different second-line treatment strategies were used including intensified salvage regimens in 22 %, conventional polychemotherapy and/or salvage radiotherapy with curative intent in 42 %, and palliative approaches such as single-agent chemotherapy and best supportive care in 31 % of the older HL patients. As patient characteristics were variable within the different treatment groups, a prognostic score applied using the risk factors (RFs) early relapse, clinical stage III/IV, and anemia identified patients with favorable and unfavorable prognosis. Median OS for the entire cohort of relapsing older HL patients was 12 months and OS at 3 years was 31 % (95 % CI, 22–40 %). Survival was significantly different within different risk groups (i.e., ≤ one RF, 3-year OS, 59 %; 95 % CI, 44–74 %; ≥ two RFs, 3-year OS, 9 %; 95 % CI, 1–18 %) (see Fig. 15.6). In low-risk patients, the impact of therapy on survival was significant in favor of the conventional polychemotherapy/

salvage radiotherapy approach. In high-risk patients, OS was low overall and did not differ significantly between treatment strategies [59]. These results might be useful in guiding treatment decisions, while there remains a significant need to evaluate novel compounds in older patients with relapsed/refractory HL.

15.7 Conclusions and Perspectives

Although outcomes have improved over time, survival rates for older HL patients remain disproportionately inferior compared with younger patients. Altogether, HL in the elderly remains a disease where standard treatment recommendations are difficult. Generally, treatment of older HL patients for all disease stages should be given with curative intent with treatment paradigms similar to younger patients. This includes abbreviated chemotherapy (two to four cycles) and involved-field radiation for early stage disease and chemotherapy for six cycles for advanced stages. Intensive regimens such as BEACOPP are too toxic for older patients, while less-intensive regimens such as CVP/CEB and ChlVPP are likely insufficient. Outside of a clinical trial, ABVD likely remains a standard regimen for older HL patients; however, caution should be given to potential severe treatment-related toxicities, especially bleomycin-related lung toxicity. Balancing the risk/benefit ratio, a priori omission of bleomycin may be considered in older patients. Finally, the impact of patient comorbidities and functional status needs to be examined in prospective studies, and the integration of novel therapeutic agents into treatment paradigms for older HL patients is needed.

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Nodular Lymphocyte-Predominant Hodgkin Lymphoma

16

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Contents

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16.1 Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare lymphoma entity representing about 5 % of all HL cases [1]. Pathobiology and clinical course substantially differ from classical HL (cHL). This chapter describes the pathologic and clinical characteristics, differential diagnoses, risk factors, and treatment options of NLPHL.

16.2 Pathology of NLPHL

The pathologic key feature of NLPHL is a malignant cell population that was originally termed lymphocytic and histiocytic (L&H). These cells were reclassified in the WHO 2008 classification as lymphocyte predominant (LP) cells [2]. LP cells carry one large single folded or polylobated vesiculated nucleus. In contrast to Hodgkin and Reed-Sternberg (H-RS) cells seen in cHL, the number of nucleoli in LP cells is increased leading to the more descriptive term "popcorn cells" [3]. In rare cases, however, LP cells can resemble classical or laguna-type H-RS cells.

While H-RS cells derive from germinal center (GC) B cells that normally would have undergone apoptosis, LP cells originate from GC B cells that were positively selected. Single-cell polymerase chain reaction assays demonstrated that LP cells typically contain rearranged immunoglobulin (Ig) genes and variably express Ig mRNA. The Ig

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_16, © Springer International Publishing 2015

heavy chain can show evidence of somatic hypermutation in line with the GC origin of LP cells. Different chromosomal abnormalities have been described in up to two-thirds of NLPHL cases. Although some genetic lesions were identified, little is known about the pathologic properties of LP cells. Constitutive activity of NF-κB, the JAK/STAT pathway, and the BCL-6 transcription factors seem to be involved. However, mutations in the genes coding for the NF-κB regulating factors IκBα and A20 are uncommon [4–7].

LP cells are embedded in a nodular or follicular background that is dominated by small B lymphocytes. Rarely, a more diffuse growth pattern can also be observed. Immunophenotyping is critical to establish the correct diagnosis of NLPHL. LP cells present a B-cell phenotype expressing CD20, CD45, CD75, EMA, and frequently CD79a but are negative for CD15, CD30, and EBV (Table 16.1).

16.3 Differential Diagnosis

The discrimination between NLPHL and cHL or other related lymphoma entities can be difficult. A consortium of European and American expert pathologists that evaluated 426 cases initially classified as NLPHL highlighted this challenge. Using classical morphology and immunohistochemistry, 51 % of cases were confirmed as NLPHL, 27 % were reclassified as lymphocyte-rich cHL, and 5 % as other cHL subtypes. The remaining 17 % of cases were identified as non-Hodgkin lymphoma (NHL) (3 %) and reactive lesions (3 %) or were not assessable (11 %) [1]. These findings underscore the need for immunohistochemistry and expert pathology review for the diagnosis of NLPHL.

Table 16.1 The immunophenotype of cHL and NLPHL

	cHL	NLPHL
CD20	–/+	+
CD30	+	–
CD15	+	–
CD45	–	+
CD79a	–/+	+
OCT-2	–	+
BCL-2	+	–
BOB-1	–/+	+
EMA	–	–/+
EBER	–/+	–

16.4 Transformation to Non-Hodgkin Lymphoma

In contrast to cHL, NLPHL tends to transform into aggressive NHL. At transformation, diffuse large B-cell lymphoma (DLBCL) is most often diagnosed with T-cell-rich B-cell lymphoma (TCRBCL) representing a frequently observed histologic subtype. Recently reported transformation rates exceeded those from previous studies.

A registry-based retrospective analysis comprising 164 patients initially diagnosed with NLPHL came from France. At a median follow-up of 9.5 years for survivors, 66 patients had lymphoma recurrence of which 19 presented with transformation into aggressive NHL at relapse. The median time from initial NLPHL diagnosis to histologic transformation was 4.7 years; the cumulative 10-year transformation rate was 12 % [8].

A retrospective study from Canada using the British Columbia Cancer Agency (BCCA) database included a total of 95 patients initially diagnosed with NLPHL. Transformation into aggressive NHL occurred in 13 of them; the median time to transformation was 8.1 years. The actuarial risks for the diagnosis of transformed lymphoma after initial diagnosis of NLPHL were 5, 7, 15, 31, and 36 % after 5, 10, 15, 20, and 25 years, respectively. Interestingly, two clusters of transformation were seen. One cluster of transformation occurred less than 3 years after initial lymphoma diagnosis (5/13), while a second cluster occurred after 10–25 years (7/13). Transformation was more likely in patients with initial splenic involvement [9].

Given the significant risk for histologic transformation into aggressive NHL, obtaining a biopsy should be mandatory in NLPHL patients presenting with suspected relapse.

16.5 Clinical Characteristics

A comprehensive analysis performed by the German Hodgkin Study Group (GHSG) compared characteristics and clinical outcome of 394 NLPHL patients with 7.904 cHL patients. Median age was 37 years for NLPHL patients and 33 years for patients with cHL. The proportion of male patients was higher in NLPHL with 75 % compared to 56 % among cHL patients. Most NLPHL patients had early favorable stages (63 % in NLPHL patients vs. 22 % in cHL patients) at diagnosis, patients with early unfavorable and advanced stages were less frequently seen (16 and 21 % in NLPHL patients vs. 39 and 39 % in cHL patients). The presence of B symptoms (9 % in NLPHL vs. 40 % in cHL) and risk factors such as involvement of three or more nodal areas (28 % in NLPHL vs. 55 % in cHL), elevated erythrocyte sedimentation rate (ESR) (4 % in NLPHL vs. 45 % in cHL), large mediastinal mass (31 % in NLPHL vs. 55 % in cHL), extranodal involvement (6 % in NLPHL vs. 14 % in cHL), or elevated lactate dehydrogenase (LDH) (16 % in NLPHL vs. 32 % in cHL) was also less common in NLPHL when compared with cHL. Relapse rates in NLPHL and cHL at a median follow-up of 50 months were comparable (8.1 % vs. 8.0 %). However, the temporal distribution differed between both HL subtypes. Late relapses occurred significantly more often in NLPHL (7.4 % vs. 4.7 % in cHL), while early relapses were more common in cHL (0.8 % vs. 3.2 % in cHL) [10].

16.6 Treatment of Early Favorable NLPHL

Patients with early favorable NLPHL have an excellent prognosis with an overall survival (OS) close to 100 %. Treatment modalities including watchful waiting, radiotherapy (RT) alone, combined-modality approaches, and anti-CD20 antibody therapy with rituximab have been evaluated in this group of patients (Table 16.2).

Generally, treatment of early favorable NLPHL aims at inducing as little acute and late toxicity as possible. Particularly in children, treatment strategies focus on avoiding long-term side effects including secondary malignancies, infertility, growth retardation, hypothyroidism, and damage of the heart and lung. In an attempt to postpone treatment, watchful waiting after diagnostic lymphadenectomy was evaluated.

A French study included 27 pediatric patients of whom 13 underwent lymphadenectomy with no further treatment, 10 were treated with combined-modality approaches, 1 had involved-field RT (IF-RT), and 3 had chemotherapy only. At a median follow-up of 70 months, OS was 100 %, and the overall event-free survival (EFS) was 69 %. However, the EFS in the watch and wait group was only 42 % compared to 90 % in children who had additional treatment. Especially in patients with residual lymphoma after lymphadenectomy, EFS was poor when no further treatment was given [11].

The European Network Group on Pediatric Hodgkin Lymphoma (EuroNet-PHL) retrospectively analyzed the outcome of children with limited-stage NLPHL treated with resection only. A total of 58 children aged 4–17 years were included in the analysis; 51 achieved a complete remission (CR) after lymph node resection, while 7 had residual lymphoma. At a median follow-up of 43 months, progression-free survival (PFS) rates were 57 % at 50 months for the entire group and 67 % at 26 months for patients in CR after lymphadenectomy. All patients with incomplete resection eventually relapsed after a median of 17 months with no impact on OS (100 %) [12].

Given relapse rates exceeding 30 % even in patients without residual lymphoma after lymphadenectomy, watchful waiting should still be regarded experimental.

For most NLPHL patients with early favorable stages at diagnosis, RT is the mainstay of treatment. Recently, increasing amounts of long-term follow-up data on RT have become available from single institutions and cooperative groups.

A retrospective analysis from Australia included 208 stage I/II patients who had mostly

Table 16.2 Key publications reporting the outcome of NLPHL patients

	Response rate	Outcome	Reference
Newly diagnosed NLPHL			
Early stages			
RT alone			
Median dose 36 Gy (different RT fields)	N/R	15-year FFP: 84 % stage I, 73 % stage II	[13]
		15-year OS: 83 %	
Median dose 40 Gy (different RT fields)	N/R	5-year RFS: 95 % stage I	[31]
		5-year OS: 100 % stage I	
RT dose 32–38 Gy (different RT fields)	N/R	10-year PFS: 89 % stage I, 72 % stage II	[15]
		10-year OS: 96 % stage I, 100 % stage II	
RT dose 30 Gy or 40 Gy (EF-RT and IF-RT)	CR/CRu: 98 % EF-RT, 100 % IF-RT	2-year FFTF: 100 % EF-RT, 92 % IF-RT	[14]
		2-year OS: 100 %	
Combined-modality treatment			
2xABVD or ABVD like	N/R	10-year PFS: 91 %	[16]
		10-year OS: 93 %	
Anti-CD20 antibodies			
4 weekly doses rituximab	ORR: 100 %	Median follow-up: 43 m	[17]
	CR/CRu: 86 %	3-year PFS: 81 % stage IA	
		OS: 100 % stage IA	
4 weekly doses of rituximab ± rituximab maintenance every 6 months for 2 years (study did also include patients with advanced stages and relapsed patients)	ORR: 97 %	30-m FFP: 52 % limited treatment, 88 % extended treatment	[24]
	CR/Cru: 69 %	10-year OS: 97 % (among all patients)	
Advanced stages			
cHL protocols			
COPP/ABVD, COPP/ABV/IMEP	CR/CRu: 78 %	Median follow-up: 50 m	[10]
$BEACOPP_{baseline}$ or $BEACOPP_{escalated}$		FFTF: 77 %	
ABVD or EVA	N/R	Relapse rate: 75 %	[32]
MOPP or MOPP/ABVD	N/R	Relapse rate: 32 %	
B-cell NHL protocols			
R-CHOP	ORR: 100 %	Median follow-up: 42 m	[21]
	CR: 92 %	PFS: 100 %	
		OS: 100 %	
Relapsed NLPHL			
High-dose Ctx +ASCT			
High-dose protocols +ASCT	N/R	Median follow-up: 50 m	[25]
		5-year EFS: 61 %	
		5-year OS: 73 %	
Anti-CD20 antibodies			
Rituximab	ORR: 94 %	Median follow-up: 63 m	[22]
		Median PFS: 33 m	
		Median OS: not reached	

Adapted and modified from Fanale [30]

received full mantle-field RT. At a median follow-up of 15 years, the PFS was 82 %, and the OS was 83 % [13].

In their studies, the GHSG treated a total of 131 stage IA NLHPL patients with extended-field RT (EF-RT) (45 patients), IF-RT (45 patients), and combined-modality approaches (41 patients). Overall, 99 % of patients achieved a CR. After a median follow-up of 78 months for the EF-RT group, 40 months for the combined-modality group, and 17 months for IF-RT group, there were no significant differences in terms of FFTF and OS between the different treatment modalities. Increased toxicity was observed in patients treated with combined-modality approaches [14].

More lately, the long-term outcome of 113 patients with stage I/II NLPHL of whom 93 were treated with RT alone was reported. Similar to the GHSG analysis, PFS and OS rates of patients receiving EF-RT and IF-RT were comparable. Overall, treatment with RT alone resulted in excellent 10-year PFS and OS rates of 85 and 96 % for stage I patients and 72 and 100 % for stage II patients [15].

A retrospective analysis from Canada compared the outcome of 32 early-stage NLPHL patients treated with RT alone between 1966 and 1993 with the outcome of 56 patients treated with two cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) or ABVD-like chemotherapy followed by RT between 1993 and 2009. At 10 years, PFS and OS rates for patients treated with RT alone were 65 and 84 %, respectively, while patients who received combined-modality treatment had PFS and OS rates of 91 and 93 %, respectively [16]. However, these findings indicating a superior outcome for patients treated with combined-modality approaches have to be interpreted with caution as the patients considered were treated over four decades and other factors could have had significant impact on the outcome. For example, supportive care may have varied considerably between individual patients. In addition, the combined-modality treatment group had a much shorter follow-up (5.7 years) than the RT alone group (18.6 years). As relapses in NLPHL occur late, the inferior outcome of patients treated with RT alone might thus simply relate to the longer follow-up in comparison with the combined-modality group.

Given the consistent expression of CD20 on the malignant LP cells in NLPHL, the GHSG conducted a prospective phase II study evaluating the monoclonal anti-CD20 antibody rituximab in 28 stage IA patients. Patients received four weekly standard doses of the antibody (375 mg/m^2). All patients responded to treatment. However, after a median follow-up of 43 months, 25 % of patients had relapsed suggesting that tumor control with rituximab is inferior when compared with RT alone [17].

A study from Stanford led to similar results. Among 13 early-stage patients treated with single agent rituximab, all responded but a relevant proportion of remissions was not durable [18].

On the basis of the data currently available, IF-RT alone is recommended as standard of care for the treatment of stage IA NLPHL without risk factors by the GHSG, the European Organisation for Research and Treatment of Cancer (EORTC), and the European Society for Medical Oncology (ESMO) [19]. Similarly, the guideline panel of the National Cancer Center Network (NCCN) recommends small-field RT as treatment of choice for stage IA NLPHL [20]. For stage IB and stage II patients, European groups recommend combined-modality approaches as used in cHL [19]. In contrast, the NCCN guidelines recommend RT alone for stage IIA NLPHL, while chemotherapy or immunochemotherapy optionally followed by IF-RT should be given in stage IB/IIB disease [20].

16.7 Treatment of Early Unfavorable and Advanced Stages

The treatment of patients with early unfavorable and advanced NLPHL is often identical to cHL (Table 16.2). This is based on retrospective analyses. According to a GHSG analysis including 394 NLPHL and 7.904 cHL patients, 86 % of NLPHL patients with early unfavorable and 77 %

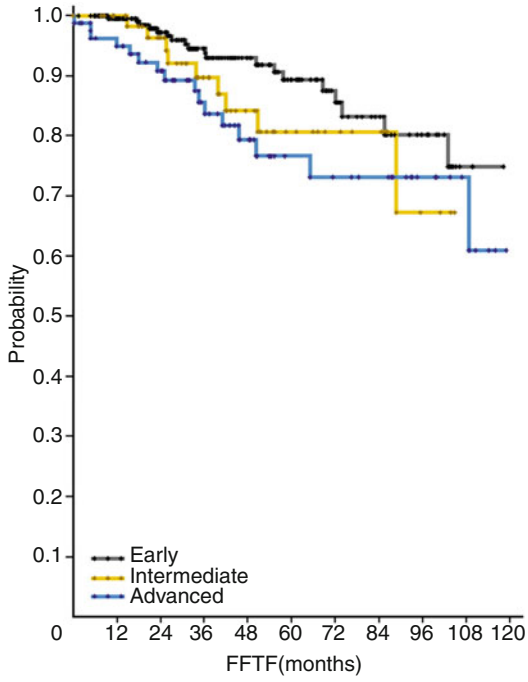

Fig. 16.1 Freedom from treatment failure among NLPHL patients according to stage at diagnosis (Adapted from Nogová et al. [10])

of NLPHL patients with advanced stages achieved a CR when treated with classical HL protocols such as ABVD or BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone). These rates are similar to those observed in cHL (83 % in early unfavorable and 75 % in advanced stages). Long-term tumor control with these regimens also seems to be comparable between NLPHL and cHL. At a median follow-up of 50 months, FFTF rates for patients with early unfavorable and advanced NLPHL were 87 and 77 % (Fig. 16.1), respectively, compared to 85 and 75 %, respectively, for cHL patients. Rates for OS were also similar in both entities [10].

Promising data on the use of the R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone) protocol in advanced NLPHL have recently been presented. A retrospective study from the MD Anderson Cancer Center including 12 patients with advanced disease who were treated with either R-CHOP alone or R-CHOP followed by IF-RT reported an overall response rate (ORR) of 100 %. At a median follow-up of 42 months, no relapse and no case of histologic transformation into aggressive NHL had occurred [21]. Although prospective data confirming these results are pending, the use of R-CHOP should be considered particularly in NLPHL patients with initial splenic involvement and thus at an increased risk of transformation into aggressive NHL.

16.8 Treatment of Relapsed NLPHL

A standard of care for relapsed NLPHL is largely undefined. Prospective data are mostly available on the use of the anti-CD20 antibody rituximab (Table 16.2).

In a phase II study conducted by the GHSG, 15 NLPHL patients with disease recurrence were treated with four weekly doses of rituximab at 375 mg/m^2. The ORR was 94 %. At a median follow-up of 63 months, the median time to progression was 33 months, and the median OS was not reached [22].

Another phase II study by the Stanford group included 22 patients (10 patients with relapsed and 12 patients with newly diagnosed NLPHL). Patients also received four weekly doses of rituximab at 375 mg/m^2. Response rate was 100 %. At a median follow-up of 13 months for the whole group, 9 of 22 patients had relapsed (three patients from the relapsed group and six patients from the newly diagnosed group) [23]. The study was subsequently modified and responding patients received rituximab maintenance (four weekly standard doses every 6 months for 2 years). At a median follow-up of 30 months for patients receiving extended rituximab treatment, the median freedom from progression (FFP) was not reached, and FFP at 30 months was 88 % [24].

Data on the use of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) in relapsed NLPHL are scarce. However, a retrospective analysis including 18 patients with histologically proven NLPHL recurrence who were treated with high-dose chemotherapy followed by ASCT was recently published.

According to this study, EFS and OS rates at 5 years were 61 and 73 %, respectively [25].

As treatment results with rituximab do not appear to be significantly worse than with more aggressive salvage strategies and the risk to develop acute and long-term toxicities is substantially lower, anti-CD20 antibodies represent a reasonable choice for the majority of patients with relapsed NLPHL. However, high-dose chemotherapy and ASCT should be considered in patients with repeated relapses or high tumor load at relapse.

16.9 Risk Factors

Due to the rarity of NLPHL, it has been difficult to recognize prognostic factors in this entity. However, some retrospective analyses could identify risk factors predicting a poorer outcome.

Within a large GHSG analysis including 394 NLPHL patients, advanced stages, low hemoglobin of less than 10.5 g/dl, and lymphocytopenia were associated with an impaired FFTF, while an age of 45 years or older, advanced stages, and low hemoglobin of less than 10.5 g/dl were identified as negative prognostic factors for OS [10]. A smaller analysis assessing the long-term course of 88 NLPHL patients revealed advanced stages, presence of B symptoms at diagnosis, low serum albumin, and insufficient response to first-line treatment as risk factors for a worse outcome [26].

More recently, a prognostic score including the risk factors low serum albumin, male gender, and variant NLPHL histology was developed using data from 413 NLPHL patients treated within 9 prospective GHSG studies (Table 16.3). On the basis of this score, three distinct risk groups with significant differences in terms of PFS and OS could be defined. Thus, 5-year PFS and OS rates ranged between 68.7 and 95.2 %, respectively, and 88.3 and 98.7 %, respectively. Histologic NLPHL variants were characterized by the presence of lymphoma cells outside the B-cell nodules or B-cell depletion of the microenvironment and therefore corresponded to the growth patterns C, D, E, and F (C, extranodular LP cells; D, T-cell rich; E, T-cell-/histiocyte-rich large B-cell lymphoma like; F, diffuse moth eaten) as described by Fan and colleagues. In contrast, growth patterns A and B (A, B-cell-rich nodular; B, serpiginous/interconnected) according to Fan et al. were considered typical [27, 28].

Table 16.3 Prognostic score defining risk groups for progress/relapse in NLPHL

		Scoring points
Variable A: Histopathologic NLPHL pattern	Typical NLPHL pattern (patterns A and B according to Fan et al.)	0
	Variant NLPHL pattern (patterns C, D, E, and F according to Fan et al.)	1
Variable B: Albumin	Albumin ≥4 g/dl	0
	Albumin <4 g/dl	1
Variable C: Gender	Female	0
	Male	2

Adapted and modified from Hartmann et al. [27]
Total score 0–1 low risk, *total score 2* intermediate risk, *total score 3–4* high risk

Another score exclusively based on the histopathologic features nodularity, type of nodules, splattering of nodules, extent of T-cell areas, and CD23 staining was recently presented in abstract form by a group from India. However, as only 50 patients were considered, this score has to be validated by other groups with a larger number of patients [29].

16.10 Summary and Conclusions

NLPHL which accounts for about 5 % of all HL cases is characterized by pathological and clinical features that substantially differ from cHL. Given the mostly indolent clinical course, RT alone appears to represent the treatment of choice for many NLPHL patients diagnosed with early stages. More advanced stages are often treated with approaches originally developed for cHL consisting of chemotherapy and/or RT. However, it is unclear whether these strategies represent the optimal treatment for NLPHL patients. For instance, treatment

might be substantially improved by combining conventional chemotherapy with anti-CD20 antibodies, but data addressing this issue are too scarce to draw valid conclusions. In relapsed NLPHL, single agent anti-CD20 antibody therapy seems to be sufficient for most patients as indicated by small phase II studies. In the future, prospective trials are needed to optimize the treatment of NLPHL patients.

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The Management of Hodgkin Lymphoma During Pregnancy

17

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17.1 Introduction

The peak incidence of Hodgkin lymphoma (HL) coincides with reproductive years, and about 0.5–1 % of all HL patients present with concurrent pregnancy. Lymphoma is the most common hematologic malignancy complicating pregnancy, with an estimated incidence of HL-associated deliveries of between 1 in 1,000 and 1 in 3,000 pregnancies [1, 2]. The medical challenge of concurrent HL and pregnancy stems from the need to manage the potentially life-threatening malignancy while giving the developing fetus the best chance of reaching term fully intact. Essentially, two patients need to be managed: one with lymphoma and the other without, both of whom will be affected by the toxicity of any treatments. Religious, ethical, psychological, social, and cultural beliefs and attitudes of the patient and her partner, family, and physicians all can affect decision-making. Thus, management of the disease and pregnancy not only involves the therapeutic approach but also requires attention to alleviating fear and anxiety and supporting the patient's emotional and social well-being. Current clinical practice for treating HL during pregnancy is based largely on case series, retrospective reports, and expert opinions. Therefore, management of HL during pregnancy requires that the advising clinician must balance the provision of expertise and knowledge about treatment options and prognosis with respect for ethical principles, compassion, and acceptance of patient autonomy.

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_17, © Springer International Publishing 2015

One of the main principles in treating patients with HL discovered during pregnancy is to provide care under the direction of a multidisciplinary team composed of a hemato-oncologist knowledgeable in the treatment of HL, an obstetrician experienced in the management of high-risk pregnancy, a pediatrician/neonatologist familiar with hematologic problems in the neonate, and a nurse coordinator who augments the communication and delivery of care. The best results are possible if the decision making is guided by a judicious mix of careful clinical judgment, the experience of involved team members, knowledge of the natural history of HL, and consideration of the patient's personal beliefs and desires [2–4].

17.2 Diagnostic Approach to HL During Pregnancy

Planning the diagnostic evaluation of HL in a pregnant patient should balance accurate disease assessment with the need to limit invasive procedures. The initial evaluation should include a complete history and physical examination with thorough palpation of all node-bearing areas and the abdomen, as well as careful documentation of B symptoms. Despite a higher rate of extranodal involvement of genital organs in non-Hodgkin lymphoma during pregnancy, non-lymphatic spread in the pregnant HL patient is rare and usually limited to the lung or liver [5]. Often complete staging is not necessary, and the guiding principle in managing the pregnant patient should be to restrict investigations determining the cause of patient symptoms, noting the bulk and anatomic location of the dominant tumor masses, and estimating lymphoma stage. The histopathologic diagnosis of HL should be based on tissue examination obtained by excisional or incisional tissue biopsy. The most common subtype encountered in pregnancy is nodular sclerosing HL. Standard laboratory tests should include hemoglobin, complete differential white blood cell count, platelet count, erythrocyte sedimentation rate (ESR), liver and renal function assessment, lactate dehydrogenase, and serum protein electrophoresis including albumin level. It is important to recall that pregnancy can affect the results of some of these tests, particularly ESR and alkaline phosphatase, and therefore, these tests must be interpreted carefully.

Radiologic staging should be limited to the minimum necessary to identify disease that seriously threatens the immediate well-being of the mother or child. Combined F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) scan is a standard imaging modality for staging HL under ordinary circumstances, but it employs ionizing radiation that is potentially harmful to an unborn fetus and should be avoided in pregnancy [5]. A single posteroanterior radiograph of the chest, with proper shielding, should be obtained to characterize the extent of mediastinal and pulmonary disease because overall radiation exposure is much lower than the dose associated with malformation during organogenesis [6]. Abdominal ultrasonography should be used to identify the extent and size of retroperitoneal nodal disease and provides sufficient detail for proper management [3]. Magnetic resonance imaging (MRI) without use of gadolinium has been used in place of CT scan with no potential toxicity to the fetus [7]. A recent study on 90 patients with lymphoma coincidental with pregnancy reported that MRI staging was performed on most patients without obvious negative consequences [2]; however, the amount of detail provided in excess of what can be found with ultrasonography is not necessary, and the safety of the intensive magnetic fields required is not fully established. Bone marrow biopsy should be performed in patients with B symptoms or abnormalities in blood counts such as anemia, thrombocytopenia, or leukopenia; however, only 1 out of 40 had marrow involved in a recently published large case series [2]. For those patients in whom chemotherapy is planned, echocardiography may be used to assess left ventricular function. The goal of clinical and radiologic staging is to provide guidance about the pace of disease progression, to determine the cause of any specific symptoms such as cough, and to evaluate whether treatment can be deferred or whether immediate treatment is required because of symptomatic disease or organ dysfunction. Hence, tests should only be performed if decisions regarding immediate management will be influenced.

17.3 Outcomes of Mother and Child in HL Coincident with Pregnancy

The complexity of caring for pregnant patients with HL requires a multidisciplinary team of experts working together to develop an individualized management plan (Table 17.1). The therapeutic options for pregnant patients with HL depend on stage, symptoms, gestational age at diagnosis, fetal risks, and the patient's wishes regarding the continuation of pregnancy. Although the evidence for managing pregnant HL patients comes from a few published case series and anecdotal descriptions, this evidence can provide useful guidance when complemented by careful clinical judgment and knowledge of the natural history of HL. The clinical challenge of managing pregnant HL patients lies in determining the effect of treatment delay on maternal survival versus the risk of previously undesired abortion, fetal malformation, and adverse perinatal outcomes associated with the use of chemotherapy and radiotherapy. Frequent communication with the patient and her family is crucial to ensure understanding and alleviate anxiety and fear.

A critical question to be considered when caring for a pregnant patient with HL is the effect of

Table 17.1 Characteristics of an ideal multidisciplinary team treating the pregnant patient with concomitant Hodgkin lymphoma

Obstetrician	Usually makes the diagnosis, arranges referral to hematologist/oncologist
	Brings experience in high-risk pregnancies (patients with active malignancy)
	Provides counseling regarding pregnancy termination (if recommended by the team and chosen by the patient)
	Establishes the timing and method of delivery
	Supervises effective postpartum contraception for a minimum of 2 years (greatest risk of relapse)
Hematologist/ medical oncologist	Performs oncologic history and physical and plans staging
	History searching for B symptoms or other symptomatic problems suggesting more advanced disease
	Physical examination for lymphadenopathy or organomegaly
	Complete blood cell counts
	Serum creatinine, alkaline phosphatase, lactate dehydrogenase, bilirubin, and protein electrophoresis (including albumin level)
	Chest radiograph, posteroanterior view only, with appropriate shielding
	Abdominal ultrasound for retroperitoneal lymphadenopathy
	Formulates therapeutic plan
	Administers chemotherapy if deemed necessary
	Provides supportive care for patients treated with chemotherapy to keep Hgb $\geq$100 g/L and platelet count $\geq 30 \times 10^9$/L and reviews safety of medications used for supportive care during pregnancy
	Coordinates delivery planning and chemotherapy administration to ensure that platelet count is $\geq 50 \times 10^9$/L at the time of delivery
	Arranges oncology follow-up after pregnancy to complete appropriate staging
Neonatologist	Has experience in high-risk pregnancies
	Has experience in childhood hematologic disorders
	Examines placenta and arranges histopathologic evaluation for presence of metastasis
	Coordinates newborn care at the time of delivery
	Delivers early postnatal care of newborn
	Registers newborn to central registry of children born to pregnant mothers with HL
	Counsels about breastfeeding
	Schedules long-term follow-up of newborn
Nurse coordinator	Coordinates communication among subspecialists
	Helps interpret complex communication with the patient

pregnancy on the survival of mother and infant. The largest published series by Evens et al. included 40 HL and 50 non-Hodgkin lymphoma cases occurring during pregnancy [2]. Data on the clinical course of the disease and pregnancy outcomes were gathered from 11 institutions that had treated these patients during the past decade. HL was diagnosed at a median of 23 weeks gestation. Of the six patients diagnosed in the first trimester, three elected to terminate the pregnancy and three elected to defer treatment until later. Most patients were diagnosed in the second or third trimester, and all patients who decided to keep the pregnancy successfully reached term delivery. In a study by Lishner et al., 48 pregnant women with HL were matched to nonpregnant controls with HL [8]. They found that stage and clinical presentation, course of the disease, response to therapy, and overall survival were similar when compared to age- and stage-equivalent nonpregnant controls. These findings are consistent with previous analyses in which no difference in survival was found among women who did not have a therapeutic abortion and those who did [9–11]. Several authors have observed that HL by itself does not appear to have an adverse effect on the course of pregnancy, fetal development, labor, or puerperium [2, 12, 13]. The primary conclusion to be drawn from these observations is that pregnancies encountered coincident with HL do not need to be terminated [14].

17.4 Treatment of Hodgkin Lymphoma During Pregnancy

17.4.1 General Therapeutic Principles

Most patients with HL and concomitant pregnancy require no immediate intervention. As a general rule, any treatment, such as radiation or chemotherapy, should be avoided during the first trimester unless severe symptoms are present or organ function is seriously compromised or threatened. Almost all chemotherapy agents have been documented to be teratogenic in animals or humans, although for some drugs only experimental data exist. Chemotherapy during the first trimester may increase the risk of spontaneous abortion, fetal death, and major malformation; the fetus is extremely vulnerable from the second to eighth week of gestation during which time organogenesis occurs. Even after primary organogenesis, several organs including the eyes, genitalia, hematopoietic system, and central nervous system remain vulnerable to chemotherapy and radiation therapy.

17.4.2 Early Stage HL During Pregnancy

The majority of HL patients diagnosed during pregnancy have stage IA or IIA disease and are asymptomatic or minimally symptomatic. Treatment for these patients can be deferred, but close monitoring and follow-up through the entire pregnancy has to be ensured. In a recent multicenter series, 75 % of patients had early stage HL and more than a third deferred treatment until the postpartum period resulting in good outcomes for both the mother and child [2]. In the Stanford series, 11 out of 17 patients required no immediate treatment for HL concomitant with pregnancy [15]. The approach of watchful waiting has also been demonstrated to be safe in a small case series of 19 patients from Royal Marsden Hospital [16]. Many patients can be monitored throughout pregnancy until normal full-term delivery without treatment for lymphoma. Nevertheless, therapy is required if severe symptoms or organ dysfunction develops. Patients with stage IA–IIA HL with localized or stable disease who have chemotherapy safely deferred can complete appropriate staging and initiate treatment soon after delivery. In two recent studies, among HL patients opting to delay treatment until after delivery, the birth weight, mean gestational age, and method of delivery were similar to normal pregnancies [8, 13].

Based primarily on experience acquired prior to the development of highly effective chemotherapy, several studies demonstrated the efficacy of irradiation for symptomatic patients with cervical

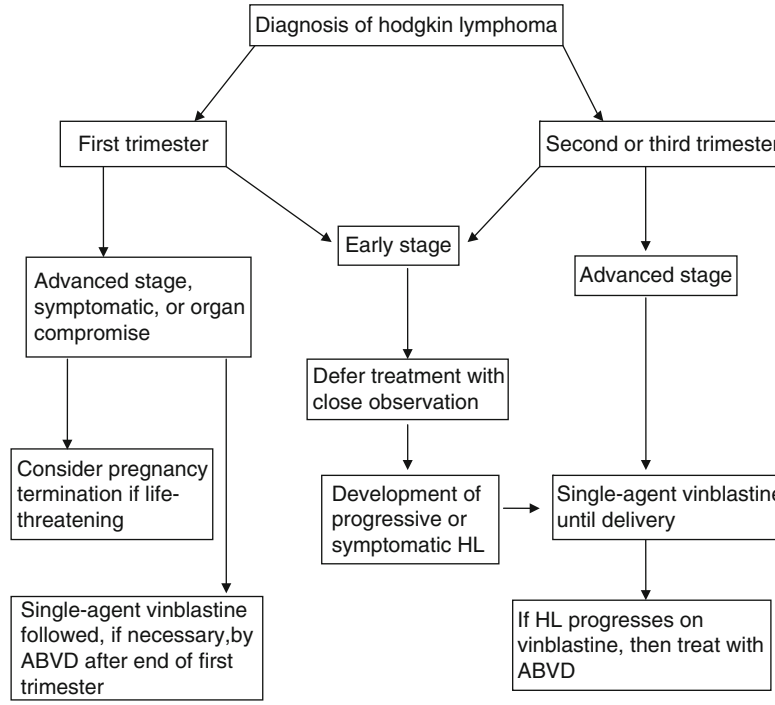

Fig. 17.1 Recommended algorithm for treatment of pregnancy-associated Hodgkin lymphoma (*HL*). *ABVD* doxorubicin, bleomycin, vinblastine, dacarbazine

adenopathy, stage IB or IIB, or respiratory symptoms due to enlarging mediastinal masses. However, at most, radiation should be reserved for cases where it is absolutely necessary, and extreme caution should be taken to provide special shielding of the fetus with ten half-value layer shields [8, 10, 17, 18]. An inverted Y field is not an option at any time during pregnancy. Radiation therapy to lymph nodes in the axilla, mediastinum, and neck-mediastinum could lead to a dose of >10 cGy and therefore should not be recommended in the first trimester [19, 20]. It is important to recall that use of any therapeutic radiation during pregnancy, especially in advanced gestational age, results in direct or scattered exposure. The effects of fetal irradiation may become evident only many years later. For example, a known risk for the fetus from radiation in the second half of gestation is acquisition of blood dyscrasias or leukemia later in life [21]. In addition, irradiation encompassing the mediastinum exposes breast tissue to scatter radiation and potentially increases the risk of later secondary breast cancer and other secondary malignancies [22].

Because radiation unnecessarily endangers the fetus, a better choice, if treatment is necessary, is systemic chemotherapy. If intervention is required, especially after the first trimester, selected symptomatic patients can be treated with single-agent vinblastine (Fig. 17.1). Vinblastine, first described for this use more than 40 years ago [23, 24], is a particularly attractive agent because of its high level of effectiveness against HL in treatment-naïve patients (>75 % response rate) and modest acute toxicity. Although teratogenic effects have been reported in mice, neither teratogenic nor carcinogenic effects are apparent in humans at doses therapeutic for lymphoma. The combination of a high level of effectiveness, minimal acute toxicity, and low likelihood of a negative effect on the fetus makes vinblastine an attractive agent to suppress HL during pregnancy. Single-agent vinblastine used as monotherapy does not cross the placenta and has been safely used in patients in all trimesters, including during early gestation when the use of other agents is more often associated with fetal malformations and increased risk of spontaneous abortions and stillbirths [9, 10, 25–28].

17.4.3 Use of Chemotherapy for Symptomatic or Advanced Stage HL in Pregnant Patients

Management of HL with advanced stage, bulky disease, visceral involvement, B symptoms, subdiaphragmatic disease, or rapid disease progression remains challenging during pregnancy. A recent large collection of cases of coincident HL and pregnancy demonstrated that this presentation is rare, and good outcomes for both the mother and fetus were achieved in most patients [2]. Alkylating agents (mechlorethamine, cyclophosphamide, procarbazine, and chlorambucil), antimetabolites (methotrexate), and multiagent regimens including these agents (e.g., MOPP [mechlorethamine, vincristine, prednisone, and procarbazine]) should be avoided during pregnancy because of a reported increased risk of spontaneous abortion, teratogenicity, carcinogenicity, and fetal malformations [8, 9, 15, 16, 25–28]. Rather than expose the fetus to the potential adverse effects of multiple agents, an alternative approach for advance stage symptomatic HL is employing single-agent chemotherapy with vinblastine. Infrequent doses at intervals of several weeks or longer can be given to control HL until delivery at term, minimizing risks to the mother and child. Standard dosing of 6 mg/m^2 is unlikely to cause significant myelosuppression, but careful timing to avoid a blood cell count nadir near delivery is prudent. Progression despite vinblastine, which occurs infrequently, should be treated with full-dose ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine) because evidence of vinblastine resistance signifies aggressive disease requiring multiagent chemotherapy (Fig. 17.1). ABVD, the current standard of care in North America, has been used during pregnancy. Although experience is limited, obvious negative effects on the fetus have not been observed [3, 4]. The largest US retrospective analysis on 40 HL patients reported 21 subjects treated with ABVD or AVD in the second and third trimester [2]. Overall, the response to therapy was excellent with a 96 % overall response rate and 83 % complete remission rate. Multiple variables were examined in this series to predict outcomes. For HL patients, multiparous status predicted improved progression-free survival (hazard ratio 0.07), and the presence of B symptoms at diagnosis predicted inferior progression-free survival (hazard ratio 10). No variable was predictive of overall survival.

We have managed 18 pregnant patients with coincident HL at the British Columbia Cancer Agency during the past 23 years using the approach described above. Eleven patients remained off treatment through term delivery, and six required vinblastine to control the disease. Fourteen of the 18 patients are still alive and well, while 4 have died, 2 from HL and 1 each from acute myeloid leukemia and retroperitoneal sarcoma. All 18 delivered normal children who now range in age from 2 to 23 years (median 17). Although these children have not been systematically assessed, no overt abnormality has become apparent [3]. The conservative use of single-agent vinblastine, which has allowed normal-term delivery of children and effective management of the mother's HL and psychological stress, appears to be a reasonable approach to this rare problem of coincident pregnancy and HL.

Data on the use of more intensive regimens such as Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, and prednisone) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine) during pregnancy are not available; however, because both contain alkylating agents, they should be avoided.

17.5 Fetal Outcomes

Patients with HL in whom gestation progresses to term need planning of the timing and mode of delivery. Fetal maturity should preferably be the criterion to induce delivery. In a multidisciplinary setting, maximal effort should be made to delay delivery until at least 35–37 weeks. A coordinated, detailed peripartum plan developed by a neonatologist, an obstetrician with experience in high-risk pregnancies, and an oncologist/hematologist is required to minimize complications.

In a recent large retrospective study from Evens et al., preterm complications among 31 patients with HL included induction of labor (40 %), preterm delivery in 14 patients, C-section in 6, low gestational age in 4 patients, and postpartum hemorrhage in 2 patients [2]. The median gestational age at delivery was 37 weeks (range 31–40 weeks). Preeclampsia and fetal demise or malformations were not observed in this retrospective series. Thus, there appeared to be no impact of antenatal chemotherapy on the frequency of these complications. The median birth weight of infants was 2,688 g (range 1,005–3,628 g) with no difference based on receipt of antenatal chemotherapy. No malformations were detected in babies exposed to ABVD or ABV chemotherapy [2]. In a smaller series of 26 children with HL with a long follow-up of 3–19 years, children born to women who received chemotherapy for HL in the second and third trimesters are delivered healthy newborns without short-term or long-term neurological, developmental, or infectious complications or secondary malignancies [13]. However, the use of anthracyclines at doses exceeding 70 mg/m^2 per cycle has been associated with a 30-fold increase in severe fetal toxicity including death, malformations, and cardiac toxicity [30]. The ABVD regimen contains doxorubicin at a lower dosage (25 mg/m^2 per dose); however, caution and careful counseling are always required when ABVD is administered in the second and third trimester. For example, one series reported stillbirth of twins in an HL patient who started the ABVD regimen at 14 weeks of gestation [30]. In addition, multiagent chemotherapy used in the last trimester of pregnancy may often result in prematurity, lower birth weights, and neonatal myelosuppression, although none of these complications were reported in the 21 patients included in the most recently reported series [2, 31, 32]. In a recent European series of 176 neonates born to mothers with malignancy, of whom 13 had HL, binomial testing revealed a significant increase in small-for-gestational-age children in the group receiving treatment during pregnancy versus those not treated during pregnancy [33]. Therefore, caution has to be taken because the adverse outcomes associated with chemotherapy are likely underreported and available evidence comes from limited, small, and heterogeneous clinical series and anecdotal descriptions [2, 8–11, 13, 15, 18, 23–25, 29, 31, 34].

17.6 Planning the Delivery and Managing the Postpartum Period in Patients with HL

Post-delivery oncologic care is a critical step in managing HL in pregnancy. Breastfeeding must be discouraged in those patients who continue chemotherapy postpartum as most cytotoxic agents can be excreted into the breast milk. In the perinatal period, patients who had not received any therapy for HL during pregnancy should be fully restaged after delivery including PET/CT staging. Patients treated with radiation, single-agent vinblastine, or other chemotherapy can no longer be accurately staged and therefore should be treated with a full course of six to eight cycles of multiagent chemotherapy. Posttreatment PET/CT imaging has a strong predictive value for overall survival and should be considered to assess the depth of post-therapy remission.

17.7 Relapsed HL and Concomitant Pregnancy

Occasionally, the patient with history of HL presents with relapsed lymphoma and concurrent pregnancy. There are limited data to guide the therapeutic decisions for such a rare clinical situation; however, we advise that care be guided by principles similar to those recommended for newly diagnosed HL and concurrent pregnancy. Individualized recommendations will depend on the initial HL stage, type of primary therapy used in the past, and the time from remission to relapse, as well as current symptoms, stage, and gestational age. Patients with minimal disease burden in the second or third trimester can often be managed by careful watching. Most patients who relapse with advanced HL or those who had

received prior chemotherapy would be considered for treatment with salvage multiagent chemotherapy followed by high-dose myeloablative chemotherapy and autologous hematopoietic stem cell rescue. Brentuximab vedotin should be avoided in pregnancy because there is no experience with this agent during pregnancy. Conservative management that allows the pregnancy to develop to term is often possible, and interventions for definitive therapy, such as autologous stem cell transplant, can be planned for soon after delivery. The decision to initiate treatment rests on careful and frequent monitoring of the patient and the pace of disease progression. If rapidly symptomatic disease develops in the first trimester, planned pregnancy interruption and subsequent standard treatment should be considered. Coordination of care with a transplant team is necessary to ensure timely post-delivery interventions.

Conclusions

The diagnostic and therapeutic approach to the patient with concurrent HL and pregnancy presents the challenge of managing two lives. The goal is to give the mother with HL the best chance of cure while preserving the healthy development of the fetus. The management of a pregnant patient with HL requires a multidisciplinary approach combining expertise in medical oncology, high-risk obstetrics and neonatology, as well as effective communication with the patient and her family. A pregnant patient with HL should be staged by clinical examination and judicious use of non-radiation imaging such as ultrasound or MRI, balancing the need for accurate disease assessment with the need to minimize invasive procedures. The treatment strategy should be individualized based on symptoms, lymphoma stage, gestational age, and the patients' wishes [34]. Therapeutic options include treatment deferral or single-agent vinblastine with reservation of multiagent chemotherapy until the second or third trimester for those patients with advanced stage disease and B symptoms. Finally, establishment of a prospective central registry for patients with concurrent HL and pregnancy to allow data collection on long-term follow-up of children born to HL patients would enhance the care of patients with this uncommon complication of pregnancy and that of their children by providing a larger database of relevant information than is currently available.

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The Management of HIV-Hodgkin Lymphoma

18

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Contents

18.1 Introduction

Since 1996, the availability of combination antiretroviral therapy (cART) has led to improvements in immune status among HIV-infected persons, reducing AIDS-related morbidity and prolonging survival. However, despite the impact of cART on HIV-related mortality, malignancies remain an important cause of death in the current era [1, 2]. The use of cART was also associated with reduced incidence of the two major AIDS-associated malignancies – Kaposi's sarcoma (KS) and high-grade non-Hodgkin lymphoma (NHL) [3]. However, among non-AIDS-defining cancers, an increased risk of Hodgkin lymphoma (HL), anal cancer, lung cancer, and liver cancer has been observed [4].

HIV-associated HL (HIV-HL) displays some peculiarities when compared with HL of the general population. First, in the pre-cART era, HIV-HL exhibited an unusually aggressive clinical behavior and was associated with a poor prognosis [5]. Second, the pathologic spectrum of HIV-HL differs markedly from that of HL in the general population [6, 7]. In particular, the mixed cellularity (MC) subtype predominates among HIV-HL [6]. Finally, despite advances in chemotherapy and supportive care, optimal treatment is still a matter of controversy.

18.2 Epidemiology

The incidence of HL in the HIV-negative population of Western countries is about 2–3 per 100,000 inhabitants [8].

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_18,

In immune-suppressed patients, HL occurs more frequently than in the general population of the same age and gender. A summary of epidemiological studies assessing the HL risk in HIV-positive people is given in Table 18.1 [4, 9–23]. Overall, HIV-infected persons have a tenfold higher risk of developing HL than HIV-negative persons. The increase in the risk was shown to be

Table 18.1 Main results reported from epidemiological studies on HL risk among HIV-infected individuals

First author/publication year	Study period	Country	Main results
Biggar (1987) [9]	1973–1984	United States	Analysis of changes in the risk of malignancies from 1973 to 1978 through 1984 in never married men (a surrogate group of homosexual men) in high- or low-risk areas for AIDS. A nonsignificant ($p = 0.13$) excess risk for HL was noted
Hessol (1992) [10]	1978–1989	United States	Cohort study of 6,704 HIV-positive homosexual men. This was the first study to demonstrate a statistically significant excess risk for HL in HIV-positive persons (RR = 5.0, 95 % CI: 2.0–10.3)
Serraino (1993) [11]	1985–1992	Italy	Clinical case series to compare the distributions of HL types between HIV-positive and HIV-negative persons. A fourfold increase of the mixed cellularity (MC) type and a 12-fold increase of the lymphocyte depletion (LD) type found in HIV-positives
Serraino (1997) [12]	1985–1995	Italy	Cohort study of 1,255 HIV-positive persons with known date of seroconversion. First observation, based on only three observed cases, of an excess HL risk of nearly tenfold (95 % CI: 8–111) in Europe
Franceschi (1998) [13]	1985–1993	Italy	Record linkage of the National AIDS registry with population-based cancer registries. The increased HL risk was confirmed (RR = 8.9, 95 % CI: 4.4–16.0) by means of a higher number of observed HL cases
International Collaboration on HIV and Cancer (2000) [14]	1985–1999	Australia, Europe, and the United States	Cancer incidence data collected from 23 studies that followed-up 47,936 persons with HIV infection. One of the first and largest evaluations of the impact of highly active antiretroviral therapy (HAART) on the spectrum of HIV-associated cancers. With regard to HL, this meta-analysis found no difference in incidence rates before (1992–1996) or after (1997–1999) the use of HAART (RR = 0.8, 95 % CI: 0.3–1.9)
Gruilich (2002) [15]	1985–1999	Australia	This record linkage study of HIV, AIDS, and cancer registries confirmed, in Australia, the excess risk for HL (RR = 7.8, 95 % CI: 4.4–13.0) previously noted in the United States and Europe

Table 18.1 (continued)

First author/publication year	Study period	Country	Main results
Dal Maso (2003) [16]	1985–1998	Italy	Update of the record linkage study between the national AIDS registry and population-based cancer registries. After 5 years, the relative risk for HL nearly doubled (RR = 16.2, 95 % CI: 11.8–21.7)
Herida (2003) [17]	1992–1999	France	Evaluation of HL risk of 77,025 HIV-positive persons during pre- and post-HAART periods, as compared to the general population of France of the same age and sex. HL risk seemed higher in the post-HAART (RR = 31.7) period than in the pre-HAART (RR = 22.8) one
Clifford (2005) [18]	1985–2003	Switzerland	Record linkage between the Swiss HIV Cohort and cancer registries. As seen in France, the findings of the study pointed to a higher risk for HL in HIV-positive persons treated with HAART (RR = 36.2), as compared to those who were never treated (RR = 11.4)
Biggar (2006) [19]	1991–2002	United States	The study focused on the relationship between degree of immune suppression and risk of HL. The findings indicated that incidence rates increased with increasing number of CD4+ cells in HIV-positive persons treated with HAART
Serraino (2007) [20]	1985–2005	France and Italy	Cohort study of 8,074 HIV-positive persons: the risk of HL did not significantly vary between those treated (RR = 9.4) or not treated (RR = 11.1) with HAART before HL occurrence
Engels (2008) [21]	1991–2002	United States	Record linkage study of 57,350 HIV-infected persons with cancer registries. Whereas the incidence of KS and of NHL declined over time, that of HL increased (RR = 2.7, 95 % CI: 1.0–7.1, 1996–2002 vs. 1991–1995). The study findings pointed to a shift in the spectrum of cancers associated with HIV infection determined by HAART
Powles (2009) [4]	1983–2007	London, UK	Chelsea and Westminster HIV cohort (n = 11.112); standardized incidence ratios (SIRs) calculated using general population incidence data; significant increase in the HL risk (SIRs) across time periods from 4.5 (1983–1995) to 11.1 (1996–2001) to 32.4 (2002–2007)
Seaberg (2010) [22]	1984–2007	United States	Multicenter AIDS Cohort study (n = 6,949), compared with SEER data; SIR for HL 7.3
Franceschi (2010) [23]	1985–2007	Switzerland	Swiss HIV Cohort study (n = 9,429); SIR for HL increased from 9.2 (1985–1996) to 21.0 (1997–2001) to 28.1 (2002–2006)

more pronounced in HIV-infected individuals with moderate immune suppression and, noteworthy, is in sharp contrast with the pattern observed for KS or NHL [19]. However, another study indicated that the risk of HL declined as the most recent CD4 count increased [24]. Further, compared with patients with CD4 count greater than 500 cells per μL, the rate ratio for HL ranged from 1.2 (95 % CI 0.7–2.2) for CD4 counts 350–455 cells per μL to 7.7 (3.9–15.2) for counts 50–99 cells per μL in the French Hospital Database on HIV cohort [25]. Another cohort study also showed that the risk of HL was highest at 50–99 per μL CD4 cells [26].

By contrast, another prospective cohort study from London demonstrated that cART was associated with an increased risk of HL (SIR 2.67; 95 % CI, 1.19–6.02) [4]. Thus, as the overall effect of cART is to increase the CD4 count level, it was speculated that, with severe immune suppression, the cellular background surrounding the RS cells may be altered. A potential mechanism emphasizes the role of the RS cells producing several growth factors that increased the influx of CD4 cells and inflammatory cells, which, in turn, provide proliferation signals for the RS neoplastic cells. In the case of severe immune suppression, leading to an unfavorable milieu, the progression of the RS neoplastic cells may be compromised [27–29]. In addition, HIV-HL is EBV associated in approximately 90 % of cases, in contrast to what is observed in the general population, in which this association is only observed in 20–50 % according to histological type and age at diagnosis [30]. Usurpation of physiologically relevant pathways by EBV-encoded latent membrane protein 1 (LMP1) may lead to the simultaneous or sequential activation of signaling pathways involved in the promotion of cell activation, growth, and survival, contributing thus to most of the features of HIV-HL. Whether this change affects its categorization as HL or whether it delays HL development is unknown.

18.3 Pathological Features

HIV-HL displays different pathological features compared to those of HL in HIV-negative patients [6]. In fact, HIV-HL is characterized by the high incidence of unfavorable histological subtypes such as MC and LD [6, 7].

HIV-HL exhibits special features related to the cellular background (presence of fibrohistiocytoid stromal cell proliferation) and the high number of neoplastic cells, and these features may pose relevant difficulties in diagnosing and classifying the disease (Fig. 18.1). This finding contrasts with the rather low population of neoplastic

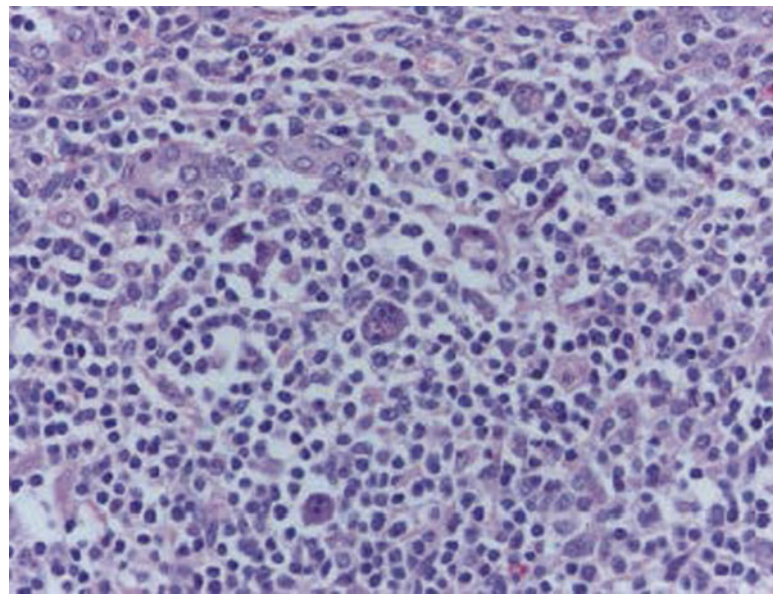

Fig. 18.1 Reed-Sternberg (RS) cells of HIV-HL with polylobate nuclei and prominent nucleoli (H&E original magnification 25×)

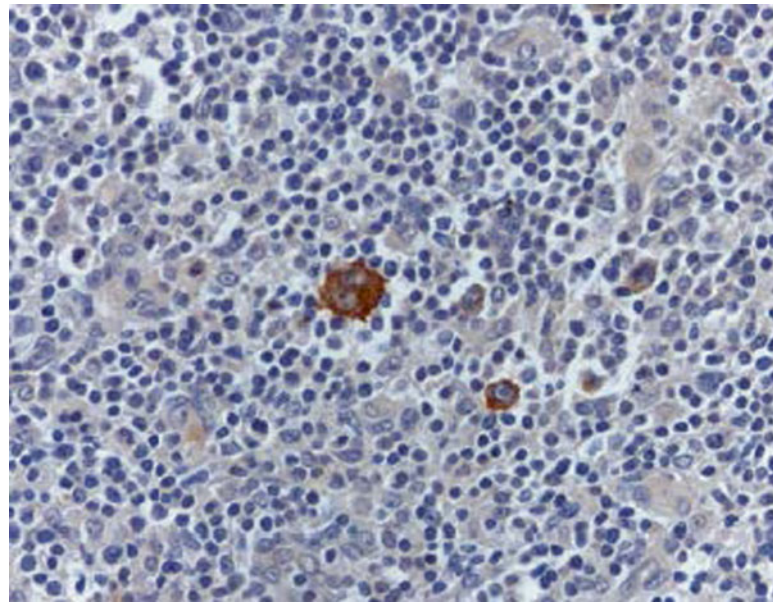

Fig. 18.2 An RS positive for LMP1. Immunostain with H counter stain (original magnification 25×)

cells usually found in HIV-unrelated HL [6, 31]. Moreover, a high frequency of EBV association has been shown in HL (80–100 %) tissues from HIV-HL [32–34]. The EBV genomes in such cases have been reported to be episomal and clonal, even when detected in multiple independent lesions. The elevated frequency of EBV association with HIV-HL indicates that EBV probably does represent a relevant factor involved in the pathogenesis of HIV-HL. An etiologic role of EBV in the pathogenesis of HIV-HL is further supported by data showing that LMP1 is expressed in the vast majority of HIV-HL cases [6, 31–35]. On these bases, HL in HIV-infected persons appears to be an EBV-related lymphoma expressing LMP1 (Fig. 18.2).

Finally, RS cells of classical HL of HIV-negative patients represent transformed B-cells that originate from pre-apoptotic germinal center (GC) B-cells [36]. Most HIV-related HL cases express LMP1 and display the BCL6–/CD138+/MUM1 IRF4+ (for Multiple Myeloma-1 Interferon Regulatory Factor-4) phenotype, thus reflecting post-GC B-cells [27, 32, 36]. The possible contribution of LMP1 to the loss of BCL6 expression seems plausible given that LMP1 can downregulate many B-cell-specific genes [37]. Loss of B-cell identity occurs during the normal differentiation of a GC B-cell into plasma cell or memory B-cell.

18.4 Clinical Aspects and Treatment

Similarly to that observed in HIV-NHL, one of the most peculiar features of HIV-HL is the widespread extent of the disease at presentation and the frequency of systemic B symptoms. At the time of diagnosis, 70–96 % of the patients have B symptoms and 66–92 % have advanced stages of disease with frequent involvement of extranodal sites, the most common being bone marrow (23–50 %), liver (10–40 %), and spleen (20–25 %) [7, 35, 38–40]. HIV-HL tends to develop as an earlier manifestation of HIV infection with median CD4+ cell counts ranging from 185 to 306/μL [7, 35, 38–40].

The widespread use of cART has resulted in substantial improvement in the survival of patients with HIV infection and HL, due to the reduction of the incidence of opportunistic infections and to the opportunity to allow more aggressive chemotherapy [41–44].

Within the Italian Cooperative Group on AIDS and Tumors (GICAT), we have collected

data on 290 patients with HIV-HL [45]. Two hundred and eighty-one patients (87 %) were males, and the median age was 34 years (range 19–72 years), and 69 % of patients were intravenous drug users. The median CD4 cell count was 240/μL (range 4–1,100/μL), and 57 % of patients had a detectable HIV viral load. MC was diagnosed in 53 % of cases, followed by NS in 24 % and LD in 14 %. Advanced stages of disease were observed in 79 % of patients and 76 % had B symptoms. The overall extranodal involvement was 59 % with bone marrow, spleen, and liver involved in 38, 30, and 17 %, respectively. With the aim to evaluate the impact of cART on clinical presentation and outcome of our patients, we split the series into two subgroups: in the first group, we included those patients who received cART since 6 months before the onset of HL (84 patients); in the second group, we included those patients who never received cART before the diagnosis of HL or less than 6 months (206 patients). Briefly, in comparison to those who never experienced cART, patients in cART before the onset of HL are older and have less B symptoms and a higher leukocyte and neutrophil count and hemoglobin level. The following parameters were associated with a better overall survival (OS): MC subtype, the absence of extranodal involvement, the absence of B symptoms, and prior use of cART. Interestingly, three parameters were associated with a better time to treatment failure: a normal value of alkaline phosphatase, prior exposure to cART, and an international prognostic score (IPS) less than 3 [45]. Table 18.2 summarizes these data.

Table 18.2 Clinical differences in 290 patients with HIV-HL according to prior HAART exposure [46]

Characteristics	Prior-HAART 84 patients (%)	HAART-naïve 206 patients (%)	*p* value
Risk group			
Intravenous	45	72	
Drug users			
Heterosexual	30	13	
Contacts			
Homosexual	25	14	0.0002
Contacts			
Age, years			
<30	5	47	
31–40	46	40	
>41	49	13	<0.0001
B symptoms	68	80	0.03
White blood cells			
<4,000	30	51	
>4,000	70	49	0.002
Neutrophil count			
<2,500	33	54	
>2,500	67	46	0.002
Hemoglobin level			
<10.5	35	49	
≥10.5	65	51	0.03

Similar studies were carried out in France, Germany, and Spain [42–44, 46]. Overall, no differences were found between groups at baseline, but complete remission (CR) and overall survival rates were significantly higher in cART groups. In the Spanish study, factors independently associated with CR were a CD4 cell count >100 cells/μL and the use of cART; CR was the only factor independently associated with OS [46].

Due to the low incidence of HIV-HL, no randomized controlled trials have been conducted in this setting, and standard therapy for HIV-HL has not clearly been defined. However, results from recent studies provide some evidence on how optimal treatment approaches for HIV-HL may look like. Because most patients have advanced stage disease, combination chemotherapy regimens were usually administered. As the widespread use of cART allows the use of more aggressive chemotherapeutic regimens, the Stanford V regimen – consisting of short-term chemotherapy (12 weeks) with adjuvant radiotherapy – was given in a prospective phase II study within the European Intergroup Study HL-HIV [47]. From May 1997 to October 2001, 59 consecutive patients were treated. Stanford V was well tolerated, and 69 % of the patients completed treatment with no dose reduction or delayed chemotherapy administration. The most important dose-limiting side effects were bone marrow toxicity and neurotoxicity. Eighty-one percent of the patients achieved a CR, and after a median follow-up of 17 months, 33/59 (56 %) patients were alive and disease-free. The estimated 5-year OS, disease-free survival (DFS),

and freedom from progression (FFP) were 59, 68, and 60 %, respectively. The FFP probability was significantly ($p=0.002$) higher among patients with an IPS of <2 than in those with IPS >2, and the percentage of FFP at 2 years were 83 and 41 %, respectively. Similarly, the OS probability was significantly different ($p=0.0004$), and the percentage of survival at 3 years were 76 and 33 %, respectively, for IPS <2 and IPS >2 [47].

Within the GICAT, 71 patients were included in a prospective phase II study aiming to evaluate the feasibility and activity of a novel regimen including epirubicin, bleomycin, vinorelbine, cyclophosphamide, and prednisone (VEBEP regimen). Seventy percent of patients had advanced stages of disease, and 45 % had an IPS >2. The CR was 67 %, and 2-year OS, DFS, and event-free survival (EFS) were 69, 86, and 52 %, respectively [48]. The German HIV-Related Lymphoma Study Group reported improved survival rates in a larger prospective study on a stage-adapted treatment of HIV-HL [35]. Patients with early favorable HIV-HL received two to four cycles of ABVD followed by 30-Gy involved field (IF) radiation. In early unfavorable HIV-HL, four cycles of BEACOPP baseline or four cycles of ABVD + 30-Gy IF were administered. Six to eight cycles of BEACOPP baseline were given in advanced stage HIV-HL. In patients with advanced HIV infection, BEACOPP was replaced by ABVD. The CR rate for patients with early favorable, early unfavorable, and advanced stage HL was 96, 100, and 86 %, respectively. The 2-year OS was 90.7 % with no significant difference between early favorable (95.7 %), early unfavorable (100 %), and advanced HL (86.8 %) [35]. Results of prospective studies on HIV-HL performed in the pre- and post-cART era are shown in Table 18.3.

In the cART era, the role of ABVD chemotherapy was investigated in two large retrospective studies [40, 53]. The first study was conducted in Spain and included 62 patients with HIV-HL. The scheduled six to eight ABVD cycles were completed in 82 % of cases. Six patients died during induction, 54 (87 %) achieved a CR, and two were resistant. The 5-year OS and EFS probabilities were 76 and 71 %, respectively. The immunological response to cART had a positive impact on OS ($p=0.002$) and EFS ($p=0.001$) [53].

Another study from the UK demonstrated that HIV status did not adversely affect OS and PFS in HL patients treated with ABVD. From 1997 to 2010, 224 patients newly diagnosed with HL, of whom 93 were HIV positive, were consecutively treated with ABVD [40]. Of note, HIV-positive patients had more high-risk disease according to

Table 18.3 Results of prospective studies in HIV-HL

Regimen/reference	Number of patients	Stage III–IV (%)	Response rate (%)	Complete remission (CR) rate (%)	Overall survival
Pre-cART era					
EBV [49]	17	88	82	53	11 months
EBVP [5]	35	83	91	74	16 months
ABVD [50]	21	81	62	43	18 months
ABVD [51]	8	75	100	100	43.5 months
cART era					
Stanford V [47]	59	71	89	81	59 % at 5 years
BEACOPP [52]	12	92	100	100	75 % at 3 years
VEBEP [48]	71	70	78	67	69 % at 2 years
BEACOPP or ABVD [35]	71	100	86	86	87 % at 2 years
ABVD [35]	23	Early favorable HL	96	96	96 % at 2 years
ABVD or BEACOPP [35]	14	Early unfavorable HL	100	100	100 % at 2 years

the IPS than HIV-negative patients (IPS ≥3: 68 % vs. 26 %, $p<.001$). The complete response rate was 74 and 79 % for HIV-positive and HIV-negative patients, respectively. After a median follow-up of 60 months (range, 8–174 months), 23 patients (16 HIV-negative and 7 HIV-positive patients) have experienced relapse at a median time of 6 months. There was no significant difference in the 5-year EFS and OS between HIV-positive and HIV-negative patients (59 % vs. 66 % and 81 % vs. 88 %, respectively).

During chemotherapy, cART should either be continued or initiated according to current guidelines for the use of ART. However, interactions between cytotoxics and antiretrovirals must be considered, as chemotherapy-related toxicity may be markedly increased by concomitant use of antiretrovirals [54]. Although controlled studies have not been performed, the potential of interactions with increased toxicities appears to be highest with antiretroviral combinations that include strong enzyme inhibitors such as ritonavir-boosted protease inhibitors [55, 56]. Thus, a raltegravir-containing antiretroviral regimen is recommended during chemotherapy if HIV treatment history and resistance patterns allow such a switch.

Because a significant proportion of HIV-HL progresses and relapses, the use of high-dose chemotherapy and autologous stem cell transplantation (ASCT) has been tested in this setting. Peripheral blood stem cells can be effectively mobilized as recently shown in an analysis of 155 patients [57]. Several data from different groups, including the GICAT, have demonstrated the feasibility of this approach that can be considered the gold standard in a salvage setting [58–64]. In a retrospective analysis of the EBMT on 68 patients with relapsed lymphoma, non-relapse mortality (NRM) at 3 and 12 months was 4.4 and 7.5 %, respectively [62]. Further, a comparative analysis between HIV-related lymphoma and a matched cohort of HIV-negative lymphoma demonstrated no significant differences in NRM, PFS, and OS [65]. Of note, immune recovery after ASCT is not different for HIV-infected versus HIV-uninfected patients with relapsed lymphoma. As shown by a prospective immunovirologic study, HDCT and ASCT in HIV-infected patients do not worsen initial immune impairment or enhance viral replication or peripheral HIV reservoir in the long term [66].

18.5 PET Scanning

Positron emission tomography using [18F]-fluoro-2-deoxy-D-glucose (FDG-PET) is now recognized as an important tool for staging and treatment response assessment in HL and NHL [67, 68]. Turning to predicting outcome, in HIV-negative patients, residual FDG-PET avidity after two cycles of ABVD has been shown to confer poor prognosis and, therefore, has been proposed to guide future therapy [69, 70]. A negative PET scan after two cycles of ABVD predicted a 96 % 2-year PFS. Nearly 80 % of HL patients achieve a complete normalization of the PET scan after two courses of ABVD [68].

Some preliminary reports suggest FDG activity may also correlate with detectable lymphoma in the setting of HIV [71, 72]. In a study of 23 patients with advanced HIV-HL, a negative interim 18F-FDG-PET result after two to three cycles of ABVD was highly predictive of treatment success with a 2-year PFS for interim PET-positive patients of 50 and 100 % for interim PET-negative patients ($p=0.0012$) [73].

However, PET scanning within the HIV framework may produce false-positive results. Pitfalls are numerous and bring a particular challenge in these patients in whom HIV-associated immunodeficiency predisposes to infection, as does the use of aggressive immunosuppressive chemotherapy regimens. PET imaging requires cautious reading and pertinent clinical correlation to avoid diagnosing benign disease as malignant, such as hypermetabolic foci seen in the lung or esophagus, which are common sites of HIV- and/or chemotherapy-promoted infections [74]. Nodal FDG uptake can be observed in lymphoma, various infections (e.g., *Mycobacterium avium-intracellulare*, *Mycobacterium tuberculosis*, herpes simplex virus, among others), and AIDS-related malignancies such as Kaposi's sarcoma [75]. In addition, stimulation of bone marrow following treatment with granulocyte

Table 18.4 Proposed criteria for PET interpretation after two cycles of chemotherapy

Negative	
0	No uptake
1	Uptake ≤ mediastinum
2	Uptake > mediastinum but ≤ liver
Positive	
3	Uptake > liver in some sites even if uptake ≤ liver or mediastinum at other sites
4	Uptake >liver in over 90 % of sites or development of new uptake consistent with progressive disease

colony-stimulating factors induces a striking increase in FDG uptake in bone marrow. To take into account the possibility of minimal residual uptake, a semiquantitative approach has recently been proposed for interim PET interpretation in the context of an international protocol for advanced stage HL (Table 18.4).

While a negative interim PET scan always seems associated with a favorable outcome, a residual uptake at sites of disease needs further evaluation (e.g., biopsy). The use of FDG in the follow-up of HIV-HL patients who achieved CR cannot be routinely recommended.

Conclusions

The outcome of patients with HIV-HL has improved with better combined antineoplastic and antiretroviral approaches. The main important challenges for the next years are (a) to validate the role of PET scan both in the staging and in the evaluation of response, (b) to better understand the interactions between chemotherapy and antiretroviral therapy in order to reduce the toxicity of both approaches, (c) to evaluate the use of new drugs (i.e., brentuximab vedotin) in this setting, and (d) to evaluate the long-term toxicity of the treatment in cured patients.

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Part IV

Relapsed and Refractory Disease

Relapsed and Refractory Hodgkin Lymphoma

19

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19.1 Introduction

High-dose therapy (HDCT) followed by autologous stem cell transplantation (ASCT) is the standard treatment for patients with relapsed Hodgkin lymphoma (HL). This is based on the results of two randomized controlled studies showing improved event-free survival (EFS) in the ASCT group compared to standard-dose salvage chemotherapy. There are also a number of single-arm institutional and registry studies also showing an advantage for HDCT/ASCT [1, 2]. Many larger single-center studies have reported that HDCT/ASCT is the best treatment option for patients with primary refractory HL providing that the disease is chemosensitive to salvage chemotherapy (SC) [3–5]. Despite this evidence, many questions remain including the utility of pre-SC prognostic factors, type and number of salvage chemotherapy needed prior to HDCT, the use of pre-ASCT fludeoxyglucose-positron emission tomography (FDG-PET) scanning to determine ASCT eligibility, the role of radiotherapy during ASCT, and the need to consider allogeneic transplantation in selected patients. The objective of this chapter is to provide hematologists/oncologists with an up-to-date review of these issues; however, we will restrict the data to refractory or relapsing HL patients who are eligible for HDCT.

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_19,

19.2 Prognostic Factors in Relapsed and Refractory Hodgkin Lymphoma

Several studies analyzed risk factors in relapsed and refractory HL. Time to relapse after first-line therapy was confirmed as important risk factor in virtually all analyses. The observation that the duration of remission has a marked effect on the ability of patients to respond to subsequent salvage treatment dates back to 1979 [6]. This finding was later confirmed in larger analyses [7–9]. In 422 patients with relapsed or refractory HL registered in the German Hodgkin Study Group (GHSG) database, patients with early (<12 months) and late relapse (>12-months) had a 4-year overall survival (OS) of 44 and 72 %, respectively. This difference in outcome between early and late relapsed patients is also present when only patients treated with HDCT and ASCT were analyzed [7–9]. The prognosis of patients with primary refractory disease is particularly poor, as demonstrated in a large prospective multicenter trial with 157 patients receiving HDCT and ASCT after failure of first-line therapy [10]. The 5-year OS estimates were 30 and 76 % for patients with refractory or relapsed disease, respectively. Many other prognostic factors have been described for patients relapsing after first-line chemotherapy. These include age, sex, histology, site of relapse, stage at relapse, bulky disease, B symptoms, performance status, extranodal relapse, anemia, and chemosensitivity to salvage chemotherapy in patients receiving HDCT and ASCT. However, the impact of these factors on outcome was less consistent than time to relapse.

The GHSG performed a larger retrospective analysis on 422 relapsed patients [7] suggesting that the prognosis of these patients can be estimated according to a number of risk factors. The most relevant factors were combined into a prognostic score (Table 19.1). This score included duration of first remission, stage at relapse, and the presence or absence of anemia at relapse. Early recurrence within 3–12 months after the end of primary treatment, relapse stage III or IV, and hemoglobin <10.5 g/dL in female or <12 g/dL in male patients contributed to a score with values 0–3 in order of worsening prognosis. This prognostic score allowed distinguishing between different prognostic groups. The actuarial 4-year freedom from second failure (FF2F) and OS for patients relapsing after chemotherapy with three unfavorable factors was 17 and 27 %, respectively. In contrast, patients with none of the unfavorable factors had an FF2F and OS of 48 and 83 % at 4 years, respectively. In addition, the prognostic score was also predictive for patient subgroups such as those relapsing after radiotherapy, for patients relapsing after chemotherapy who were treated with conventional treatment or HDCT followed by ASCT, and for patients under 60 years having a Karnofsky performance status ≥90 %. This prognostic score used clinical characteristics that can be easily collected at the time of relapse separating groups of patients with clearly different outcomes.

Table 19.1 Prognostic score in relapsed Hodgkin lymphoma evaluated in 422 patients [7]

Factor		Groups with 4-year OS (%)
Duration of first remission	Early relapse vs.	47
	Late relapse	73
Stage at relapse	Stage III/IV vs.	46
	Stage I/II	77
Hemoglobin	F <10.5 g/dL; M <12.0 g/dL vs.	40
	F >10.5 g/dL; M >12.0 g/dL	72

This score was confirmed in the prospective European HDR2 trial that was conducted by the GHSG, EORTC, GEL/TAMO, and EBMT comparing two pre-HDCT regimens in 241 patients [11]. Stage III patients had a similar risk in terms of progression-free survival (PFS) compared to stage II patients in univariate analysis. Thus, the prognostic score was slightly modified in that only stage IV (and not stage III) was scored as additional risk factor. Moreover, both multiple relapses and early relapse were scored as risk factors. Patients with none of these risk factors ($n = 117$) had a PFS of 81 % (95 % CI, 72–87 %)

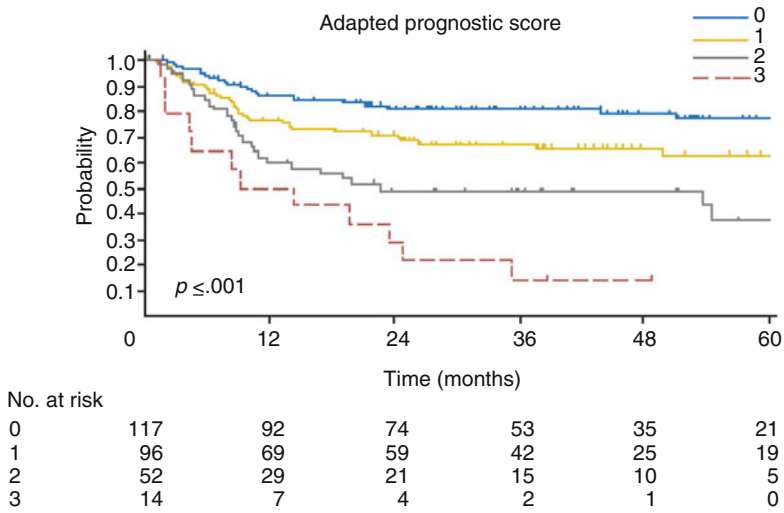

Fig. 19.1 Kaplan-Meier curves of progression-free survival in four groups of patients differentiated with an adapted prognostic score. Presence of stage IV disease, early or multiple relapse, and anemia summed up to a score ranging from 0 to 3 [11]

at 3 years (Fig. 19.1). Conversely, almost all patients in the small group of those having three risk factors ($n=14$) relapsed or died within 3 years (PFS, 14 %; 95 % CI, 2–37 %). Other analyses have identified extranodal disease [8, 12] and B symptoms [8, 13] as risk factors. Moreover, in patients receiving HDCT and ASCT, chemosensitivity to salvage chemotherapy was described as important prognostic factor in several reports [9, 12]. More recently, FDG-PET after salvage therapy has been established as prognostic tool that overshadows classical risk factors (see Sect. 19.4) [14, 15].

Although a plethora of risk factors have been described in relapsed/refractory HL, there is currently no generally accepted risk-adapted treatment approach. The French Lymphoma Study Association (LYSA) has proposed a risk-adapted strategy based on the three risk factors, primary refractory disease, early relapse, and stage III/IV at relapse [16]. The lymphoma group of the Memorial Sloan Kettering Cancer Center (MSKCC) also uses three risk factors (early relapse, extranodal disease, and B symptoms) to stratify patients into three different treatment groups [8, 17]. Risk-adapted therapy with different SC and/or HDCT approaches should be further evaluated in prospective clinical trials.

19.3 Salvage Therapy

Possibly the most important goal in the management of patients with relapsed or primary refractory HL is establishing chemosensitive disease with SC. It has been clearly demonstrated in multiple studies that chemorefractory disease to SC predicts for a poor long-term EFS and excludes patients from receiving a curative transplant [18].

An effective salvage regimen must have a favorable toxicity profile, in addition to having a high response rate. Older regimens such as mini- or dexa-BEAM have limited utility in 2014 because of toxicity to hematopoietic stem cells, leading to an inadequate stem cell harvest [19–21]. The optimal choice of a salvage regimen is unclear, because different regimens have not been directly compared with one another and in general as opposed to diffuse large B cell lymphoma response rates are quite effective approaching 80 %. Unfortunately, the clinician is left to choose from a variety of reasonable salvage options without clear knowledge of the superiority of one regimen vs. another. At MSKCC, the ICE (ifosfamide, carboplatin, etoposide) chemotherapy regimen has been used since 1994 and has become the standard SC used in the USA [3, 8]. ICE is regularly administered

as an inpatient treatment for two cycles. In a series of prospective clinical trials, the complete response (CR) rate is approximately 50 % and the overall response rate is 80 %. An augmented dosing has been evaluated in patients with unfavorable risk factors [8, 17] with following doses: ifosfamide 10 g/m^2 as a 48-h continuous infusion, etoposide 200 mg/m^2 for three doses, and carboplatin at an AUC of 5. It is likely that cytarabine-based regimens such as DHAP (dexamethasone, high-dose ara-C [=cytarabine], cisplatin), ESHAP (etoposide, methylprednisolone, high-dose ara-C [=cytarabine], cisplatin), and DHAX (dexamethasone, high-dose ara-C [=cytarabine], oxaliplatin) have similar response rates, and centers tend to be passionate concerning the type of salvage regimen that is employed. The GHSG and other European cooperative groups regard DHAP as standard SC [22, 23].

The other popular choice is to incorporate gemcitabine into the SC program. Gemcitabine-based regimens are better tolerated, show similar activity, and have the advantage of easier outpatient administration. GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) was evaluated in 91 patients with relapsed or refractory HL, and overall response rate (ORR) was 70 %, albeit with a modest 19 % CR rate based upon CT imaging [24]. Another program, IGEV (ifosfamide, prednisolone, gemcitabine, and vinorelbine) was administered to 91 patients of which 49 (54 %) achieved a CR and 25 patients (27.5 %) had a PR for an ORR of 81.3 %, based upon PET imaging [25]. Lastly, Kuruvilla et al. compared GDP (gemcitabine, dexamethasone, and cisplatin) with mini-BEAM; response rates were similar but GDP was far less toxic [26].

Depending upon prognostic factors, favorable patients are likely to have a high CR rate to any of these regimens, and it is prudent to minimize toxicity if possible. Recently, brentuximab vedotin (BV) was incorporated into the salvage programs. A prospective clinical trial evaluated the sequential administration of BV followed by ICE only in patients not achieving a CR with the antibody-drug conjugate based upon PET response. It is hoped that this approach can obviate the need of extensive SC in a proportion of patients (Fig. 19.2) [27].

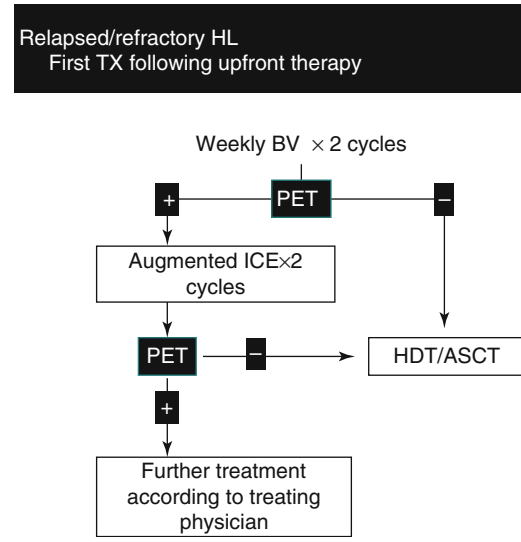

Fig. 19.2 Brentuximab vedotin as initial salvage therapy in relapsed/refractory HL. *HL* Hodgkin lymphoma, *TX* chemotherapy, *BV* brentuximab vedotin, *PET* positron emission tomography, *ICE* ifosfamide, carboplatin, etoposide, *HDCT* high-dose therapy, *ASCT* autologous stem cell transplant

Alternatively, one can combine other novel agents with SC. Investigators at MD Anderson conducted a phase I study of oral panobinostat in combination with standard ICE; panobinostat was administered Monday/Wednesday/Friday starting 1 week prior to the first cycle of ICE and continued through the second cycle. The overall response rate was 86 %, with complete response rate of 71 % as determined by FDG-PET. All responding patients (86 %) proceeded to ASCT [28]. These results are very encouraging, and the platform of combining HDAC inhibitors with standard-dose salvage chemotherapy needs to be expanded. Similarly, the GHSG is currently evaluating a combination of the oral mTOR inhibitor everolimus with standard DHAP in a phase I/II trial. Lastly there is an ongoing clinical trial led by Hagenbeek and colleagues combining BV and DHAP with the goal of achieving a high CR rate pre-ASCT (Fig. 19.3) [29].

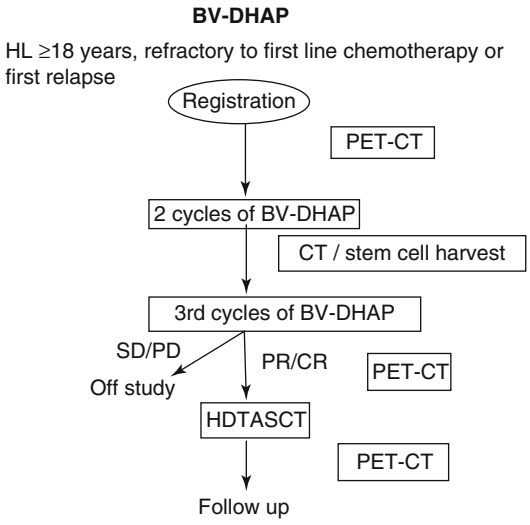

Fig. 19.3 Brentuximab vedotin-DHAP as salvage therapy in relapsed/refractory HL. *BV* brentuximab vedotin, *DHAP* dexamethasone, high-dose ara-C, cisplatin, *HL* Hodgkin lymphoma, *yr* year, *PET-CT* positron emission tomography-computed tomography, *SD* stable disease, *PD* progressive disease, *PR* partial remission, *CR* complete remission

19.4 Pre-ASCT FDG-PET

FDG-PET-CT has revolutionized the way oncologists manage HL. FDG-PET-CT imaging is more sensitive and specific than either modality alone, and in 2014 most HL patients have a combined FDG-PET-CT scan for staging and to determine remission status at the conclusion of a chemotherapy program [30]. It is also recommended that the CT component includes intravenous and oral contrast which can be helpful for patients requiring subsequent consolidative radiotherapy. Some of the basic "rules" in PET scanning for HL is that it is always abnormal at diagnosis and normalization after therapy is highly predictive of a good outcome. However, controversy remains concerning its role for interim evaluation.

Since second-line treatment employs a comprehensive approach, the pre-ASCT PET in reality is an interim PET (iPET). Reporting should be similar to that of untreated HL; scores 1–3 are considered negative via the 5-point or Deauville scale and 4/5 are positive [31]. The question that investigators face is should a patient who is deemed chemosensitive by CT but with an abnormal iPET be excluded from curative therapy; 30 % of patients achieve long-term EFS if there is tumor shrinkage after one course of salvage therapy despite an abnormal iPET.

Recent studies have reported that chemosensitive disease should be defined by pre-transplant PET status; those patients with a negative scan have a 5-year EFS of approximately 75 % compared to 30 % for those patients with improvement of CT but with persistent PET positivity [14, 32, 33]. This data was confirmed by the MD Anderson group where 3-year PFS and OS rates were 69 and 87 %, respectively, versus 23 and 58 %, respectively, for patients with positive functional imaging. MSKCC investigators recently reported the results of a large phase II second-line treatment program where iPET was prospectively evaluated. Patients who achieved normalization of the post-ICE PET scan were transplanted with the expected 77 % long-term EFS. Patients achieving cytoreduction to ICE but with a persistently abnormal PET received a second, non-cross-resistant salvage treatment with four doses of GVD administered biweekly. Interestingly, 50 % of patients had a PET-negative response to GVD, and these patients also had a 77 % long-term PFS. Patients with a persistently positive PET scan after two salvage chemotherapy programs had only 22 % 5-year EFS [34].

In our opinion, the goal of salvage chemotherapy should be a negative PET scan; however, owing to the lack of randomized trials, the best strategy for patients not achieving a negative PET after the first salvage program is currently unclear. A second, non-cross-resistant salvage program or tandem ASCT (see Sect. 19.7) seems to be a reasonable option. It must be stressed that patients with nodal only HL at this point can still achieve a negative PET with involved or extended field radiotherapy, a reasonable approach in this patient population. The treatment decision should be based on pretreatment, risk factors, and comorbidities of the individual patient.

19.5 Salvage Radiotherapy

As stated above, SC followed by HDCT/ASCT is standard therapy for transplant eligible patients with HL. The incorporation of radiotherapy (RT) to selected sites integrated into the salvage program either before or after transplantation can improve EFS for a subset of patients. An increasing number of patients who failed primary treatment are RT naïve, and this number will only increase since the evolving trend in many centers is to use short-course chemotherapy alone for early stage HL. An important argument in support of incorporating RT into high-dose salvage programs is that the pattern of relapse after HDCT is similar to that after primary therapy, i.e., in sites of moderately bulky nodal involvement.

The issues of optimal timing of RT, pre- or post-HDCT/ASCT, are center dependent. At MSKCC, involved field RT (IFRT) is administered prior to HDCT as part of the salvage program for further tumor reduction, and interestingly at times it is the IFRT that normalizes the pre-ASCT PET scan. From 1985 to 2008 it was MSKCC policy to employ both IFRT and total lymphoid irradiation (TLI) for RT naïve patients without extranodal involvement. A cohort of 186 patients of which 53 % had primary refractory disease to ABVD was recently updated. These patients received involved field RT (IFRT) at 18 Gy followed by total lymphoid radiation at 18 Gy as part of the conditioning regimen; the 5- and 10-year OS was 68 and 56 %, and the 5- and 10-year EFS was 62 and 56 %, respectively [35]. This data was confirmed by the group at northwestern where TLI was found to be an independent predictor for improved EFS on multivariate analysis [36]. Within the GHSG, RT in case of residual disease after HDCT and ASCT is preferred aiming at a dose-dense salvage and high-dose chemotherapy.

Currently, the use of RT can help a substantial number of patients in the salvage setting. Since nodal only relapses are common, the avoidance of RT in this setting makes little sense in patients whose major cause of death will clearly be HL if HDCT/ASCT is not successful.

19.6 HDCT Regimens

Similar to SC regimen selection, the choice of the HDCT regimen before ASCT is not evidence based: no randomized controlled trials comparing different regimens have been conducted, and the choice of regimen is mostly made on personal experience. Historical comparisons of different regimens are limited by high patient heterogeneity in terms of pretreatment, risk factors, and comorbidity [37]. Because BEAM (BCNU [=carmustine], etoposide, cytarabine, melphalan) was used in both of the randomized controlled trials that established ASCT in relapsed/progressive HL [1, 2] and yielded excellent results in the large HDR2 trial, this is the HDCT regimen of choice for most groups. CBV (-Mx) (cyclophosphamide, carmustine, etoposide, mitoxantrone) and (sub)total lymphoid irradiation ([S] TLI)-based conditioning regimens are frequently used alternatives [34, 38]. Phase I/II trials with modified HDCT regimens aiming at a reduced toxicity of BCNU using bendamustine [39] or gemcitabine/vinorelbine [40] have been published, but owing to the lack of randomized trials, these approaches currently remain experimental.

The addition of sequential HDCT after SC was evaluated as a potential alternative to the commonly used multi-agent HDCT regimens. Based on the challenging results of a phase II trial [41], sequential HDCT was tested in the prospective GHSG, EORTC, GEL/TAMO, and EBMT HDR2 trial. Patients with histologically confirmed early or late relapsed HL and patients in second relapse with no prior HDCT received two cycles of DHAP. Patients achieving at least SD after DHAP were randomized to receive either BEAM followed by ASCT (arm A of the study) or high-dose cyclophosphamide, followed by high-dose methotrexate plus vincristine, followed by high-dose etoposide and a final myeloablative course with BEAM (arm B of the study). A total of 284 patients with relapsed HL were included in this largest randomized trial performed in this setting so far; 241 patients were randomized after DHAP. The intensified experimental arm showed significantly longer mean treatment duration and higher toxicity before

BEAM. Mortality was nearly identical in both arms (20 and 18 %), and there were no differences in terms of PFS and OS. The respective 3-year rates for the standard arm and the intensified arm were PFS 72 vs. 67 % and OS 87 vs. 80 %. In conclusion, both regimens tested showed equally favorable results in outcome and survival. Since further intensification did not improve results, two cycles of conventional SC followed by HDCT and ASCT remain the standard of care for patients with relapsed HL.

19.7 Tandem HDCT/ASCT

The prognosis of high-risk patients with relapsed HL and especially the prognosis of refractory patients remain unsatisfactory despite HDCT and ASCT. Tandem autologous transplant is a potential strategy to improve the prognosis of these patients. In the French H96 prospective multicenter trial [38], 150 high-risk patients (primary refractory disease, $n=77$, or two or more of the following risk factors at first relapse: time to relapse <12 months, stage III or IV at relapse, and relapse within previously irradiated sites, $n=73$) were assigned to tandem ASCT. In the intent-to-treat analysis, the respective 5-year FF2F and OS estimates were 46 and 57 %, with similar outcomes in primary refractory and high-risk relapsed patients. The 45 % 5-year OS in patients with chemotherapy-resistant disease who completed tandem transplant compares favorably with previously reported 5-year OS rates of 30 %. In the recently published long-term follow-up analysis, these relatively favorable results were confirmed: 10-year FF2F and OS in the high-risk patients were 40 and 47 %, respectively [42]. Additionally, two other analyses also suggested a benefit of tandem ASCT in high-risk relapsed/refractory HL patients [17, 43].

More recently, a series of 111 consecutive patients who had relapsed or refractory HL achieving CR (PET negative) or PR (PET positive) after SC was reported; these patients underwent single or tandem ASCT [15]. In line with other analyses, outcomes were significantly better in patients with negative PET compared to patients who were PET positive after salvage with PFS and OS rates of 79 % versus 23 % and 90 % versus 55 %, respectively. In the PET-positive subgroup, tandem transplant improved 5-year PFS from 0 to 43 % ($p=0.034$) compared to single ASCT. In summary, tandem ASCT is an alternative for high-risk relapsed and primary refractory patients and for patients not sufficiently responding to SC.

19.8 Posttransplant Therapy

There is limited data on the role of maintenance or post-ASCT therapy in HL; however, this question will likely be answered by the AETHERA trial. This is a phase 3, randomized, double-blind, placebo-controlled, multicenter study. After ASCT, patients received brentuximab vedotin at 1.8 mg/kg q 3 weeks and best supportive care (BSC) or placebo and BSC for up to 16 cycles (approximately 12 months). The primary endpoint is PFS, and additional endpoints include overall survival and safety/tolerability. A total of 329 patients were enrolled and randomized; patients were enrolled in one of three high-risk categories: refractory to frontline therapy, 195 patients (59.6 %); relapse <12 months after frontline therapy, 107 patients (32.7 %); and relapse ≥12 months after frontline therapy with extranodal disease, 27 patients (8.2 %). The results will likely be reported in late 2014.

19.9 Allogeneic Transplantation After Reduced Conditioning in Hodgkin Lymphoma

In most cases, allogeneic transplantation is not recommended for patients with HL. The reduced relapse rate associated with a potential graft-versus-tumor effect is offset by lethal graft-versus-host toxicity. Nevertheless, patients with first-line therapy failure or relapsed patients with additional risk factors such as insufficient response to SC face a poor prognosis after HDCT and ASCT. Therefore, the role of allogeneic transplant should be further evaluated within

clinical trials in these patients. While allogeneic transplant after myeloablative conditioning led to poor results because of the exceedingly high non-relapse mortality, several retrospective analyses have suggested that dose-reduced allogeneic transplant (RIC-allo) could be an option for HL patients relapsing after ASCT. More recently, the largest multicenter phase 2 prospective clinical trial of RIC-allo in relapsed or refractory HL so far reported favorable results in a subset of patients [44]. The role of allogeneic transplant in HL is discussed in detail in Chap. 20.

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Allogeneic Transplantation for Relapsed Hodgkin Lymphoma

20

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Contents

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Hodgkin lymphoma (HL) is highly responsive to conventional chemotherapy (CT). Close to 90 % of patients even with advanced disease are cured with modern CT sometimes followed by irradiation [1, 2]. Patients who prove refractory to or relapse after first-line therapy, do significantly worse. High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) is the standard of care for medically fit patients with relapsed HL [3, 4]. The results of ASCT, however, vary significantly depending on a number of prognostic factors – the most important of which are the time interval between first-line treatment and relapse, the clinical stage at relapse, and the sensitivity of the tumor to salvage CT [5–9]. More recently, the capacity to achieve a positron emission tomography (PET)-negative complete remission (CR) with the salvage regimen has also been demonstrated to be a good prognostic factor [10]. For example, approximately 70 % of patients with late first relapse can be salvaged by HDT/ASCT, whereas not more than 40 % of patients suffering from early first relapse are rescued by this modality [4]. Only 20–35 % of patients with refractory HL may achieve long-term survival after ASCT [11–14]. In addition, a significant proportion of

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_20, © Springer International Publishing 2015

patients with HL still relapse after ASCT. Therefore, although HDT/ASCT may cure a significant proportion of patients with relapsed or refractory HL, subsets of patients carry a high risk of failure and are candidates for more experimental procedures such as allo-SCT.

20.1 Myeloablative Allogeneic Stem Cell Transplantation in Hodgkin Lymphoma: A Historical Perspective

The first reports on allogeneic stem cell transplantation (allo-SCT) in patients with HL appeared in the mid-1980s [15, 16]. Patient numbers were low and a realistic evaluation of the therapeutic potential of allo-SCT was not possible. Two larger registry-based studies published in 1996 gave disappointing results. Gajewski et al. analyzed 100 HL patients allografted from HLA-identical siblings and reported to the International Bone Marrow Transplant Registry (IBMTR) [17]. A significant proportion of these patients was not in remission before transplant and had a poor performance status and active infections before transplantation. Almost 50 % of the patients received total body irradiation (TBI)-containing regimens. The 3-year rates for overall survival (OS), disease-free survival (DFS), and the probability of relapse were 21, 15, and 65 %, respectively. The major problems after transplantation were persistent or recurrent disease or respiratory complications, which accounted for 35–51 % of deaths. Acute and/or chronic graft versus host disease (GVHD) did not significantly reduce the risk of relapse. At the same time, a case-matched analysis including 45 allografts and 45 autografts reported to the European Group for Blood and Marrow Transplantation (EBMT) was performed by Milpied et al. [18]. The matching criteria were sex, age at time of transplantation, stage of disease at diagnosis, bone marrow involvement at diagnosis and at transplantation, year of transplantation, disease status at time of transplantation, time from diagnosis to transplantation, and conditioning regimen with or without TBI. The 4-year actuarial probabilities of survival, progression-free survival (PFS), relapse, and nonrelapse mortality (NRM) were 25, 15, 61, and 48 % and 37, 24, 61, and 27 % after allo-SCT and ASCT, respectively. The toxic death rate at 4 years was significantly higher for allo-SCT patients ($p=0.04$). Even for patients with sensitive disease at the time of transplantation, the 4-year actuarial probability of survival was 30 % after allo-SCT and 64 % after ASCT ($p=0.007$). This difference was mainly due to a higher NRM rate after allo-SCT (65 versus 12 %, $p=0.005$) that was basically associated with the development of acute GVHD after transplantation and/or concomitant infectious episodes. Although a GVHD > or = grade II was associated with a significantly lower risk of relapse, it was also associated with a lower OS rate.

A number of reports confirmed the registry data: allo-SCT resulted in lower relapse rates but significantly higher toxicity with no improvement over ASCT when PFS or OS were considered [19–21]. Although the poor results after myeloablative conditioning could at least partly be explained by the very poor-risk features of many individuals included in these early studies, the high procedure-related morbidity and mortality prevented the widespread use of allo-SCT.

20.2 Reduced-Intensity Regimens

Given the high NRM seen in adults with HL following myeloablative allo-SCT, the use of reduced-intensity or nonmyeloablative conditioning regimens would appear to be a potentially attractive option. The goal of these therapies is to reduce regimen-related toxicity while still providing sufficient immunosuppression to facilitate donor engraftment and a subsequent GVL effect. There are many published regimens ranging from the truly nonmyeloablative single fraction 2 Gy TBI to moderately myelosuppressive chemotherapy-based regimens which often combine fludarabine with an alkylator agent such as melphalan or busulfan. The aim of all of these regimens is to shift the balance from the antilymphoma activity of the conditioning regimen to the immune cells transferred with the donor graft which may mediate a graft

Table 20.1 Conditioning regimens

Study and regimen		Reference	Patient number	Median age (years)	NRM (%)	Relapse (%)	OS (%)	PFS (years)
EBMT	Various	[22]	285	31	21	59	29	25 % at 3 years
UCL	AMF/ ABEAM	[28]	76	31	17	44	64	39 % at 4 years
GEL/TAMO	MF ± ATG	[30]	92	28	17	59	43	18 % at 4 years
Seattle	F + TBI	[24]	90	28–33	0–18	40–63	53–58	23–51 % at 2 years
Houston	MF	[32]	58	32	15	55	57	32 % at 2 years
GITMO	Various	[39]	104	31	13	54	32	31 % at 2 years

NRM non-relapse mortality, *OS* overall survival, *PFS* progression-free survival, *EBMT* European Group for Blood and Marrow Transplantation, *A* alemtuzumab, *BEAM* BCNU, etoposide, ara-C, melphalan, *M* melphalan, *F* fludarabine, *ATG* antithymocyte globulin, *TBI* total body irradiation, *GITMO* Gruppo Italiano Trapianto di Midollo Osseo, *GEL/TAMO* Grupo Espanol de Linfomas/Trasplante de Medula Osea

versus lymphoma (GVL) response. The marked reduction in upfront toxicity of these regimens has extended the applicability of allo-SCT to older patients, those with comorbidities, and patients who had previously failed a prior ASCT.

The literature now contains several reports detailing the outcomes of reduced-intensity transplants for patients with relapsed HL (Table 20.1). These results can be difficult to compare due to the differing patient populations and conditioning regimens; however, in general, the TRM has been impressively reduced when compared to myeloablative conditioning regimens. This reduction in transplant mortality was confirmed by the lymphoma working party (LWP) of the EBMT which compared Hodgkin patients having standard myeloablative conditioning to those having reduced-intensity regimens between 1997 and 2002 [22]. Transplant-related mortality was 48 % at 3 years in the myeloablative group and 24 % in the reduced-intensity group ($p=0.003$; Fig. 20.1).

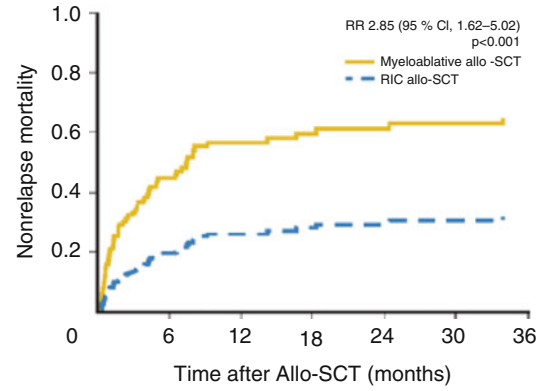

Fig. 20.1 Non-relapse mortality after allo-SCT for Hodgkin lymphoma, according to the type of conditioning regimen (Sureda et al. [22])

Although reduced-intensity conditioning (RIC) has allowed allo-SCT to be performed more safely, relapse is now the most common cause of treatment failure. Conditioning intensity/antilymphoma activity may be an important factor in determining relapse rates. This may be secondary to the requirement for a lengthy period of clinical remission to allow the incoming donor immune system to eradicate residual disease. An early GVL response is often delayed by the use of immunosuppressive drugs to prevent GVHD following T-cell-depleted transplantation or by the use of a T-cell-depleted graft which often necessitates the use of posttransplant donor lymphocyte infusions (DLIs). Some of the truly non-myeloablative regimens have been associated with particularly high relapse rates [23, 24]. This concept of regimen intensity being important is also supported by the EBMT analysis which showed a 32 % relapse rate following myeloablative conditioning compared to 58 % with reduced-intensity regimens [22]. Furthermore, within the

reduced-intensity group, there was a higher relapse and lower OS rate in patients who were conditioned with low-dose TBI which is one of the regimens with the least toxicity ($p<0.04$). Other studies have also shown a better outcome using more intensive regimens like the combination of fludarabine and melphalan when compared to less intensive regimens [25], and the BEAM-alemtuzumab regimen has also been demonstrated to give good disease control in the medium term [26].

There is mounting evidence that successful allogeneic transplantation for HL needs a combination of effective salvage CT and a moderately intensive pretransplant conditioning regimen to keep the disease under control for several months to allow the withdrawal of immunosuppression and/or the use of DLI to mount an effective GVL response.

20.3 Prognostic Factors of Long-Term Outcome for Allogeneic SCT

The introduction of RIC regimens in the allogeneic field has allowed a significant reduction in the NRM associated with the procedure in the population of HL patients [22]. The identification of independent prognostic factors may help to guide physicians in the choice of therapy for individual patients. However, the reported experience of RIC-allo in HL is limited in terms of number of patients included [24, 25, 27–29], making it difficult to identify independent predictors of outcome. The largest study published to date includes 78 patients with relapsed/refractory HL, most of them being treated with an allo-SCT because of a relapse after an ASCT [30].

The LWP of the EBMT performed a retrospective analysis comprising a population of 285 patients with relapsed or refractory HL treated with a reduced-intensity allo-SCT in order to try to identify prognostic factors for long-term outcome [31]. Sixty patients died of NRM at a median of 91 days (range 1 day–20 months) following transplantation. The cumulative incidence estimates of NRM at 100 days and 1 and 3 years posttransplant were 10.9, 19.5, and 21.1 %, respectively. In multivariate analysis, NRM was associated with poor performance status, chemorefractory disease at transplantation, age greater than 45, and transplantation before 2002. Identifying poor PS, chemorefractory disease, and older age as adverse risk factors for NRM, patients with no adverse risk factors had a 3-year NRM rate of 12.5 % compared with 46.2 % for those with two or three risk factors. Interestingly, the use of an unrelated donor and a single prior high-dose procedure had no impact on the NRM. With a median follow-up of 26 months (range 3–94 months), 126 patients remained alive and 159 have died. The Kaplan-Meier estimates of OS and PFS at 1, 2, and 3 years were 67 and 52 %, 43 and 39 %, and 29 and 25 % respectively. In multivariate analysis, patients in complete remission (CR) or with chemosensitive disease, those with a good performance status, transplants other than sex-mismatched male recipients, and CMV −/−transplants had a significantly better OS. For PFS good performance status, CR or chemosensitive disease at transplantation and transplants other than male recipients from female donors were associated with a significantly better PFS in the multivariate analysis. Considering chemorefractory disease and poor performance status as risk factors for a poor OS and PFS, patients with neither of these risk factors have a 3-year PFS and OS of 42 and 56 % compared to 8 and 25 % for patients with one or two of these risk factors. In an analysis restricted to patients who had relapsed after a prior ASCT, relapse within 6 months of the autograft was associated with a significantly worse disease progression rate (RR = 1.9 (1.2–3.1) $p=0.01$) and PFS (RR = 1.9 (1.2–2.9) $p=0.003$) following reduced-intensity allo-SCT. Reduced-intensity allo-SCT may be an effective salvage strategy for patients with good risk features who relapse after an ASCT (Fig. 20.2), and those outcomes are similar for both sibling and matched unrelated donor (MUD) transplants. Conversely for patients with chemorefractory disease or a poor performance status, the overall outcome is poor, and it is difficult to recommend reduced-intensity conditioning allo-SCT for these patients.

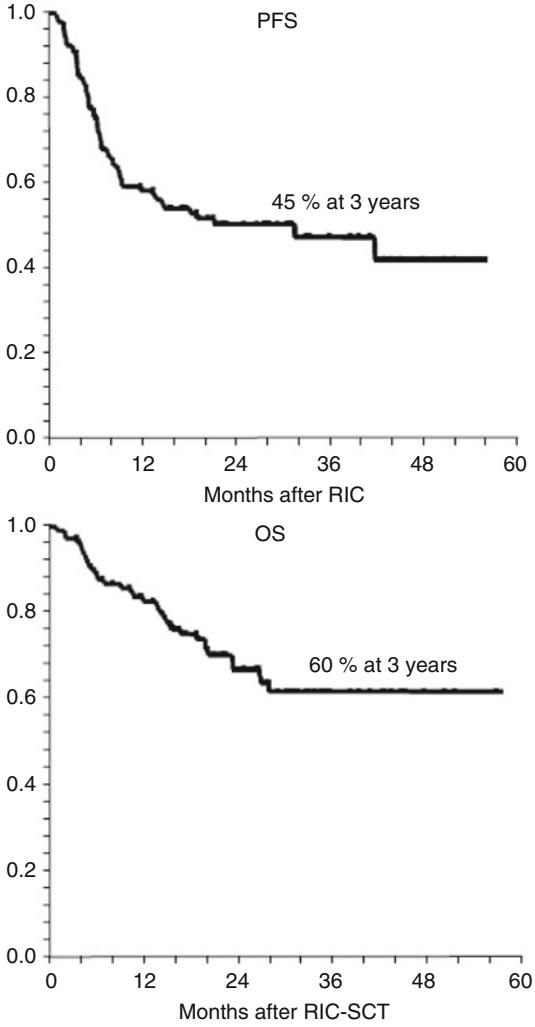

Fig. 20.2 Progression-free survival (*PFS*) and overall survival (*OS*) in patients with HL treated with a reduced-intensity conditioning regimen allogeneic transplantation and showing good prognostic factors at the time of allo-SCT. Patients with chemosensitive disease and good performance status at SCT treated with a RIC SCT in the period 2002–2005 ($n=104$) (Robinson et al. [31])

These results are in agreement with what has already been published in smaller series of patients. The UK Cooperative Group reported that disease status before allo-SCT was the strongest prognostic factor for PFS and OS, the results being significantly better for those patients allografted in CR [28]. Disease status was also the strongest factor predicting for survival in the Spanish series [29] as well as in the updated MDACC [32], although both studies include small number of patients that preclude more specific studies. In the HDR-Allo trial [30], chemosensitivity was the most important prognostic factor (HR = 2.3; 95 % CI, 1.3–3.1; $P=0.001$) for PFS. Patients allografted in CR had the best outcome, with PFS rates at 1 and 4 years of 70 % (95 % CI, 67–73) and 50 % (95 % CI, 47–53), respectively. Refractory disease and a poor performance status were associated with a significantly worse OS (HR 1.9, 95 % CI, 1.0–2.7, $P=0.001$ and HR 2.5, 95 % CI, 1.3–4.2, $P=0.01$, respectively) in the same study.

20.4 Evidence for Graft Versus Hodgkin Lymphoma

Despite the theoretical reliance of reduced-intensity transplantation on a GVL effect, there are relatively few studies which convincingly demonstrate this activity in Hodgkin lymphoma. Many of the myeloablative transplants done in adults had such a high NRM that it would have been almost impossible to see a GVL effect if one had existed. In the context of reduced-intensity transplantation, there is some evidence of a reduction in relapse in association with GVHD. Conversely, the apparent lack of impact of T-cell depletion on relapse risk is unexpected. This finding might simply be a function of the relatively small numbers of patients reported or it is possible that the in vivo monoclonal antibody used to facilitate T-cell depletion may have anti-Hodgkin lymphoma activity.

The most convincing evidence of GVL activity in HL comes from the use of DLI to treat patients who relapse following allo-SCT (Table 20.2). Response rates to DLI have been reported to be between 15 and 60 %, with complete responses seen in around 30 % of patients. Many of these patients had received concurrent CT or radiotherapy but responses have been seen to DLI alone and some of these have been durable. There appears to be a higher response rate in the UK series and it is not known whether the high incidence of mixed chimerism seen in patients who received alemtuzumab promotes

Table 20.2 Donor leukocyte infusions for relapse

Study and regimen	Reference	Patient number	CR/PR	Response at last follow-up
UK	[28]	24	14/5	12 CR/2 PR at 2+ years
Houston	[32]	14	3/3	1 PR at 3+ years
GEL/TAMO	[29]	20	6/5	None ongoing
SFGM/TC	[47]	30	3/5	Not reported
EBMT	[22]	41	13/4	Not reported
Total		129	39/22	12 CR/3 PR

CR complete remission, *PR* partial remission

GVL responses as it does in some animal models. The optimal T-cell dose for GVL remains unclear, although many groups use an escalating dose schedule to try and reduce the risk of severe graft versus host disease. Unlike follicular lymphoma, there is preliminary evidence that in relapsed HL, GVL responses are unlikely in the absence of GVHD. However, when DLI are given for mixed chimerism, there appears to be a GVL effect that is independent of GVHD [33]. There are a number of factors that may increase the toxicity of DLI including: increasing age of the patient, HLA mismatching, use of unrelated donors, and short time interval from transplant to DLI infusion. Although the DLI responses are impressive in some patients, the majority of patients will not achieve long-term benefit from DLI and further study is needed to optimize this potential effect.

20.5 Role of Allogeneic SCT in Autograft Failures

It has been demonstrated that HDT with autologous stem cell rescue can successfully salvage many of these relapsed/refractory patients, with two randomized studies demonstrating the superiority of such treatment over conventional-dose salvage CT [3, 4].

In contrast, results with myeloablative allogeneic transplantation in adults with HL have been disappointing, with high NRM. No randomized studies comparing autologous transplantation and allogeneic transplantation exist, but a retrospective EBMT registry study reported improved outcome post autograft, and this has become the consolidation of choice in relapsed or refractory disease [18]. Despite the success of autologous transplantation, there remains a cohort of patients whose disease progresses/relapses following transplant, and the outcome in this group is extremely poor, with a median survival post relapse of less than 1 year [34, 35].

Although some patients achieve good outcomes following a second autologous transplant, these have generally represented a highly selected group who relapsed more than 3 years post first autologous transplant [36]. In addition to the small group of patients who may benefit from a second autograft, there are a number of patients who relapse following autologous transplantation who may not be suitable candidates for a reduced-intensity allo-SCT. These might include patients with poorly controlled aggressive relapse and patients who have multiple comorbidities who have either a high relapse rate or treatment-related mortality with allogeneic transplantation.

With the advent of RIC regimens, there has been renewed interest in allogeneic transplantation for patients who relapse following an autograft [25, 37]. This is because of the introduction of RIC protocols which have dramatically reduced the NRM [28]. Although there are no randomized trials comparing the results of CT ± radiotherapy in patients who relapse post autograft, comparisons have been made with the outcomes of historical controls. The UK group identified a group of patients who had relapsed following a BEAM autograft, who were chemosensitive at relapse and had survived at least 12 months from relapse, and who would

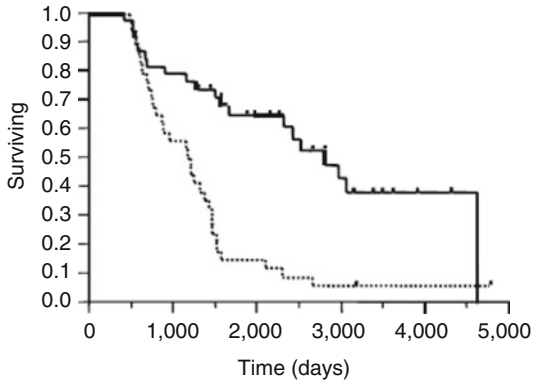

Fig. 20.3 Overall survival from autograft for the allogeneic transplant group ($n=38$; *solid line*) and the control group ($n=34$; *dotted line*). Estimated OS for the allogeneic group at 5 years is 65 % and the control group 15 %, $p \leq 0.0001$ (Thomson et al. [40])

therefore have been eligible for a reduced-intensity transplant [38]. This was a highly selected group representing 44 % of all relapses who were predicted to have the best survival. These conventionally treated patients were compared to more recently treated patients who received a reduced-intensity allograft. The groups did not differ significantly in age, number of lines of prior therapy, or in time from diagnosis to autograft, but there was a small difference in time from relapse to autograft (13 months for the allograft group versus 10 months in the CT ± radiotherapy group). Conversely, 34 % of the allograft group were chemorefractory following salvage. Despite the selection of a control group with a relatively good prognosis, both overall survival from time of diagnosis and time of autograft were significantly improved following allogeneic transplant, when compared to the historical control group. The estimated current PFS for the allografted patients was 34 % at 5 years and 42 % if in chemosensitive relapse at the time of transplant, suggesting the early promising results might translate into a favorable long-term outcome (Fig. 20.3). A recently published study had similar outcomes and showed an advantage for allogeneic transplant over CT alone in patients with poor-risk HL who had relapsed following ASCT [39].

20.6 Moving Allogeneic Stem Cell Transplantation to Earlier Stages of the Disease

The more recent investigation of a response-adjusted transplantation algorithm identifies a further potential strategy for evaluation of allo-SCT in those deemed to be at high risk of failure of ASCT, targeting the intensification to those who have residual FDG-avid disease following salvage therapy [40]. The 3-year PFS of 68 % in this high-risk group was encouraging, with 80 % current PFS following DLIs. Such approaches may require refinement according to delineation of number of lines of salvage and according to the outcome of prospective studies evaluating maintenance strategies following ASCT (e.g., the AETHERA trial). It is thus recommended that they be evaluated within the context of prospective national studies. In fact, these results have constituted the basis for a phase II prospective clinical trial (CRUK-PAIReD, EUDRACT-2008-004956-60) already closed for recruitment that analyzes long-term outcome of relapsed/refractory HL patients that do not achieve a metabolic CR with first-line salvage chemotherapy and undergo an allo-SCT with BEAM protocol as conditioning regimen and the use of Campath-1H as GVHD prophylaxis. Final results of this trial are eagerly awaited by the transplant community.

20.7 Role of Allogeneic SCT in the Pediatric Population

Information regarding the role of allo-SCT for HL in the pediatric population is very limited. Children undergoing allogeneic HSCT have been occasionally included in series of adult patients [19–22], whereas exclusively pediatric series were limited to fewer than ten patients [41].

The most extensive analysis of allo-SCT in the pediatric population comes from the LWP of the EBMT, and it comprises a group of 91 children and adolescents 18 years or younger treated with an allograft (myeloablative, $n=40$; reduced

intensity, $n=51$) for relapsed or refractory HL [42]. Comparing patients who received MAC with RIC, the latter group had a longer time interval between diagnosis and allo-SCT, had failed more lines of therapy including HDT and ASCT, and was significantly older than patients who underwent transplantation after conventional conditioning. No significant differences existed in the percentages of patients grafted in CR, partial remission (PR), refractory disease, or untreated relapse and the performance status at the time of transplantation. In addition, the percentages of patients with HLA-identical sibling donors, other matched related or unrelated donors, as well as mismatched donors were not significantly different. Not surprisingly, patients with reduced-intensity conditioning underwent transplantation more recently and preferentially received mobilized peripheral blood stem cells. NRM at 1 year was 21 %, with comparable results after reduced-intensity or myeloablative allo-SCT. Probabilities of relapse at 2 and 5 years were 36 and 44 %, respectively. Reduced-intensity conditioning allo-SCT was associated with an increased relapse risk compared with myeloablative transplantation, which was most apparent beginning 9 months after allo-SCT ($p=0.01$). PFS was 40 and 30 % and OS was 54 and 45 % at 2 and 5 years, respectively. Beyond 9 months, PFS after reduced-intensity allograft was lower compared with myeloablative protocols ($p=0.02$). The development of GVHD did not have any impact on PFS after allo-SCT. Of note, the 26 patients with sensitive disease and good performance status who underwent transplantation between 2002 and 2005 showed a PFS of 60 % (95 % CI: 33–87 %) and OS of 83 % (95 % CI: 67–98 %), respectively, at 3 years. Fifteen of these patients (58 % of the group) had previously failed ASCT. This retrospective analysis in a pediatric population of patients raises again the question of the exact dose intensity needed in HL patients. Because relapse now is the major problem after allogeneic transplantation for HL in pediatric as well as in adult patients, it may be wise to use myeloablative or "intermediate" conditioning at least in those children and adolescents who have a good performance status. Alternatively, other attempts to debulk the tumor before SCT – using aggressive salvage therapy or HDT – should be considered.

20.8 Alternative Donor Transplants

In Europe and North America, only around a third of patients will have an HLA-matched sibling donor; therefore the use of alternative donors is essential to expand the number of patients eligible for the procedure. The advent of molecular techniques has improved the accuracy of tissue typing reports but the associated increase in HLA polymorphism has made finding an exact molecularly matched donor more difficult. However, the continual increase in unrelated donor numbers, the availability of cord blood, and the use of T-cell depletion have allowed a rise in the number of alternative donor transplants to be performed.

Although the number of published studies using unrelated donors remains limited at present, the transplant outcomes appear similar to those using sibling donors [22, 28, 32, 43]. Not surprisingly, rates of GVHD may be higher and many groups have used T-cell depletion strategies with either alemtuzumab or ATG to reduce the incidence of this complication. Interestingly, unrelated donor transplants in patients with HL appear to have a similar overall survival and PFS to sibling donor transplants [22, 28]. Therefore, consideration of an unrelated allogeneic transplant may be an appropriate option for patients relapsing after autologous transplantation.

The published experience with cord blood donors in HL is much more limited but may be feasible [44, 45]. While cord blood may have a GVL effect on its own, the high relapse rate seen with reduced-intensity regimens may restrict the use of this donor source where there is no opportunity to use DLI. A Eurocord-Netcord study showed a 30 % progression-free survival at 1 year in patients with relapsed Hodgkin lymphoma [46]. A recently published French study showed that use of a cord blood donor was associated with inferior survival [47]. Longer-term follow-up of these patients will obviously be

necessary to determine whether the GVL activity of the cord blood obviates the need for posttransplant DLI. Finally, haploidentical donors have been used in a small series, indicating that this may also be a useful donor source, although follow-up is too short to determine the long-term impact of this approach [24, 48].

20.9 The Role of Allogeneic Stem Cell Transplantation in the Era of New Drugs

Brentuximab vedotin (BV) is an antibody-drug conjugate that selectively delivers monomethyl auristatin E, an antimicrotubule agent, into CD30-expressing cells. In phase I studies, BV demonstrated significant activity with a favorable safety profile in patients with relapsed/refractory CD30-positive lymphomas. The interesting results seen in the phase I trial lead to a phase II that evaluated the efficacy and safety of BV. The drug was given at doses of 1.8 mg/kg by intravenous infusion every 3 weeks up to a maximum number of 16 cycles in 102 patients with relapsed or refractory HL after ASCT [49]. Overall response rate (ORR) was 75 % with a CR in 34 % of patients. The median PFS for all patients was 5.6 months, and the median duration of response for those in CR 40.5 months. After a median observation of 3 years, 31 patients were alive and free of documented progressive disease. The drug was quite well tolerated: the most common treatment-related adverse events were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea. BV has been used in the pre-allo-SCT setting, as a "bridge to allo" and in the post-allogeneic setting to treat patients with relapsed/progressive disease after the allogeneic procedure. Chen et al. [50] have recently published their experience on 18 patients with multiply relapsed HL undergoing a RIC/allo-SCT after being treated with BV as salvage therapy. NRM and acute and chronic GVHD preferred incidence after the allogeneic procedure were not significantly different from what was previously described. With a median follow-up of only 12 months, PFS was 100 %. In a retrospective analysis comparing outcomes after allo-SCT in relapsed/refractory HL patients, Chen et al. [51] also found that the administration of BV as a bridge to transplant significantly increased the percentage of patients achieving a CR. Thus improving comorbidity of patients before the allo transplant might decrease NRM and increase both response and overall survival in these patients.

The widespread use of BV in patients with HL relapsing after ASCT will most certainly change the treatment paradigm of this subgroup of patients, either avoiding the allogeneic procedure in some patients or by increasing the group of potential candidates to an allogeneic transplant being used as a "bridge to allo." Additional information on long-term outcome of patients being treated with this drug or the development of prospective clinical trials in this setting will most probably give some light to this questions we have nowadays.

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Targeting CD30 in Patients with Hodgkin Lymphoma

21

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21.1 Introduction

The introduction of multi-agent chemotherapy for the treatment of Hodgkin lymphoma is one of the major breakthroughs in clinical oncology. Chemotherapy and improved radiation methods have significantly improved the chance of curing these patients from less than 5 % in 1963 to about 80 % at present [1–3]. However, there is still a substantial need to improve current treatment approaches particularly for elderly patients or those with relapsed and refractory disease [4–6]. Cured patients unfortunately are at high risk for late side effects including second malignancies, cardiac toxicity, infertility, and fatigue [7–9]. Thus, there is a clear need for new and safer drugs that are more selective in targeting the malignant Hodgkin and Reed-Sternberg (HRS) cells in this disease while sparing normal tissues.

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_21,

CD30 is a cell surface protein that is highly expressed on HRS cells. CD30 is rarely expressed by normal tissue, making it ideal for targeted therapy. In fact, soon after the identification and characterization of CD30, monoclonal antibodies against this protein were evaluated as potential therapeutics. Although several preclinical experiments established the proof of principle for this treatment strategy, early clinical trials with either naked monoclonal antibodies or a variety of immunoconjugates, including immunotoxins and radioimmunoconjugates, against CD30 either did not demonstrate sufficient clinical activity or were too toxic [10–15]. The lack of meaningful clinical efficacy of naked anti-CD30 antibodies in patients with Hodgkin lymphoma (HL) remains poorly understood, but several hypotheses have been proposed: CD30 is internalized and, thus, does not allow sufficient time for engagement with effector cells. In addition, CD30 is shed in the serum in a soluble form, which may neutralize the efficacy of the antibodies; the early versions of anti-CD30 antibody were not ideal for binding CD30 or effector cells. More recently, advances in linker technology allowed the development of novel and potent antibody-drug conjugates (ADC), such as brentuximab vedotin. This overview will highlight pathophysiology and current clinical experience when targeting CD30 in patients with Hodgkin lymphoma.

21.2 Structure and Function of CD30

In a landmark paper published in 1982, Stein and colleagues identified a new monoclonal antibody called Ki-1 that recognized a new antigen expressed on HRS cell, called CD30 [16]. Originally thought to be specific for HRS cells of Hodgkin lymphoma (HL), it was later found on small subsets of paracortical lymphocytes and a few other malignancies, inlcuding anaplastic large cell lymphoma (ALCL) [17–19]. The major limitation of the Ki-1 antibody was the need for fresh or frozen material, which allowed its application only in a limited number of reference centers. This was overcome by the generation of the Ber-H2 monoclonal antibody detecting an epitope of the molecule different from Ki-1 and applicable in routine formalin-fixed paraffin-embedded tissue samples.

Ten years after the identification of the CD30 antigen, the same group cloned the cDNAs coding for CD30 from expression libraries of the human HUT-102 cell line using the monoclonal antibodies Ki-1 and Ber-H2. The open reading frame of the cDNA predicted a 595-amino acid transmembrane protein. The extracellular domain contained six cysteine-rich motifs and shared sequence homology with members of the tumor necrosis factor (TNF) superfamily [20, 21]. The cytoplasmic tail contains several TNF receptor-associated-factor (TRAF)-binding sequences that mediate activation of pleiotropic signals, including activation of nuclear factor kappa-B (NK-κB) [22, 23]. CD30 has a broad range of biologic effects depending on the cellular context, including regulation of cytokine secretion and inflammation, induction of apoptosis, and promotion of cell survival and proliferation [24]. The ligand for CD30 (CD30L, CD153) is a 26-kDa type II transmembrane protein that belongs to the TNF superfamily and maps to chromosome 9q33 [25]. CD30L is expressed in both resting and activated B cells, activated T lymphocytes, monocytes, granulocytes, and natural-killer cells [26, 27].

The exact physiologic function of CD30/CD30L in healthy individuals remains poorly understood, as no human diseases have been associated with alterations in CD30 or CD30L genes. Furthermore, CD30 knockout mice experiments gave conflicting results regarding a possible role of CD30 in thymocyte negative selection [28, 29]. Other studies suggested that CD30-CD30L signaling may be involved in immunoregulation, such as class-switch DNA recombination and antibody production in B cells [30]. CD30 may also play a role in self-tolerance and pathogenesis of autoimmune disorders [31, 32], in addition to regulating Th1 and Th2 cell responses [33–35], CD4+ T-cell-mediated graft-versus-host disease [36], and CD30+ Treg cells [37].

21.3 Therapeutic Targeting of CD30

CD30 is an excellent target for monoclonal antibody therapy due to its restricted expression. A few years after the initial description of the first monoclonal antibody against CD30, Ki-1 [16], monoclonal antibodies such as Ki-4 and Ber-H2 were generated that had higher affinity for the CD30 antigen [30]. Subsequently, these antibodies were conjugated to ricin A chain to form specific immunoreagents. These so-called immunotoxins were extremely effective and specific in vitro and in different animal models [10, 11]. However, a subsequent clinical phase I/II trial using the ricin A-chain immunotoxin Ki-4.dgA targeting CD30 showed little clinical activity in a total of 18 patients with refractory HL. This immunotoxin was associated with vascular leak syndrome as dose-limiting toxicity [14]. In addition, most patients developed anti-ricin antibodies so that further clinical development of this immunotoxin in HL was abandoned. An alternate strategy used the murine anti-CD30 monoclonal antibody (Ber-H2) as carrier for a cytotoxic agent by covalently linking Ber-H2 to saporin (SO6), a type-1 ribosome-inactivating protein [12]. Four patients with advanced refractory HL were treated, and three patients had transient tumor reduction [13]. Human antibodies, however, developed against the murine antibody and the toxin in all patients preventing repeat dosing; thus, further development of this immunotoxin was also stopped.

21.4 Monoclonal Antibodies

Clinical results from first-generation naked monoclonal antibodies targeting CD30 were disappointing, possibly due to their poor antigen-binding properties, ineffective activation of effector cells, and neutralization by soluble CD30 [14, 38, 39]. MDX-060, a fully human anti-CD30 monoclonal antibody, was tested in a phase I/II study in patients with HL, ALCL, and CD30+ PTCL. This antibody had minimal toxicity, and the maximum tolerated dose (MTD) was not reached [15]. However, MDX-060 had minimal clinical activity with 6 responses in 72 patients and was subsequently abandoned. SGN-30, a CD30-specific chimeric antibody constructed from the variable regions of the anti-CD30 murine monoclonal AC10 and human gamma 1 heavy chain and kappa light chain constant regions, was also tested in phase I/II studies. A phase I study of SGN-30 in 24 HL or CD30+ non-Hodgkin lymphoma (NHL) patients demonstrated that SGN-30 was well tolerated, but only one patient with cutaneous ALCL achieved a complete response (CR) [38]. The phase II results of SGN-30 also showed only modest clinical activity with 9 % overall response (2 CRs and 5 partial responses (PR) of 79 patients treated); all responses were limited to patients with ALCL [40]. Given preliminary evidence of selective efficacy of SGN-30 in cutaneous ALCL, SGN-30 was further tested in a phase II study of cutaneous diseases including cutaneous ALCL, lymphomatoid papulosis, and transformed mycosis fungoides; the response rate in this trial was 70 % [41]. SGN-30 was subsequently combined with chemotherapy because preclinical data showed that SGN-30 sensitizes tumor cells to cytotoxic agents and single-agent phase I/II data demonstrated only modest efficacy [42]. In a Cancer and Leukemia Group B randomized phase II trial of SGN-30 with gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD) in relapsed HL patients, 30 patients were treated; however, five patients developed grade 3–5 pneumonitis, leading to premature closure of the trial [43]. The combination of SGN-30 and GVD was not only associated with significant toxicity, but also was not associated with better outcomes compared to GVD alone. Given the disappointing results with first-generation naked monoclonal antibodies, a second-generation anti-CD30 humanized antibody, XmAb2513, with improved antigen-binding and enhanced Fcγ receptor IIIA affinity was developed demonstrating increased efficacy in vitro when compared to MDX-060 or SGN-30 [44]. Preliminary results of the phase 1 study of

XmAb2513 found the drug to be well tolerated, but not associated with superior efficacy compared to first-generation monoclonal antibodies. Of 13 HL patients treated, tumor reduction was observed in 3 patients [45].

21.5 Bispecific Monoclonal Antibodies

A different approach to targeting CD30 was the development of bispecific monoclonal antibodies, engaging NK cells or neutrophils as effector cells [10, 46]. A construct based on the anti-CD30 monoclonal antibody Ki-4 and the human anti-CD64 monoclonal H22 showed very promising preclinical activity. In the phase I clinical trial, H22xKi-4 was very well tolerated; responses included one CR, four PRs, and four SDs in a total of ten patients treated [10]. More recently, a bispecific TandAb antibody, AFM13, was reported [47]. AFM13 targets both CD30 on HL tumor cells and CD16A on NK cells. Preclinical data demonstrated antitumor activity with engagement of NK immune effector cells. A phase 1 study of AFM13 in 28 HL patients found the drug safe and well tolerated, but with a modest activity. Overall, 3 of 28 patients achieved partial remissions [47].

21.6 Radiolabeled Antibodies

Schnell et al. developed a radioimmunoconjugate consisting of the murine anti-CD30 monoclonal antibody Ki-4 labeled with iodine-131 (^{131}I). Twenty-two HL patients were treated with ^{131}I-Ki-4 to total body doses ranging from 0.035 to 0.99 Gy. Although there were six responses (one CR and five PRs), a significant rate of severe hematologic toxicity was observed with seven patients having grade 4 hematologic toxicity 4–8 weeks posttreatment, leading to the cessation of its further development [48].

21.7 Antibody-Drug Conjugates

Brentuximab vedotin is an antibody-drug conjugate (ADC) consisting of the chimeric monoclonal antibody, cAC10, that was conjugated to monomethyl auristatin E (MMAE) [49, 50]. MMAE is a synthetic analog of the natural product dolastatin 10 and functions as a tubulin inhibitor. MMAE is covalently linked to cAC10 via a maleimidecaproyl-valyl-citrullinyl-*p*-aminobenzylcarbamate linker [51]. On average, four molecules of MMAE are conjugated to one cAC10. The mechanism of action of brentuximab vedotin is shown in Fig. 21.1 and involves

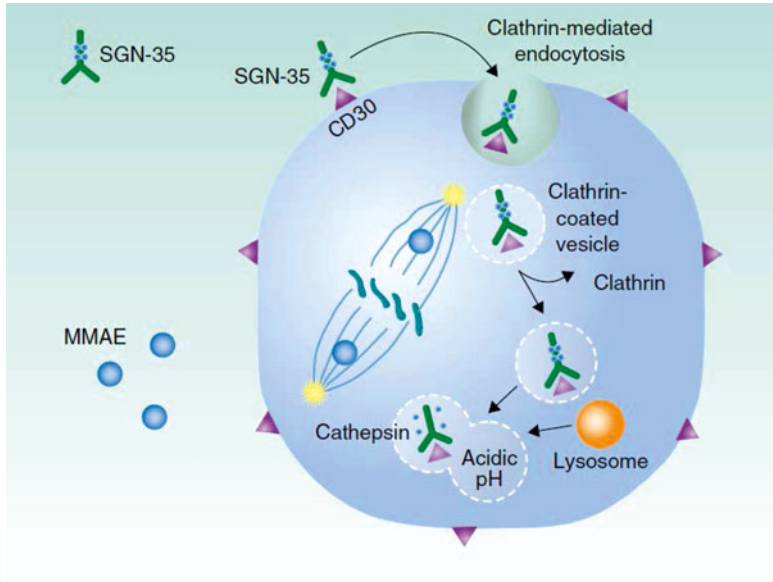

Fig. 21.1 Mechanism of action of brentuximab vedotin (SGN-35) (Figure was adapted from: Katz et al. [50])

the following steps: (1) binding of the anti-CD30 ADC via the antibody moiety to CD30 expressed on tumor cells in high density, (2) receptor-mediated endocytosis of brentuximab vedotin and intracellular internalization occurring via clathrin-mediated uptake, (3) uptake of the drug into lysosomal vesicles, (4) MMAE is released from the antibody by reduction or acid hydrolysis within lysosomes, and (5) MMAE is released into cytoplasm and inhibits microtubule polymerization leading to arrest of the G2/M phase of the cell cycle, thereby inducing cellular apoptosis [50]. In addition, there is also a small amount of MMAE released into the tumor microenvironment that may alter survival signaling to the HRS cell. Preclinical studies with cAC10-vcMMAE demonstrated stable linkage of the ADC in circulation and efficient release upon internalization into target cells. In addition, cAC10-vcMMAE was found to have significant antitumor activity in HL and ALCL cell lines with an IC_{50} of 10 ng/ml and antitumor activity in subcutaneous disease xenograft models [51].

21.8 Single-Agent Experience with Brentuximab Vedotin

21.8.1 Phase I Studies

The initial first-in-man, multicenter, dose-escalation phase I study enrolled 45 patients with relapsed or refractory CD30-positive hematologic cancers, including 42 HL and 3 ALCL patients. Brentuximab vedotin was administered intravenously every 3 weeks at doses ranging from 0.1 to 3.6 mg per kilogram. Dose-limiting toxicities were grade 4 thrombocytopenia, grade 3 hyperglycemia, and febrile neutropenia. Remarkably, tumor regression was seen in 86 % of evaluable patients, and the MTD was defined at 1.8 mg/kg every 3 weeks. Eleven patients achieved complete responses and 6 achieved partial remissions. The median duration of response was at least 9.7 months. When the analysis was restricted to patients receiving the dose of 1.8 mg/kg or greater, 6 of 12 patients responded (50 %), including 4 complete remissions.

A second phase I study evaluated the safety and efficacy of brentuximab vedotin given on days 1, 8, and 15 in a 28-day cycle (3 weeks on, followed by 1 week of rest). This study demonstrated similar efficacy (ORR 59 % and tumor regression in 85 % of patients). Given the ease of administration of every 3-week dosing and similar response rates across the two dosing schedules, the 1.8 mg/kg every 3 weeks was selected for further development in phase II studies.

21.8.2 Phase II Studies

A pivotal phase 2 study was conducted in 102 patients with relapsed and refractory HL after receiving autologous stem cell transplantation (ASCT), to determine the efficacy and safety of brentuximab vedotin [52]. Patients received 1.8 mg/kg brentuximab vedotin every 3 weeks as a 30-min outpatient infusion (capped dose at 180 mg) for up to 16 cycles. There was no limit on the number of prior treatment regimens (median of 3.5; range 1–13 regimens). All patients had failed ASCT with a median time to relapse after ASCT of 6.7 months (range 0–131 months). Patients received a median of 9 cycles of brentuximab vedotin, and the overall response rate was 75 % (33 % CRs). In a waterfall plot analysis (Fig. 21.2), 94 % of patients had tumor regression. Responses were rapid, with a median time to treatment response of 5.7 weeks and the median time to achieving complete remission of 12 weeks. The median progression-free survival for all patients was 5.6 months [53]. An updated analysis with a median follow-up time of 32.7 months found that the median overall survival was 40.5 months; this was highly impacted by treatment response: median OS for patients with CR ($n=34$), not reached yet; partial remission ($n=42$), 31.6 months; stable disease ($n=22$), 20.6 months; and progressive disease ($n=3$), 10.2 months. Of the 51 patients alive in May 2013, 14 remained in durable remission after BV treatment, and of these, 9 have not started a new anticancer therapy, and 5 patients received consolidative allogeneic SCT. Of these 14

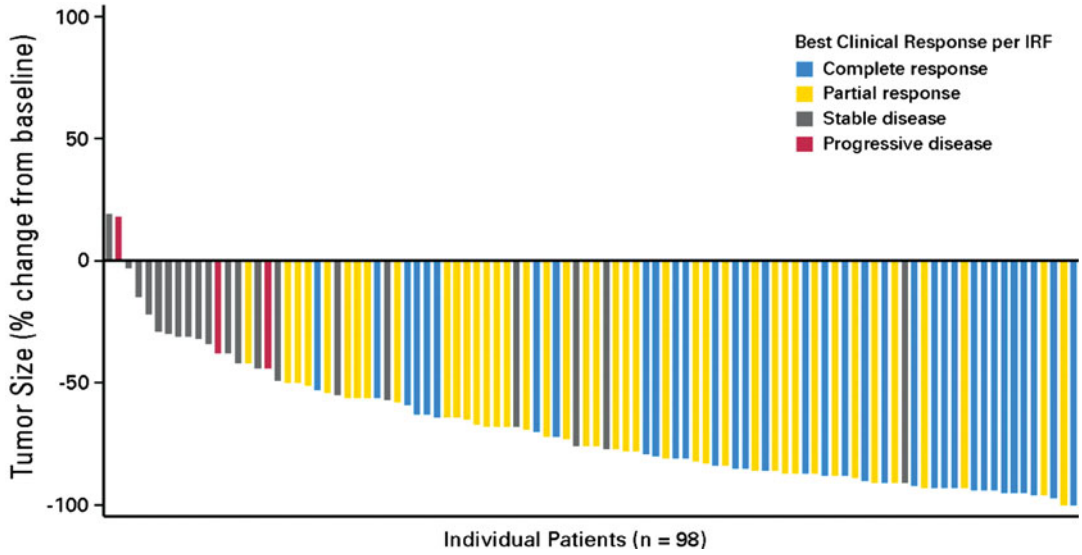

Fig. 21.2 Maximum percent reduction in sum of the product of diameters in individual patients ($n = 98$) in the pivotal phase II trial of brentuximab vedotin for relapsed and refractory Hodgkin lymphoma (Figure was adapted from Younes et al. with permission [52])

patients, 11 had CRs and 3 had PRs following brentuximab vedotin (the patients who achieved PR received consolidative allo-SCT). These data suggest that a fraction of multiple relapsed and refractory HL patients achieving CR after treatment with brentuximab vedotin have long-term durable remissions and may be cured with this drug alone. In addition, the safety and efficacy of brentuximab vedotin (1.2 or 1.8 mg/kg every 3 weeks) in 25 patients who relapsed after allogeneic stem cell transplantation has also been demonstrated [54].

Brentuximab vedotin was also studied in 58 patients with relapsed or refractory ALCL in a phase 2 study [55]. The overall response rate was 86 % and CR rate 59 %. In addition to HL and ALCL, single-agent brentuximab vedotin is being studied in ongoing phase II studies in patients with various CD30+ malignancies, including peripheral T-cell lymphoma, B-cell non-Hodgkin lymphoma including DLBCL, and cutaneous T-cell lymphoma with varying response rates (Fig. 21.3) [56–58].

21.9 Safety and Tolerability of Brentuximab Vedotin

In the two phase I studies of brentuximab vedotin, the dose-limiting toxicities included cytopenias, diarrhea, vomiting, and hyperglycemia [59, 60]. Data from phase I and II studies of brentuximab vedotin have characterized the adverse effects of the drug, including peripheral sensory neuropathy, nausea, fatigue, neutropenia, diarrhea, pyrexia, vomiting, arthralgia, pruritus, myalgia, peripheral motor neuropathy, and alopecia [52, 55]. In phase II studies, approximately 55 % of patients experienced adverse grade 3 and 4 events including peripheral sensory neuropathy (8–12 %), neutropenia (20–21 %), anemia (6–7 %), and thrombocytopenia (8–14 %). The associated peripheral neuropathy is typically cumulative and most commonly grade 1–2 characterized by numbness or tingling in the fingers and toes. In addition, 11–14 % of patients had grade 3 peripheral neuropathy; no grade 4 was seen. Approximately 80 % of patients with

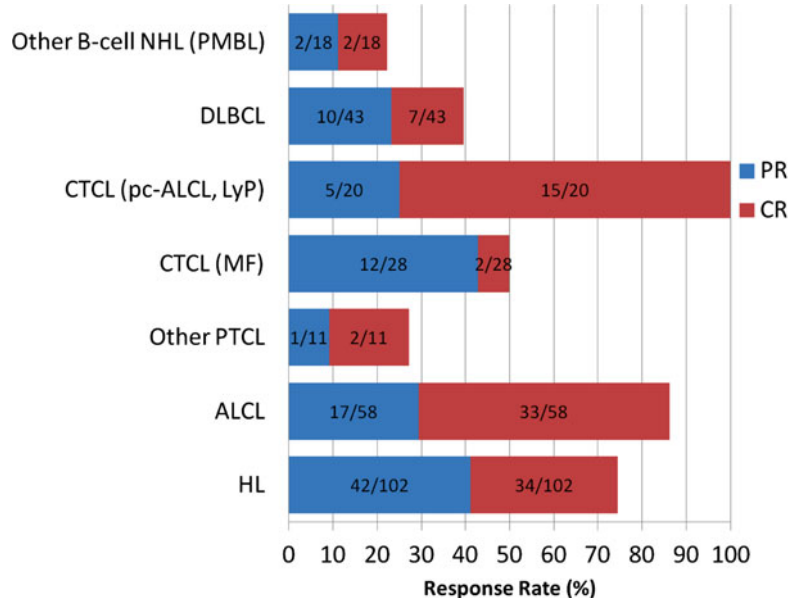

Fig. 21.3 Response rates in phase II studies with single-agent brentuximab vedotin. Abbreviations: *CR* complete response, *PR* partial response, *HL* Hodgkin lymphoma, *ALCL* anaplastic large cell lymphoma, *PTCL* peripheral T-cell lymphoma, *CTCL* cutaneous T-cell lymphoma, *MF* mycosis fungoides, *pc-ALCL* primary cutaneous anaplastic large cell lymphoma, *LyP* lymphomatoid papulosis, *DLBCL* diffuse large B-cell lymphoma, *NHL* non-Hodgkin lymphoma, *PMBL* primary mediastinal B-cell lymphoma

peripheral neuropathy experienced clinical improvement after dose reduction or cessation of drug, and 50 % experienced complete resolution. As a result of these data, significant cytopenias or neuropathy should prompt consideration for dose modification, delay, or discontinuation. Overall, brentuximab vedotin is well tolerated with manageable side effects and few serious adverse events. A few cases of fatal progressive multifocal leukoencephalopathy associated with John Cunningham (JC) virus infection have been reported in patients treated with brentuximab vedotin resulting in the addition of a boxed warning to the drug's label [61]. The pathogenesis of JC virus reactivation and PML in patients treated with brentuximab vedotin is not clear. It is hypothesized that patients who are multiply treated and immunocompromised are likely at higher risk.

Brentuximab vedotin is currently being combined with chemotherapy for the up-front treatment of lymphoid malignancies in ongoing clinical trials, and new toxicities are emerging. For example, in a phase I study of brentuximab vedotin combined with ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) chemotherapy, significant pulmonary toxicity (40 %) was described in conjunction with bleomycin. Therefore, these drugs cannot be safely administered together [62]. In older patients treated with brentuximab vedotin, higher rates of cytopenias, neuropathy, fatigue, and grade 3 toxicity occurred when compared to younger patients [63]. In a study of sequential brentuximab vedotin and AVD for older patients with untreated Hodgkin lymphoma, single-agent brentuximab vedotin resulted in six of seven patients with ≥ grade 3 serious adverse events (SAE) including diarrhea ($n=3$), pancreatitis ($n=2$), and infection ($n=2$). There was a grade 5 SAE due to pancreatitis, and the study subsequently excluded patients with risk factors for pancreatitis. In addition, monitoring of pancreatic enzymes (i.e., amylase) in all elderly patients treated with brentuximab vedotin in this trial was required [64]. Finally, brentuximab vedotin and chemotherapy are associated with higher rates of febrile neutropenia than with either treatment alone. A grade 5 septic event occurred in an elderly patient with early stage classical Hodgkin lymphoma enrolled on a clinical trial, leading to mandated

growth factor support administration in all patients treated with brentuximab vedotin plus AVD chemotherapy [65].

21.9.1 Brentuximab Vedotin Approved Indication

Based on the high-response rates in HL and ALCL seen in these phase II studies, brentuximab vedotin was FDA approved for the following indications: (1) Hodgkin lymphoma after failure of ASCT, (2) HL patients who are not ASCT candidates after failure of at least two prior therapies, and (3) relapsed or refractory systemic ALCL.

21.9.2 Brentuximab Vedotin Retreatment

Patients who have been previously treated with brentuximab vedotin having at least stable disease with the first treatment have been successfully retreated with the agent. Among the 21 HL and 8 ALCL patients, there was an ORR of 60 and 88 % with brentuximab retreatment, respectively. This has therapeutic implications not only for patients who are treated with brentuximab in the relapsed setting after ASCT failure, but also as brentuximab is increasingly being incorporated into earlier phases of treatment, these results are of consequence for patients who receive BV as part of frontline and salvage regimens [66].

21.9.3 Brentuximab Vedotin Adjuvant Therapy Post Autologous Stem Cell Transplant

To study the role of adjuvant brentuximab vedotin after autologous stem cell transplant, the randomized phase III ATHERA study includes an investigational arm of brentuximab vedotin 1.8 mg/kg administered every 3 weeks for approximately 1 year (a maximum of 16 doses) versus placebo after ASCT in high-risk HL patients. In September 2014, Seattle Genetics and Takeda Pharmaceutical Company Limited announced preliminary results of this phase 3 clinical trial that included 329 patients. The AERTHA trial met its primary endpoint with brentxuimab vedotin resulting in a statistically significant improvement in progression-free survival versus placebo (hazard ratio = 0.57; p-value = 0.001). There was no difference in overall survival. The results will be further described at the 2014 American Society of Hematology (ASH) annual meeting.

21.10 Brentuximab in Combination with Chemotherapy

21.10.1 Frontline Regimens

To improve cure rate of HL in the frontline setting, brentuximab vedotin was recently combined with standard ABVD and AVD chemotherapy in a phase I study [62]. Escalating doses of brentuximab vedotin were combined with chemotherapy (0.6, 0.9, and 1.2 mg/kg, every 2 weeks). Although the clinical efficacy was high with brentuximab vedotin + ABVD, 40 % of patients developed pulmonary toxicity. As a result, bleomycin was eliminated, and brentuximab vedotin was combined with AVD in 26 patients at the 1.2 mg/kg dose with excellent results; 92 % of patients achieved a complete remission at the end of 6 cycles, and the treatment was generally well tolerated without pulmonary toxicity.

Several phase III randomized studies are currently underway studying the role of brentuximab vedotin in the frontline treatment of lymphoid malignancies in combination with chemotherapy. The ECHELON-1 study is an international, phase III randomized study of brentuximab vedotin + AVD chemotherapy versus standard ABVD chemotherapy for untreated advanced-stage HL (NCT01777152). A large phase III randomized trial conducted by the GHSG is comparing six cycles of BEACOPP escalated with a new variant (BrECADD) that includes brentuximab vedotin [67].

For the up-front treatment of T-cell lymphoma, the ECHELON-2 study is currently

enrolling patients with untreated CD30+ mature T-cell lymphoma in a randomized phase III study of brentuximab vedotin + CHP chemotherapy versus standard CHOP chemotherapy (NCT01777152). In addition, there is an ongoing phase III study for CD30+ cutaneous T-cell lymphoma with brentuximab vedotin in combination with physician's choice of methotrexate or bexarotene (NCT01578499).

21.10.2 Pre-transplant Salvage Regimens

Brentuximab vedotin is also being evaluated in relapsed/refractory HL as a second-line salvage prior to high-dose therapy and autologous stem cell transplant (HDCT-ASCT) in two phase II studies (NCT01393717 and NCT01508312). These studies evaluate whether brentuximab vedotin can eliminate the need for standard cytotoxic salvage chemotherapy, such as ICE, prior to HDT-ASCT. In one of these studies, patients are treated with single-agent brentuximab vedotin for two cycles, followed by response assessment using PET imaging. Patients who achieved a complete remission with a negative PET were allowed to proceed to stem cell collection followed by ASCT, thus avoiding chemotherapy. Patients with PET positive scans after two cycles of brentuximab vedotin were treated with augmented ICE chemotherapy, followed by ASCT. Using this PET-adapted strategy, 30 % of patients achieved CR after two cycles of brentuximab vedotin, avoiding ICE-based therapy [68].

21.10.3 Brentuximab Vedotin-Based Combinations in Posttransplant Settings

Although brentuximab vedotin produces a high overall response rate in patients with relapsed HL, most responses are partial and of short duration. Therefore, there is an urgent need to combine brentuximab vedotin with other active patients to increase the proportion of complete remissions and to prolong the duration of response. Based on preclinical data to suggest synergy between brentuximab vedotin and other agents, it is being combined with bendamustine and temsirolimus (NCT01874054 and NCT01902160, respectively). Future trials should consider combining brentuximab vedotin with HDAC inhibitors or with PD1/PDL1 monoclonal antibodies.

Conclusions

The approval of brentuximab vedotin has opened the door to a new era of therapy for patients with HL. Brentuximab-based combinations are being evaluated in newly diagnosed patients, in pretransplant setting, and in posttransplant settings. Results from these ongoing trials may change the standard of care for these patients in the near future.

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Other New Agents for Hodgkin Lymphoma

22

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22.1 Introduction

The efficacy seen with brentuximab vedotin (BV) has set the bar high for evaluating other new agents in Hodgkin lymphoma (HL). Several additional promising agents are being investigated for HL, and while no single agent has yet demonstrated response rates as high as BV, these agents are good candidates for building combinations. A lot has been learned about the underlying biology of HL that has revealed potential targets for therapy. HL tumors are characterized by their extensive microenvironments made up primarily of T cells as well as eosinophils, B lymphocytes, and plasma cells that surround the rare tumor cells called Reed-Sternberg (RS) cells. There is extensive cross talk through cytokines and chemokines between RS cells and the surrounding inflammatory infiltrate which contributes to support of RS cell survival and suppression of antitumor immunity [1]. Newer agents for HL (summarized in Table 22.1) target the various aspects of HL biology and include PI3K/Akt/mTOR pathway inhibitors, histone deacetylase (HDAC) inhibitors, and immune modulators.

22.2 PI3K/Akt/mTOR Pathway

Constitutive activation of the PI3K/Akt/mTOR pathway (Fig. 22.1) is present in both HL cell lines and primary tissue [2, 3]. The significance of this pathway in HL was demonstrated by the

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_22, © Springer International Publishing 2015

Table 22.1 Summary of new agents for Hodgkin lymphoma (other than brentuximab vedotin)

Class	Drug	*n*	ORR (%)
HDAC inhibitor	Vorinostat [12]	25	4
	Panobinostat [13]	129	27
	Mocetinostat [14]	51	33
	Entinostat [15]	38	16
mTOR inhibitor	Everolimus [4]	57	42
PI3K inhibitor	Idelalisib [6]	25	12
Immunomodulator	Lenalidomide [20]	36	19
Chemotherapy	Bendamustine [21]	36	53

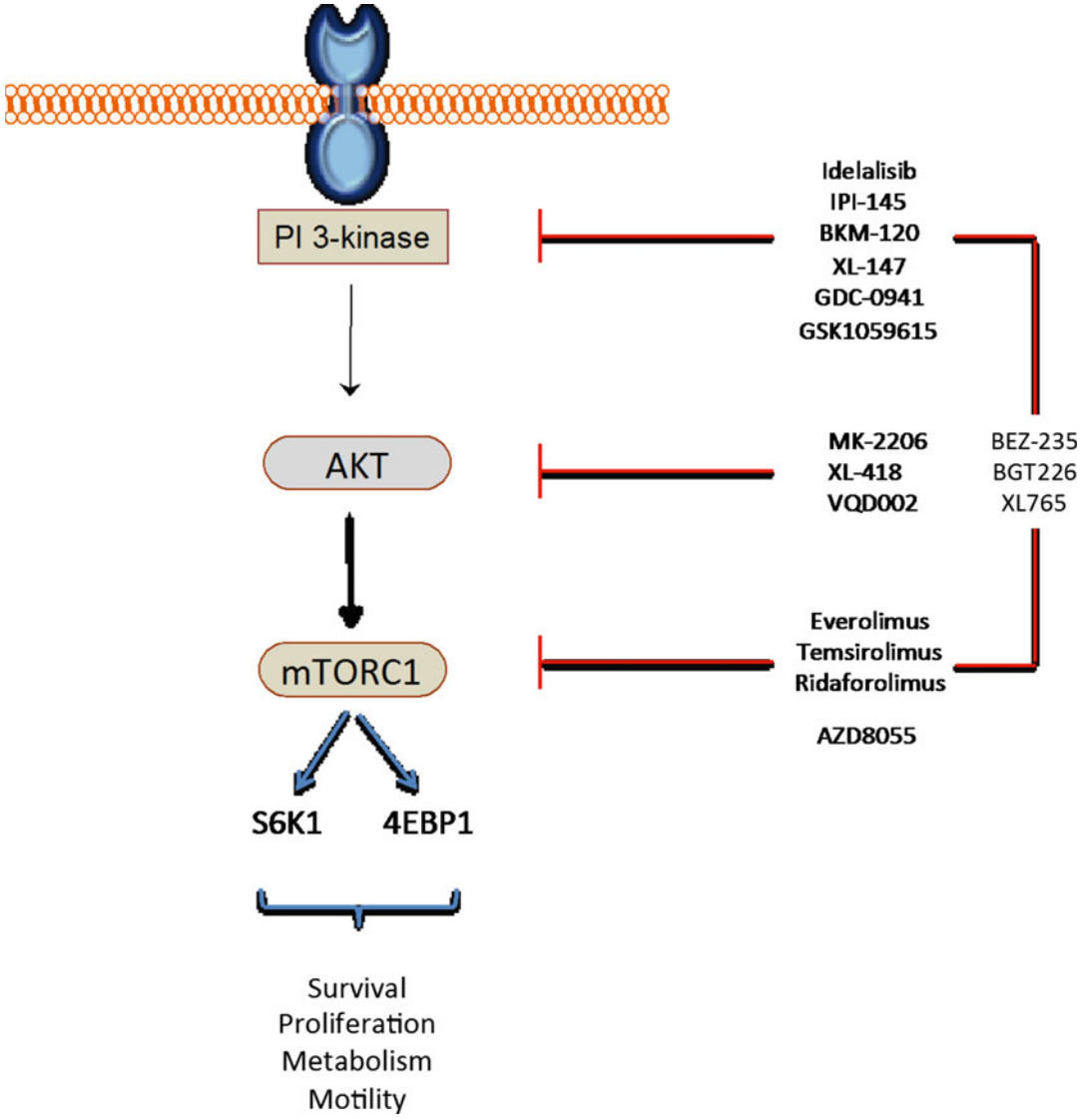

Fig. 22.1 Overview of the PI3K pathway and drugs targeting various aspects of the pathway

efficacy of everolimus, an mTOR inhibitor, in patients with relapsed or refractory (rel/ref) HL. In the phase II study evaluating everolimus in rel/ref HL, patients received 10 mg/day until progression of disease [4]. Among the 57 patients enrolled, the overall response rate (ORR) and disease control rate (DCR) were 42 and 77 %, respectively. Several patients experienced prolonged disease control reporting median responses lasting as long as 2 years. Treatment was well tolerated with grade 3 or 4 thrombocytopenia and anemia occurring in 21 and 12 %, respectively. Furthermore, only 3.5 % of patients experienced grade 3 stomatitis, and pneumonitis occurred in 10.5 % (all grade 1 or 2).

The value of targeting this pathway in HL was further tested through a phase II study evaluating idelalisib, a delta-specific PI3 kinase (PI3Kδ) inhibitor. PI3Kδ is preferentially expressed in cells of hematopoietic origin, particularly B cells, and is highly expressed in HL cell lines compared to other PI3K isoforms [5]. Twenty-five patients with rel/ref HL enrolled on this study and were treated with idelalisib 150 mg BID until progression, with the option to increase to 300 mg BID. The ORR was 12 % with one complete response, two partial responses, and nine patients with stable disease [6]. As was seen with everolimus, a few prolonged responses were observed with one patient achieving CR lasting 7+ months and another with stable disease for 11+ months.

Preclinical studies have led to several clinical trials evaluating novel regimens involving drugs affecting this pathway. For example, the demonstration of synergy between everolimus and panobinostat in HL cell lines led to a phase I/II study evaluating this combination [7, 8]. In addition, a phase I/II study evaluating everolimus in combination with DHAP (dexamethasone, cytarabine, cisplatin) in rel/ref HL is ongoing based upon preclinical data demonstrating synergy between everolimus and cytotoxic chemotherapy (clinicaltrials.gov: NCT01453504) [2]. Finally, enhanced antitumor activity observed with BV plus temsirolimus in an HL xenograft model provided the rationale for an ongoing phase I study evaluating the safety of combining these drugs (clinicaltrials.gov: NCT01902160) [9].

22.3 HDAC Inhibitors

The histone deacetylase (HDAC) inhibitors target both HL Reed-Sternberg cells and their tumor microenvironment and therefore are particularly attractive agents for HL. Their epigenetic effects on gene expression support apoptosis of RS cells and cause disruption of the cytokine- and chemokine-mediated interactions between the RS cells and their microenvironment [10, 11]. The available HDAC inhibitors differ by their specificity for particular HDAC isotypes, and the more selective HDAC inhibitors may have the advantage of causing less hematologic toxicity.

Both pan-HDAC inhibitors (vorinostat and panobinostat) and more selective inhibitors (mocetinostat and entinostat) have been evaluated in HL. Vorinostat demonstrated only modest activity in rel/ref HL in a phase II study by the Southwest Oncology Group (SWOG), with only 1 out of 25 patients achieving PR [12]. Panobinostat demonstrated more promising activity in an international phase II study in rel/ref HL [13]. Of 129 patients, there were 35 (27 %) responses, which included 5 (4 %) CRs and 30 (23 %) PRs. Furthermore, tumor reductions were observed in 74 % of patients (Fig. 22.2). Responses were durable with median duration of response of 6.9 months. Common toxicities seen with this agent were thrombocytopenia (79 % grade 3/4), diarrhea, nausea, and fatigue.

Mocetinostat (MGCD0103), which selectively inhibits class I and IV HDACs, was evaluated in 51 patients with HL and demonstrated an ORR of 33 % [14]. In contrast to panobinostat, hematologic toxicity was rarely seen with mocetinostat; however, 6 % of patients developed nonfatal pericardial effusions. Given its excellent hematologic toxicity profile, further evaluation of this agent is warranted; however, close cardiac monitoring in future studies will be necessary. Entinostat, a selective class I HDAC inhibitor,

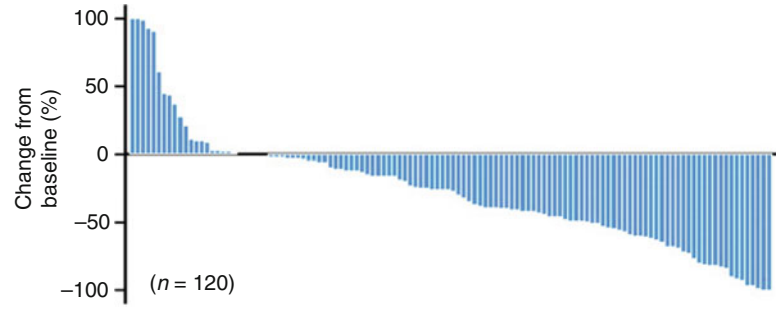

Fig. 22.2 Observed tumor reductions for patients treated with panobinostat on the phase II clinical trial in relapsed and refractory Hodgkin lymphoma (Reprinted with permission. © (2012) American Society of Clinical Oncology. All rights reserved. Younes et al. [13])

demonstrated an ORR of 16 % (6 PRs among 38 patients) and tumor reductions in 61 % of patients [15]. Common grade 3 or 4 toxicities included thrombocytopenia (55 %), neutropenia (41 %), and anemia (43 %).

Based upon preclinical data showing reduced secretion of the thymus and activation-regulated chemokine (TARC) in HL cell lines treated with HDAC inhibitors, serum TARC was measured in 15 patients following 1 week of treatment with mocetinostat in the phase II study [14]. In five patients, TARC serum levels decreased by at least 40 %, and these reductions correlated with subsequent achievements of PR or CR to treatment. These data suggest that early changes in serum TARC levels may be useful in predicting response to HDAC inhibitors and continue to be evaluated in ongoing studies.

Overall, the HDAC inhibitors consistently demonstrate activity in HL and cause only moderate toxicity; therefore, they are good candidates for evaluation in combination with other agents for HL. As described above, synergy between HDAC and mammalian target of rapamycin (MTOR) inhibition was observed in preclinical studies and led to the evaluation of panobinostat in combination with everolimus [8]. Among 14 patients with HL treated with this combination, 6 (43 %) responses were observed; however, dose interruptions were frequent, often due to thrombocytopenia. It is possible that an alteration of the treatment schedule or perhaps inclusion of a more selective HDAC inhibitor may allow for fewer treatment delays and better efficacy. Support for studies evaluating HDAC inhibitors in combination with chemotherapy comes from preclinical data demonstrating down-regulation of chemotherapy-resistant genes following treatment with HDAC inhibitors, as well as synergy between HDAC inhibitors and various chemotherapy agents [10, 16]. Preliminary results from a phase I study evaluating panobinostat plus ICE in rel/ref HL look promising with ORR and CR rates of 86 and 71 %, respectively, among 21 patients [17]. As expected with both ICE and panobinostat, frequent grade 4 thrombocytopenia was observed; however, an alternative treatment schedule is currently being investigated that may result in less toxicity.

22.4 Lenalidomide

The antitumor activity of lenalidomide in HL is not well defined but may include direct cytotoxicity, alteration of tumor cell microenvironment, and/or antiangiogenesis [18]. Evidence of activity of lenalidomide in HL was initially report by Böll and colleagues among 12 patients with rel/ref HL treated on a named patient program; all of the patients achieved clinical benefit and 50 % achieved objective responses [19]. One patient achieved a complete response which was ongoing after 2 years of therapy. In a larger phase II study of 36 patients with rel/ref HL, lenalidomide induced objective responses in 7 (19 %) patients. An additional 5 (14 %) patients achieved stable disease for 6 months or more, and prolonged responses were observed yielding a median time to treatment

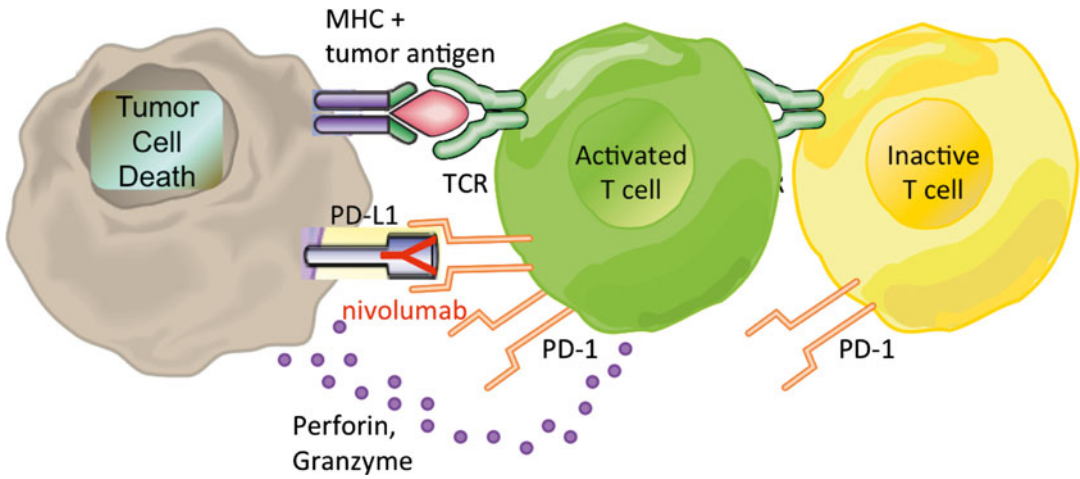

Fig. 22.3 PD-L1 expressed on tumor cells (such as Hodgkin lymphoma Reed-Sternberg cells) binds PD-1 expressed on activated T cells leading to T-cell inactivation and suppression of an antitumor immune response. Interruption of PD-L1-PD-1 binding with an anti-PD-L1 antibody or anti-PD-1 antibody, such as nivolumab, allows T cells to remain activated and thus restore the antitumor immune response [22, 23]

failure of 15 months [20]. Although not tremendously active as a single agent in HL, lenalidomide produces durable responses and represents another good candidate for combination. Lenalidomide combinations currently under investigation in HL alone or HL and non-Hodgkin lymphoma include lenalidomide in combination with everolimus (clinicaltrials.gov: NCT01075321), temsirolimus (clinicaltrials.gov: NCT01076543), panobinostat (clinicaltrials.gov: NCT01460940), romidepsin (clinicaltrials.gov: NCT01755975), and bendamustine (clinicaltrials.gov: NCT01412307). In addition, a study evaluating lenalidomide as maintenance therapy following autoSCT in rel/ref is underway (clinicaltrials.gov: NCT01207921).

22.5 Chemotherapy

Among the newer agents for HL is an old drug, bendamustine, which was developed in East Germany in the 1960s. Bendamustine was designed as a bifunctional agent with both alkylating and antimetabolite properties, although it primarily acts as an alkylator. In a phase II study that enrolled 36 patients with heavily pretreated HL, it produced responses in 53 %, including 33 % complete responses [21]. Given the relatively short remission duration observed on this study (5 months), bendamustine is better suited for patients heading for consolidation with transplant. Several studies are evaluating bendamustine combinations aimed to increase response rate and prolong remission duration; these include bendamustine plus brentuximab vedotin (clinicaltrials.gov: NCT01657331, NCT01874054), lenalidomide (clinicaltrials.gov: NCT01412307), and gemcitabine (clinicaltrials.gov: NCT01535924).

22.6 Emerging Therapies

22.6.1 PD-1/PD-L1 Inhibitors

Programmed death-1 (PD-1) signaling limits T-cell activity and is one of the mechanisms of immune suppression in the setting of chronic viral infection and cancer (Fig. 22.3). Expression of PD-1 ligands (PD-L1 and PD-L2) on tumor cells leads to immune evasion through binding of PD-1 on tumor-infiltrating cells [22, 23]. PD-L1 is overexpressed on Hodgkin lymphoma RS cells and therefore represents a likely mechanism of immune escape in HL. Further evidence of the role of PD-1 signaling in HL is the presence of

PD-1 expressing CD4+ T cells in the tumor microenvironment as well as circulating PD-1-positive T cells in the peripheral blood of HL patients [24]. Targeting of this pathway is likely to restore antitumor immunity in HL and is an attractive treatment approach for HL. Several PD-1 and PD-L1 inhibitors are under investigation in clinical trials which are enrolling patients with rel/ref HL.

22.7 News Ways of Targeting CD30

Given the success of targeting CD30 with brentuximab vedotin, other anti-CD30 therapies are under development. Although naked anti-CD30 antibodies were not effective in HL, CD30-specific cytotoxic T cells may prove to be a promising treatment strategy in HL [25, 26]. CD30 chimeric receptor-activated T cells are currently being tested in phase I studies for CD30-positive malignancies (clinicaltrials.gov: NCT01316146 and NCT01192464).

Conclusion

Even with the availability of brentuximab vedotin (BV), there is considerable room for improvement in the treatment of HL. In the rel/ref setting, treatment options quickly become exhausted as many patients ultimately progress following BV-based treatment. Furthermore, more individualized and better-tolerated therapies are needed in the frontline and second-line treatment setting for HL. Therapies currently under investigation in HL target activated pathways within the RS cells, the HL microenvironment, or both, and the key challenge will be to identify markers that predict likelihood of response and to determine the optimal way to combine these agents to produce well-tolerated, effective regimens. Unfortunately, preclinical studies are not always helpful for predicting successful combinations in HL since models that effectively recapitulate the complex microenvironment characteristics of HL tumors are not yet available. Thus, we must rely upon our understanding of individual drugs and HL biology to optimally pair drugs with complimentary mechanisms of action and toxicities. Several clinical trials evaluating novel combinations are already underway; however, multi-institutional collaborations will be needed to test additional promising combinations. Along with BV, the new agents currently under investigation in HL have the potential to greatly impact the treatment paradigm for HL by providing effective, well-tolerated, and more individualized therapy.

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Part V

Survivorship

Quality of Life in Hodgkin Lymphoma

23

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23.1 Quality of Life in Hodgkin Lymphoma

The long-term cure rates for Hodgkin lymphoma (HL) patients are above 80 % for all stages. Given this impressive long-term outcome for a patient population with a median age of about 30 years at diagnosis, the quality of survivorship has become more and more important. Organ dysfunctions including hypothyroidism, hypogonadism, cardiopulmonary complications, and secondary neoplasia as well as health-related quality of life (HRQoL) are major factors contributing to the patient's general well-being.

Accordingly, we have experienced an increasing amount of research over the past 10–20 years focusing on HRQoL in HL survivors. Most HL-related HRQoL research has been limited by the use of cross-sectional approaches and small patient numbers, with inadequate patient and treatment history and variable follow-up. So far, only two prospectively planned HRQoL studies in HL are available: one from the SWOG (Southwest Oncology Group) and the other from the EORTC (European Organisation for Research and Treatment of Cancer) [1, 2]. Both studies included only early-stage disease patients, and only in the SWOG study pretreatment baseline values were documented. All in all, there is still only very limited validated knowledge on HRQoL in HL patients.

Impaired HRQoL is a major problem for many HL survivors, often related to high levels of

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_23,

fatigue and persisting cognitive and gonadal dysfunction. Very little is known on factors contributing to this poor long-term outcome of the affected patients. Treatment-induced organic dysfunctions, like endocrine, immunological, and cardiopulmonary changes, have been discussed but were not confirmed in more recent studies. Also, psychological consequences might play a role. These include emotional distress, especially depression and anxiety. In addition, social or role functioning difficulties might influence HRQoL, including inability to return to work and adjustment to the workplace environment secondary to diminished capacity to complete work tasks. Finally, the long-term outcome in terms of HRQoL might only reflect patients' coping capacity facing the existential crisis of a malignant disease. Another factor is the patients' spirituality that might help to get back to "normal" life after the end of cancer treatment.

Thus, many very different factors contribute to the complexity of HRQoL. Most of them are difficult to measure and render research in this field challenging. Fortunately, there is an increasing recognition that the survivorship experience among young adults needs to be better understood in order to develop intervention strategies. Currently, large study groups including EORTC and GHSG (German Hodgkin Study Group) have focused their research on HRQoL, and new perspectives are evolving. As a result from these studies, we will hopefully learn to better understand the patient and his or her well-being and not only to treat the lymphoma successfully. In this chapter, we describe the methods to determine HRQoL and then summarize the currently available results from cross-sectional and longitudinal studies in HL.

23.2 Health-Related Quality-of-Life Assessment

As indicated above, a major problem is the assessment of HRQoL due to its multiple dimensions. HRQoL includes many aspects of physical, psychological, and social functioning. It therefore mirrors the physical, psychological, and social health of patients after treatment for cancer. The determination of HRQoL relies on the patient-reported outcomes (PRO) – a term which is used for health status measurement that comes directly from the patient. According to the FDA (US Food and Drug Administration), PRO measures include "such extremely complex concepts as HRQoL, which is widely understood to be a multi domain concept with physical, psychological, and social components" [3].

23.2.1 HRQoL Instruments

To obtain information from the patients' point of view, validated instruments are needed. Until recently, HRQoL assessment was predominantly conducted during phases of active treatment and in palliative settings, and questionnaires such as the EORTC QLQ-C30 were developed for patient groups in palliative settings (e.g., lung cancer), more focusing on short-term effects of treatment and disease. Accepting this limitation, the most suitable cancer-specific core instruments for international assessment are EORTC QLQ-C30 and FACT that are both available in different languages and are brief and economical to administer [4, 5]. One of the difficulties in designing HL-specific HRQoL modules is that, unlike other cancers, the particular problems are not easily identified. The general disadvantage of all available standard instruments is the lack of a HL-specific module. The wide range of key interval times (treatment period, follow-up, long-term surveillance) is not adequately reflected in available instruments. Most published trials in HL addressing late effects and HRQoL use different instruments (mainly questionnaires but also mixed questionnaire–interview approaches) that focus on psychological outcome including mood, depression, psychosocial adaptation, and psychiatric symptoms. Besides this complex of psychological outcomes, the socioeconomic impact of the disease is also evaluated. This includes living circumstances, occupational situation, leisure activities, family life, drinking, and smoking habits. Infertility and sexual problems as a consequence of treatment have received particular attention.

As outlined above, these instruments derived from the general assessment of late effects and came from a variety of research fields and illnesses. Only recently, explicit HRQoL instruments such as the EORTC QLQ-C30 have been included in cross-sectional studies. Few published reports addressed both late effects and longitudinal HRQoL assessment. Most new instruments use patient self-reporting of the perceived HRQoL. Apart from the broader and general domains of HRQoL, there is agreement on the necessity of assessing specific disease- and treatment-related problems such as body image, sexuality, fatigue, spirituality, and gender issues, as well as issues pertaining to very old or very young patients. To accomplish this, a number of groups followed the modular approach in the development of questionnaires (FACT-G and the QLQ-C30 represent core instruments) and supplemented the core instrument with specific tumor- or treatment-related modules. A major challenge to prospective multicenter trials using longitudinal data on HRQoL is the completeness of data sets, as missing data limit the value of the results. A high standard of data collection is essential for a given trial to be successful, and HRQoL assessments have to be a mandatory component of the clinical trial design and part of the inclusion criteria.

23.2.2 HRQoL Assessment in European Cooperative Study Groups

Since no HL-specific modules for the assessment of HRQoL and fatigue were available, the EORTC Lymphoma Group (EORTC LG) together with the French Groupe D'Etude des Lymphomes de L'Adulte (GELA) and the GHSG, in close collaboration with the EORTC QL Group (EORTC QLG), devised an alternative way to measure HRQoL and fatigue in patients with HL [6]. The main elements of the EORTC QLQ C30 core instrument were supplemented by already existing instruments or modules addressing particularly fatigue, sexuality, and fear of childlessness and, as single questions, special side effects of chemotherapy and radiotherapy. The first use of this so-called EORTC H8-QL questionnaire, developed for repeated measurements and extensively tested within the trial groups, has yielded promising results on psychometrics, applicability, and appropriateness of content. The H8-QL questionnaire to date is available in ten European languages and is complemented by the Life Situation Questionnaire (LSQ), developed originally in Caen, France. The LSQ is currently available in French, German, and English and is being prepared for further international evaluation. It addresses the following areas: general living circumstances (e.g., housing), work history and current occupational status, marital status and family relationships, health records, family medical history, current health status, leisure activities, and economic and insurance problems related to HL.

23.2.3 HRQoL as Study Endpoint

HRQoL assessment in HL patients is not yet established as a standard procedure in clinical trials. It remains thus unclear whether HRQoL scales can detect clinically meaningful differences between defined patient subgroups. Furthermore, the question "Which score difference constitutes a clinically relevant difference for the patient?" has gained considerable attention [2, 7]. Data are available from a number of HRQoL studies that suggest that score differences of at least 8/100 but preferably above 15/100 would mean a clinically relevant change in HRQoL for a given patient. Considering that it is unknown how much time is required before long-term disadvantages in HRQoL become obvious, the length of time during which patients should be evaluated cannot be anticipated. The EORTC, GELA, and GHSG are including longitudinal HRQoL assessment in ongoing trials. Preliminary analyses suggest that 2–3 years after completion of therapy is a crucial time period and a possible turning point for either recovery or long-term limitations [2]. HRQoL assessment is usually regarded as a secondary outcome endpoint. Before it can be used as a primary endpoint,

HRQoL assessment must fulfill various requirements, and the method of assessment must clearly be applicable in a multicenter setting. Since these instruments are available (e.g., QLQ-C30), assessment of HRQoL should be mandatory in any clinical trial in HL patients, and HRQoL should be included at least as a secondary endpoint. As long as no model of HRQoL impairment in HL has been established, no evidence-based intervention strategies can be developed, and, therefore, HRQoL is not yet suited to serve as a primary endpoint in randomized clinical trials.

23.2.4 Measuring Fatigue

A frequently reported problem in the aftermath of treatment for HL is fatigue. Although certainly not restricted to HL, fatigue seems to occur in a high proportion of patients successfully treated for HL. Over the last years, research activities on fatigue have established instruments that are now available to measure the different aspects of this symptom [8]. As with HRQoL in general, the current opinion perceives fatigue as a combined construct with a number of dimensions. One dimension refers to physical and mental fatigue in accordance with what would be seen after intensive exercise or work. Other aspects include motivation, activity, and cognition and the connection with mood states such as depression. Interestingly, available data suggest that a substantial proportion of fatigue reported by patients is not primarily due to their physical condition. Particularly in surviving patients after HL or breast cancer, high levels of fatigue occur with normal levels of physical functioning. An example of an instrument measuring fatigue is the Multidimensional Fatigue Inventory (MFI-20), which uses 20 items on five subscales.

23.2.5 HRQoL in Special Patient Groups

Only recently there has been progress in the development of instruments to measure HRQoL and late effects in pediatric oncology [9]. HRQoL assessment in children must address normal developmental issues in areas such as peer relations, school, family, and play, which differ from the topics addressed in adult instruments. Questionnaires must also be suitably administered. In children under the age of 10 or 11, self-reporting by questionnaires is in general neither reliable nor feasible; proxy ratings by the parents or caregivers are necessary. A number of proxy and self-rating tools are already available from pediatric psychology and psychiatry, but no established and tested instruments exist specific for HRQoL research in children and adolescents with HL. In a recently published [10] cross-sectional trial looking into the long-term outcome of pediatric HL patients, the HRQoL assessment used a combination of instruments for children and adults. Further analyses will also deal with the comparison of the psychometric properties of these instruments.

As with the HRQoL assessment in pediatric oncology, only in the last few years the problems of elderly patients have been noticed. HRQoL assessment in elderly patients must address the aspects of daily living and the adjustment to physical and mental disabilities. Questionnaires must be suitably devised and administered, and the patients may need assistance in filling out forms. For a subgroup of patients, self-reporting is no longer reliable or feasible; proxy ratings by caregivers are necessary. Some proxy and self-rating tools are meanwhile available from geriatrics, but no validated instruments exist for HRQoL research in elderly HL patients.

23.3 HRQoL in Clinical Trials for Hodgkin Lymphoma

23.3.1 Lessons from Retrospective and Cross-Sectional Studies

More than 30 studies can be identified since 1986 dealing with HRQoL in HL as reviewed recently [11]. In brief, mainly cross-sectional studies in HL survivors have been performed over the last two decades including some retrospective studies. A variety of HRQoL instruments were employed in these studies and some trials used a

matched control design or compared patient data with data from general population surveys. Follow-up periods ranged from 0 to 40 years after end of treatment. These analyses have shown that a substantial number of patients still carry a substantial burden even many years after the end of therapy. To illustrate these findings, the work by Fobair and colleagues is well suited [12]. They reported that ongoing fatigue was a major concern for 37 % of 403 survivors. This was influenced by age, time after diagnosis, stage of disease, and type of treatment. Factors associated with better outcome were younger age, longer time since diagnosis, earlier stage, and radiation therapy without chemotherapy. Fatigued survivors also reported higher rates of depression. Other concerns identified were marital disruption, problems with infertility, and low sexual activity. In addition, 29 % of patients in this sample were unemployed, with 18 % currently looking for a job. It was also noted that HL survivors performed more poorly on measures of physical and psychosocial function when compared with either patients having acute leukemia, testicular cancer, or healthy population samples. These studies suggested a relationship between outcomes and the intensity of treatment; however, their retrospective and uncontrolled design limits the chance to determine causality.

Some relevant findings from case-control studies, which deliver somewhat better evidence, performed in HL survivors are listed in Table 23.1. All but one study involved healthy controls from regional population registries or from the general population. In summary, results of these studies are related to a variety of areas but consistently report on emotional strain and fatigue even years after the end of treatment. The newest study on survivors of pediatric HL confirms the findings from the previous adult studies. To summarize, these cross-sectional studies have shown persisting impaired HRQoL especially with regard to fatigue for a substantial number (up to 40 %) of HL patients, but besides age no risk factor was consistently reported. Although these studies used control groups, their design neither allows firm conclusions on the etiology of persisting impaired HRQoL nor to develop a model for a persisting defective HRQoL in HL.

23.3.2 Results from Prospective Trials

The first study reporting a longitudinal prospectively designed investigation on HRQoL in HL was conducted by the SWOG [1]. In the early 1990s, there was considerable debate about the necessity for staging laparotomy in early-stage HL (clinical stage IA and IIA), which was driven by the morbidity of the procedure. Thus, there was increasing interest in using short courses of chemotherapy with more limited radiotherapy to maximize cure and minimize toxicity. The SWOG designed a treatment protocol (SWOG 9133) to investigate alternative strategies for the management of early-stage HL, investigating subtotal lymphoid irradiation (STLI) vs. three cycles of doxorubicin and vinblastine followed by STLI (combined-modality therapy (CMT)) in early-stage HL patients. This study was accompanied by a prospective quality-of-life study termed SWOG 9208. The objectives of this study were to evaluate prospectively the health status and HRQoL of early-stage HL patients receiving either STLI or CMT, to describe the short-term effects of the treatments on symptoms and QoL, and to evaluate the intermediate and long-term effects of the two treatments on HRQoL. Short-term and intermediate outcomes during the first 2 years after random assignment were reported. Both treatment groups experienced a short-term increase in symptoms, fatigue, and poorer QoL as a result of the treatment, which was more severe in the CMT group at 6 months after diagnosis due to more prolonged treatment. However, 1 year after random assignment, outcomes in the two treatment groups were indistinguishable. In this study, increased fatigue was identified in favorable HL patients before treatment that persisted after successful curative treatment. Importantly, fatigue levels for both study groups (CMT 45.9 and STLI 49.7) were increased at baseline. These scores were lower than scores for the general population. Before any treatment, these early-stage HL patients reported scores that were about a half SD below normal and were more consistent with scores from older patients with ischemic heart disease. While fatigue is a known symptom for HL, it was unexpectedly prominent

Table 23.1 Selected results from HRQoL studies in long-term survivors of HL

Study	Cases (patients)	Controls	Main results
Joly et al. [13]	93 patients issued from the regional cancer registry	186 matched controls (age and sex) from the regional population registry	More physical, role, and cognitive impairments among cases. Major limitation in borrowing from banks remained the major problem in cases
Loge et al. [14]	459 patients (1971–1991) treated at the Norwegian Radium Hospital	General Norwegian population	Higher levels and longer lasting of fatigue among cases. Disease stage predicted fatigue. No association with treatment characteristics
Wettergren et al. [15–17]	121 patients treated in Stockholm County (1972–1991)	236 matched controls (age and sex) from the regional population registry	Most important reported life areas were family, personal health, work, relations to other people Lower physical health in patients
Rüffer et al. [18]	836 patients from the GHSG trials HL1-6 (1981–1993)	935 matched controls (age, sex, living area) from regional population registries	Higher levels of fatigue in cases. Fatigue associated with systemic symptoms, Karnofsky, occurrence of relapse
			Time since end of treatment had no influence on the reported fatigue levels
Holzner et al. [19]	126 patients treated at a single institution (1969–1994)	926 controls from the general Austrian population	Higher functional, social well-being, and total scores in cases compared to controls
Hjermstad et al. [20]	475 patients (1971–1997) treated at the Norwegian Radium Hospital	General Norwegian population	Higher levels of total fatigue (TF) in cases. Persisting chronic fatigue (CF) was associated with B-symptoms at diagnosis and treatment period 50 % of patients reporting CF in 1994 did not report CF 8 years later. No correlation of fatigue levels with treatment variables (e.g., radiation fields)
Calaminus et al. [10]	1,202 patients from the pediatric German–Austrian therapy studies HD-78, HD-82, HD-85, HD-87, HD-90, HD-95 (1978–2002)	General German population	"Global" and "physical QoL" scores comparable to general population, "emotional" and "social functioning" more than 10 points lower. Higher symptom scores for "fatigue" and "sleep." Gender effects showing lower functioning and higher symptom levels in women, most prominently in the group of young women (21–25 years). No association with the time since treatment, the age of HD survivors at diagnosis, or the extent of therapy burden

in this patient cohort having a favorable prognosis and without B-symptoms. It was expected to improve subsequent to treatment and induction of remission. However, the fatigue level did not improve to normal values. The Vitality Scale scores at 1 and 2 years were slightly below the baseline score and were substantially lower than comparative data from a breast cancer survivor sample after adjuvant treatment and radiotherapy. Though this is one of the most important studies on HRQoL in HL, no conclusions can be drawn with regard to tumor stage at baseline or aggressiveness of the chemotherapy being a risk factor for HRQoL impairment, since only early-stage low-risk patients were included.

The second study was published in 2009 by Heutte and colleagues [2]. They reported the results of their longitudinal HRQoL study examining short-term and long-term HRQoL among HL survivors from a large phase 3 trial (EORTC-H8). The study included early favorable HL patients and compared chemotherapy plus radiotherapy with radiotherapy alone; in patients with early unfavorable disease, different chemotherapy–radiotherapy combinations were compared. Of 1.577 patients recruited to the trial throughout Europe, 2.666 assessments from 935 patients were available for the analysis with median follow-up of 92 months. Interestingly, therapeutic modality (radiotherapy vs. chemotherapy) did not have significant effects on HRQoL, and many patients experienced recovery within 18 months of completing treatment. However, high-level fatigue more than 2 years after therapy was common (Fig. 23.1).

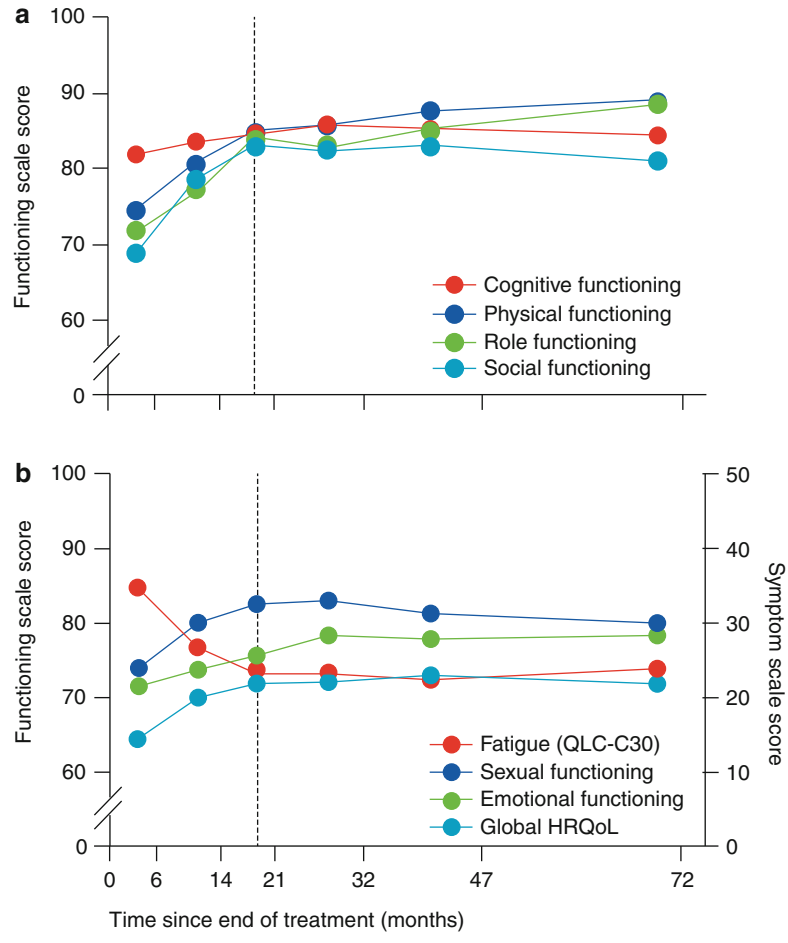

Fig. 23.1 Course of the EORTC QLQ-C30 functional and symptom mean scores over time in 935 patients. (**a**) For functional scales, a higher score indicates better functioning, (**b**) while for the symptom scales a higher score reflects higher symptom burden (Adapted by Heutte et al. [2])

The only factor that predicted long-term fatigue was fatigue at the end of treatment. Factors associated with significantly impaired HRQoL were older age and female sex. Furthermore, age affected all functioning and symptom scores. Also, of note, emotional domains did not show the same magnitude of improvement after treatment as physical domains.

Strengths of this report were the longitudinal design, large cohort size, homogeneous patient population, and long-term follow-up. These aspects allowed a sufficient analysis of clinically relevant patient-based and disease-based subgroups. A major limitation was the fact that the authors did not capture HRQoL data before treatment, which would have shed light on the potential role of pretreatment fatigue in predicting long-term outcomes. In addition, the number of patients at a given time point within defined treatment arms is rather small, and advanced-stage patients were not included. Thus, again only a subgroup of patients was evaluated in this study, and, without baseline (i.e., pretreatment) values for HRQoL, the findings cannot be used to develop a model of HRQoL outcome in HL.

With regard to this limited knowledge on quality of life in HL patients, the results of the GHSG G4 (HD10–12) were eagerly awaited. First data of these trials was presented on the annual meeting of the American Society of Hematology in 2010.

A total of 3.208 patients were evaluable for the analysis, and patients in all stages of HL were enrolled. HRQoL was assessed by using a questionnaire containing the EORTC QLQ-C30, the MFI 20 as well as items for assessing sexual quality of life as well as some specific items. The patients answered the questionnaire at baseline before the start of treatment, during the treatment, and after the end of therapy and in the follow-up.

As in the SWOG HL patients showed clearly poorer mean scores already at baseline in each scale of the EORTC QLQ-30 when compared to reference values of the German reference population. The scales were negatively influenced by female gender and more advanced stage. At this time point, age over 50 years was positively related to social functioning but negatively to cognitive and physical functioning. During chemotherapy, a decrease of HRQoL was observed, but after the end of treatment, all scales showed a considerable improvement. However a complete recovery to normal values was not found. The impairment was most pronounced in patients over the age of 50 years and advanced stages. Interestingly once more a relevant effect of the type or the intensity of treatment could not be detected.

In a further step, a model of HRQoL was developed which showed a very good fit (RMSEA <0.05) and a high stability of HRQoL 12 months after diagnosis. The model will have to be validated in the GHSG G5 and G6, but it is a promising progress in predicting HRQoL.

When looking into details, severe fatigue defined as a value of more than 50 on the EORTC QLQ-C30 scale was found in 12.8 % patients 27 months after therapy. Of those patients, 6 % were affected already at baseline, while 6.8 % developed severe fatigue after the start of treatment. Almost the same amount of patients were cured by severe fatigue after the end of treatment (15.1 %), and 17.4 % showed only temporary fatigue during chemo- or radiotherapy. All others had never suffered from severe fatigue.

Interestingly, the cox regression for overall survival revealed that severe fatigue at baseline was a significant, strong, and independent risk factor of death from any cause ($p<0.05$, HR = 1.5) [21].

Even though this is preliminary data and a full text publication will have to be awaited before drawing final conclusions, the results are clearly meaningful. As fatigue is relevant for the patient outcome, more research is required to understand influencing factors of baseline fatigue, and interventions will have to start even before tumor treatment. Furthermore the data supports the work done by Heutte et al. as well as by the SWOG and highlights the influence of patient or tumor related factors instead of treatment.

Besides these important findings, Behringer et al. were able to publish further results of the

GHSG G4 with special emphasis on sexual quality of life (SX) [22]. Here also an impaired SX was found at baseline which was more pronounced in advanced stages and in patients over the age of 50 years. Interestingly a benefit from therapy was found in advanced stages with more patients that improved after therapy than suffering from therapy-induced impaired SX. But a normalization of SX was only reached in early stages. Furthermore as well as in the other domains of HRQoL, a clear impact of therapy could not be detected in early or advanced stages. Only in early unfavorable stages, the comparison of ABVD versus BEACOPP showed a small but significant advantage in favor of ABVD. As for fatigue, the authors developed a model to predict long-term SX. The model showed that SX from 12 to 18 months after therapy are highly predictive for further SX scores up 27 months (Fig. 23.2).

Final analysis of the GHSG G4 HRQoL will be published in 2014 and hopefully help to establish new models in predicting HRQoL as well as to create new intervention strategies. The current results suggest that measuring HRQoL before, during, and after therapy with a follow-up of at least 12–18 months will be necessary for studies conducted in HRQoL.

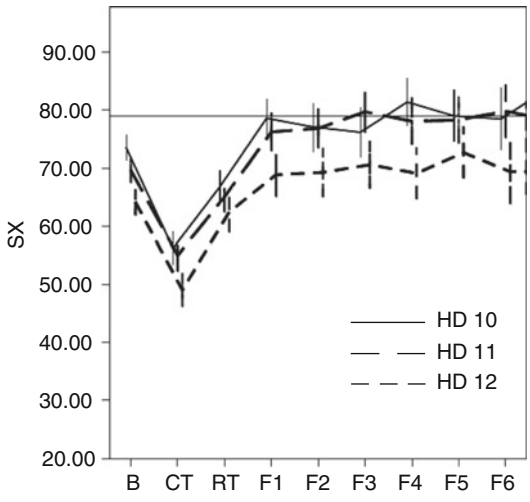

Fig. 23.2 Course of SX mean scores with 95 % confidence interval according to stage and to reference values (*horizontal line*) over time (Adapted by Behringer et al. [22])

Conclusions

The number of clinical trials evaluating HRQoL assessment is increasing. It has become widely accepted that the multidimensional approach of HRQoL assessment reflects the patient's situation and presents very important information for the process of treatment evaluation. With the constantly growing cohort of long-term survivors indicating the progress of cancer therapy in different subgroups, there is a need of new approaches in HRQoL assessment dealing with the particular problems of these long-term survivors. Several studies have highlighted the difficulties that survivors may experience long after treatment ends, such as general fatigue, health fragility, and social and financial problems. These findings have been demonstrated in studies where a HRQoL approach has been used. Since these studies mostly were using a cross-sectional design, there is a need for new approaches to describe more precisely the patients' situation, to detect reasons for maladaptation, and to identify patients at high risk.

Combined comprehensive approaches like the one by the EORTC/GELA and the GHSG using a HRQoL questionnaire for survivors and a life situation evaluation could help overcome the difficulties in assessing HRQoL in long-term survivors. Furthermore, this approach can be used with few modifications in the assessment of normal control persons from population registries. It seems plausible that many years after treatment the daily living circumstances have a stronger impact on patients' HRQoL. Therefore, it is essential to also have reference data from age- and gender-matched healthy population for the interpretation of HRQoL results. In addition, a more comprehensive approach that accounts for the patients' life situation is necessary to represent the complexity of HRQoL. The results from the studies by the EORTC/GELA and the GHSG within the next few years will reveal whether this approach proves successful. Quality-of-life assessment should benefit patients by defining relevant issues, even long after initial treatment. Disease- and therapy-independent predisposing factors for long-term HRQoL

functions on one hand and those factors associated with therapy or the lymphoma itself on the other hand must be evaluated in well-designed prospective studies.

The final results of the GHSG-G4 HRQoL evaluation will be published 2014 and might provide more information to understand how persisting impaired HRQoL develops and which factors contribute to a poor outcome. This will give us the opportunity to develop prevention strategies, to improve our study designs, and to better accompany and support our patients back on their way to a "normal" life.

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Second Malignancy Risk After Treatment of Hodgkin Lymphoma

24

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Contents

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24.1 Introduction

In view of the excellent cure rates that are currently achieved in the relatively young population of patients with Hodgkin lymphoma (HL) [1], it has become increasingly important to evaluate and limit the long-term complications of treatment. Research conducted over the last three decades has clearly demonstrated that, paradoxically, some treatments used to treat cancer have the potential to induce new (second) primary malignancies. Of all late complications of treatment, second malignant neoplasms (SMNs) are considered to be among the most serious because they cause not only substantial morbidity but also considerable mortality. Among long-term survivors of HL, second cancer deaths have been reported to be the largest contributor to the substantial excess mortality that these patients experience [2–4].

Increased risk of SMNs has been observed both after radiotherapy (RT) and chemotherapy (CT). In 1972, Arsenau and colleagues [5] were the first to report an increased risk of second cancer after HL treatment. Based on 12 second malignancies in 425 patients treated at the US National Institutes of Health from 1953 to 1971, they estimated a 3.5-fold risk increase compared to the general population. MOPP combination chemotherapy (mechlorethamine, vincristine, procarbazine, and prednisone) for HL was introduced in 1967; the leukemogenic potential of this regimen and similar ones became evident in reports

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_24, © Springer International Publishing 2015

published in 1973 [6], 1975 [7] and 1977 [8]. In the 1980s several studies showed that, after an induction period of 5–10 years, radiotherapy for HL increased the risk of solid malignancies, especially lung cancer [9–12].

It is important to recognize that not all SMNs are caused by treatment. The occurrence of two primary malignancies in the same individual may have several causes. It may represent a chance occurrence (in which case the two cancers developed as a result of unrelated factors); it may result from host susceptibility factors (e.g., genetic predisposition or immunodeficiency); it may be linked to carcinogenic influences in common, or a clustering of different risk factors in the same individual; or it may represent an effect of treatment for the first tumor [13, 14]. In view of the high prevalence of cancer in the general population and the increasing incidence of most cancers with age, background etiological factors other than treatment are likely to be responsible for a substantial proportion of second cancer, especially in older populations. Therefore, whenever a clinical impression arises that a specific combination of two distinct primary malignancies occurs more frequently than expected, comparison with cancer risk in the general population is imperative. If a SMN has been demonstrated to occur in excess, the contributions of other risk factors and the role of host susceptibility factors should be ruled out convincingly before the risk increase can be attributed to treatment. Even then, host factors may modify treatment effects, so that the risk associated with a given treatment will vary among individuals. The evaluation of the carcinogenic effects of therapy is further complicated by the fact that therapeutic agents are frequently given in combination. Appropriate epidemiologic and statistical methods are required to quantify the excess risk and to unravel treatment factors responsible for it.

In this chapter we address major aspects of SMN risk following treatment for HL. After an overview of the methods used for assessing second cancer risk, we discuss major contributors to second risk, i.e., radiation therapy and chemotherapy. Subsequently, a review is given of the risks of leukemia, non-Hodgkin lymphoma (NHL), and selected solid tumors in patients treated for HL. Emphasis is on large studies that were published recently. Finally, clinical implications of the most important findings are discussed.

24.2 Methods of Assessing Second Cancer Risk

Estimates of second cancer risk after treatment for HL derive from several sources, including population-based cancer registries, hospital-based cancer registries, or clinical trial series. The cohort study and the nested case-control study are the epidemiologic study designs generally used in second cancer research [15, 16]. Case reports have an important role in the early recognition of potential associations between different malignancies. However, because of lack of information on the underlying population at risk, they are not useful in quantifying risks.

In a *cohort study*, a large group of patients (the cohort) with a specified first malignancy is followed up for a number of years to determine the incidence of second (and subsequent) malignancies. Because most patient cohorts in which second cancer risk has been assessed were identified retrospectively, follow-up of all patients in such studies is completed up to some point in the recent past. To evaluate whether second cancer risk in the cohort is increased compared with cancer risk in the general population, the observed number of SMNs in the cohort is compared with the number expected on the basis of age-, gender-, and calendar year-specific cancer incidence rates in the general population. This can be done in a so-called "person-years" type of analysis. In this approach, adjustment is made for the distribution of the cohort according to age, sex, and calendar period, while the observation period of individual patients (person-years at risk) is also taken into account. The *relative risk* (RR) of developing a SMN is estimated by the ratio of the observed number of SMNs in the cohort to the number expected. In epidemiologic terminology, the *observed-to-expected ratio* is often called the *standardized incidence ratio* (SIR). For cancer deaths, the equivalent measure is the *standardized mortality ratio* (SMR), in which observed second malignancy deaths are compared with expected numbers of deaths.

A disadvantage of the person-years method as applied in its simplest form is that it assumes the risk of SMN development to be constant over time; that is, it assumes the second cancer experience of 1,000 patients followed for 1 year to be comparable to that of 100 patients followed for 10 years. When this assumption is inappropriate (as with treatment-related cancers developing after an induction period), it is more informative to calculate SIRs within specified post-treatment intervals (usually 5-year periods) [17, 18]. A temporal trend of excess SMN risk may in itself provide an important initial clue to treatment-related causes; for example, the SIR of solid malignancy following RT for HL generally increases with time since exposure.

When the observed-to-expected ratio is increased, the question arises whether the risk increase is caused by the treatment. This can be evaluated by comparing SIRs between treatment groups, preferably with a reference group of patients not treated with RT or CT. Such a comparison group is available when second cancer risk is examined in patients with breast or testicular cancer, who may be treated with surgery alone, but, unfortunately, not for patients with HL. When the observation period (or survival rate) differs between treatments, their overall observed-to-expected ratios cannot be validly compared. Poisson regression analysis can be used to adjust treatment-specific observed-to-expected ratios for differences in age and time since treatment (see below).

Second cancer risk in the cohort (and in different treatment groups) can also be expressed by the *cumulative* (actuarial estimated) *risk* [19], which gives the proportion of patients expected to develop a SMN by time t (e.g., 5 years from diagnosis) if they do not die before then. When the cohort's death rate from causes other than SMNs is high, the assumption of "non-informative censoring" underlying the actuarial method is often not valid. In particular, the assumption that patients who died due to other causes would have the same temporal pattern of SMN risk as those who survived is incorrect. In such cases actuarial risk tends to overestimate the true risk and *competing-risk techniques* should be used to estimate cumulative risk [15, 20–23]. In comparing estimates of cumulative risk across studies, it is important to keep in mind that this measure of risk depends strongly on the age distribution of a specific cohort; because of the low background incidence of cancer at young ages, cohorts of HL patients including childhood HL will report much lower cumulative risks than cohorts including adults only.

Most studies reporting cumulative risks make no comparison with cancer risk in the general population, yet population-expected cumulative risks over time can be easily calculated on the basis of cancer incidence rates from a population-based registry [24]. Because certain treatment-related cancers are rare in the general population (e.g., leukemia, sarcoma), a high SIR (compared to the population) may still translate into a rather low cumulative risk. *Absolute excess risk* (AER), which estimates the excess number of SMNs occurring per 10,000 patients per year (beyond those expected from rates in the general population), best reflects the clinical burden of SMN in a cohort. Consequently, this risk measure is also the most appropriate one to judge which second malignancies contribute most to the excess morbidity or mortality.

The calculation of observed-to-expected ratios on the basis of person-years analysis, and the calculation of cumulative risks using life table analysis, involves rather simple statistical methods, which have a strong intuitive appeal. Besides these elementary methods, statistical modeling with Cox proportional hazards model and Poisson regression techniques is increasingly being used to refine the quantification of second cancer RRs (e.g., by estimating dose– and time–response relationships) and to examine the interplay between treatment variables and other factors [25–27].

Each of the data sources that are commonly used to constitute cohorts has specific advantages and disadvantages. *Population-based cancer registries* have large numbers of patients available, which allows the detection of even small excess risks of second cancers [27–30]. An additional advantage is that the observed and expected numbers of cancers come from the same reference population. Disadvantages include limited availability of treatment data and underreporting of SMNs [13, 30, 31] (in particular hematologic

malignancies). Population-based registries differ greatly in these aspects and hence in their usefulness for second cancer studies. If treatment data are not available, it is impossible to know whether excess risk for a SMN is related to treatment or to shared etiology with the first cancer. Underreporting of SMNs clearly leads to an underestimation of second cancer risk. Far higher risks of second leukemia following HL have been found in hospital series [11, 32] than in population-based studies [29]. Part of this difference, however, may be attributable to the more intensive treatments administered in large treatment centers [33]. Despite their disadvantages, population-based registries are well suited to evaluate broadly which SMNs occur in excess following a wide spectrum of different first primary malignancies. They are also a valuable starting point for case-control studies that evaluate treatment effects in detail (see below).

A major advantage of *clinical trial databases* is that detailed treatment data on all patients are available. Comparison of SMN risk between the treatment arms of the trial controls for any intrinsic risk of SMNs associated with the first cancer. However, a limitation of most trials is the small number of patients involved. Although this problem can be overcome by combining data from a number of trials [34], multicenter trial series pose other problems, such as that the main end points of interest in most clinical trials are treatment response and survival. Many trials do not routinely collect information on SMNs or on full systematic long-term follow-up, so that follow-up data to a fixed end date may be very incomplete (and biased). Ideally, routine reporting and assessment of SMN risk should become an integral part of clinical trial research [15, 35, 36].

Most *hospital-based tumor* registries have been in existence for decades and collect extensive data on treatment and follow-up. They share the advantages of clinical trial databases without having their disadvantages. Investigators using hospital tumor registries have ready access to the medical records; often a review of the histologic slides of the first and the second malignancy can also be arranged easily. An additional advantage is that, compared with trial data, hospital registries provide a wider range of treatments and dose levels, which may yield important information on drug and radiation carcinogenesis. Most studies of second cancer risk following HL have been based on hospital registries [8, 32, 37, 38]. As with trial data, however, loss to follow-up and surveillance bias compared to population-based studies can be problematic.

The cohort study is not an efficient study design for examining detailed treatment factors (e.g., cumulative dose of alkylating agents) in relation to second cancer risk. Large cohorts are required to yield reliable estimates of second cancer risk, rendering the collection of detailed treatment data for all patients prohibitively expensive and time consuming. In such instances, the so-called nested case-control study within an existing cohort is the preferred approach [15]. The case group consists of all patients identified with the SMN of interest, and the controls are a random sample of all patients in the cohort who did not develop the cancer concerned, although they experienced the same amount of follow-up time. To achieve maximum statistical power, most case-control studies of second cancer risk use a design in which more than one control is individually matched to each second cancer "case." Matching factors employed in most studies include sex, year of birth, and year at diagnosis of the first primary cancer. The most important criterion for control selection is that each control must have survived, without developing the SMN of interest, for at least as long as the interval between the diagnosis of the first and the second malignancy of the corresponding case. Even if the control group is three times as large as the case group, detailed treatment data need be collected for only a small proportion of the total cohort. It is critical to the validity of the study results that the controls are truly representative of all patients who did not develop the second cancer of interest. For example, biased results may be obtained when controls with untraceable records are replaced by controls with traceable records [15].

In the analysis of a case-control study of second cancer risk, treatment factors are compared between cases and controls. Treatments that have been administered more often, for a longer duration, or with a higher dose to the case group than to the controls are associated with increased risk of developing the SMN of interest. It is important

to understand that in a nested case-control study, the risk associated with specific treatments is estimated relative to the risk in patients receiving other treatment and *not* relative to the risk in the general population. The cumulative risk of developing a SMN cannot be derived using data from a case-control study alone. Estimates of the AERs associated with specific treatments can be derived, however, if the case-control study follows a cohort analysis in which observed-to-expected ratios were calculated for broad treatment groups. Although case-control methodology has only come into widespread use for the investigation of SMN risk in recent decades, several landmark studies have already demonstrated its strengths [33, 39–42].

24.3 Magnitude of the Risk Increase of Second Malignancy, Temporal Patterns, and Age Effects

The largest overall SIR (10- to 15-fold increase) compared to the general population is observed for leukemia (with the greatest risk seen for AML (22-fold), followed by a 6- to 14-fold increased risk for non-Hodgkin lymphoma (NHL), and 4- to 11-fold excesses for connective tissue, bone, and thyroid cancer (Table 24.1). Moderately increased risks (two- to sixfold) are observed for a number of solid tumors, such as cancer of the lung, stomach, esophagus, colon, breast, cervix, and mouth and pharynx and melanoma (Table 24.1) [27, 32, 43, 44, 48]. Because leukemia and NHL are diseases with a low incidence in the population, even a high relative risk compared to the population translates into a relatively low cumulative risk.

Many studies show that, over the long term, the cumulative risk of solid tumors far exceeds that of leukemia and NHL (e.g., 25-year cumulative risks of 23 and 3 % for solid tumors and leukemia, respectively) (Tables 24.2 and 24.3) [32]. Several studies [32, 43, 44, 48] show that, compared with the general population, HL patients experience an excess of about 45–80 malignancies per 10,000 person-years of observation (Tables 24.2 and 24.3). Solid tumors account for the majority of excess cancers (approximately 30–60 per 10,000 patients per year), with lung cancer contributing 10–12 excess cases per 10,000 person-years. Leukemia and NHL each account for about 8–9 cases per 10,000 person-years.

Although SMN risks are often summarized as a single relative risk (SIR) or AER value for the sake of simplicity, it is important to recognize that variation over time is one of the fundamental features of second cancer risk. Further, the nature of this variation is different for different second malignancy sites, and ages at treatment, and additionally relative risks vary over time differently than AERs (Figs. 24.1 and 24.2). Consequently, no single risk value fully describes the SMN risk that patients experience at different times after treatment. Leukemia risk increases approximately 2–4 years following alkylator-based chemotherapy, with the SIR peaking 5–9 years after treatment and decreasing thereafter [32, 33, 43, 44, 47, 48, 53, 54]. The SIR of NHL is increased in the first 5 years after treatment, and study findings disagree regarding whether NHL risk increases [11, 54] or remains constant over time [37, 43, 44, 53].

Most studies report that the overall SIR of solid tumors is minimally elevated in the 1–4-year follow-up period and increases thereafter [11, 32, 37, 44, 48, 53–55]. In studies that include data on HL patients who survived 20 years or more, the RR of solid tumors continued to increase through the 15–20-year follow-up period and stabilized thereafter [32, 37, 38, 43, 44, 47, 48, 54–56]. A Dutch study of patients diagnosed with HL before age 40 reported an SIR of solid tumors of 8.8 in the 20–24-year interval and 5.3 among 25-year survivors, suggesting a possible decrease in very long-term survivors [32]. However, Ng et al. [37] reported an increasing RR of solid malignancy throughout follow-up among patients, all of whom received RT. Reports from the Late Effects Study Group on survivors of pediatric HL and the US Childhood Cancer Survivor Study reported a stable 20- to 24-fold increased relative risk from 15 to over 30 years after diagnosis [47, 50]. An international registry-based study of 5-year HL survivors employed Poisson regression methods comparable to those used to evaluate the temporal trends of cancer risk among atomic bomb survivors [27]. Variation in the risk of solid cancer was found to depend strongly on age at exposure, and attained age, with distinctly different patterns for female

Table 24.1 Relative risks of second malignancy after HL for selected sites in large† cohort studies published since 2000

Site	Swerdlow et al. [43]		Van Leeuwen et al. [32]	Dores et al. [44]	Foss Abrahamsen et al. [45]	Ng et al. [37]	Metayer et al. [46]	Bhatia et al. [47]	Hodgson et al. [27]
	Britain		Netherlands	International	Norway	International	International	USA	International
	$N=5{,}798^{a}$		$N=1{,}253^{a}$	$N=32{,}591^{a}$	$N=1{,}024^{a}$	$N=32{,}591^{a}$	$N=5{,}925^{a}$	$N=1{,}380^{a}$	$N=18{,}862^{a}$
	All ages		Ages <40	All ages	All ages	All ages	Ages ≤20	Ages ≤16	All ages
	Yrs of dx 1963–2001		Med. fup 14.1 years	Med. fup <10 years	Med. fup 14 years	Med. fup 12 years	Med. fup 10.5 years	Med. fup 17 years	Med. fup 12.2 years
			Yrs of dx 1966–1986	Yrs of dx 1935–1994	Yrs of dx 1968–1985	Yrs of dx 1935–94	Yrs of dx 1935–94	Yrs of dx 1955–1986	Yrs of dx 1970–1997
	SIR (*N* observed)		SIR (*N* observed)	SIR (*N* observed)	SIR (*N* observed)	SIR (*N* observed)	SIR (*N* observed)	SIR (*N* observed)	RR[d] (*N* observed)
	Chemo[§]	Ch+RT[§]							
All sites	2.0[b](157)	3.9[b](302)	7.0 (137)	2.3[b] (2,153)	3.5[b] (194)	4.6[b] (181)	7.7[b] (195)	18.5[b] (143)	–[c]
All solid	–[c]	–[c]	6.1[b] (106)	2.0[b] (1,726)	–[c]	3.5[b] (131)	7.0[b] (157)	18.5[b] (109)	–[c] (1,490)
Leukemia	18.4[b](33)	22.7[b](42)	37.5[b] (18)	9.9[b] (249)	13.0[b] (14)	82.5[b] (23)	20.9[b] (28)	174.8[b] (27)	– (–)[e]
NHL	11.5[b](31)	17.1[b](51)	21.5[b] (16)	5.5[b] (162)	24.2[b] (31)	16.5[b] (24)	6.9[b](10)	11.7[b] (7)	– (–)[e]
Female breast	0.5 (5)	2.4[b](30)	5.2[b] (27)	2.0[b] (234)	3.8[b] (23)	6.7[b] (39)	14.1[b] (52)	55.5[b] (39)	6.1[e] (–)
Lung	2.9[b](40)	5.1[b](60)	7.0[b] (13)	2.9[b] (377)	5.1[b] (26)	4.9[b] (22)	5.1[b] (6)	27.3[b] (4)	6.7[e] (–)
Stomach	1.1 (4)	2.7[b](8)	10.9[b] (7)	1.9[b] (80)	4.4[b] (12)	–[c]	13.8[b] (5)	63.9[b] (3)	9.5[e] (–)
Colon	1.1 (10)	2.0[b](17)	2.8 (3)	1.6[b] (129)	1.9 (9)	–[c]	4.7[b] (4)	36.4[b] (8)	4.3[e] (–)
Pancreas	1.0 (2)	2.9 (5)	–[c]	1.5[b] (40)	1.3 (2)	–[c]	10.8[b] (2)	–[c]	4.7[e] (–)
Bone	0	9.0[b] (2)	–[c]	3.8[b] (9)	–[c]	–[c]	9.7[b] (5)	37.1[b] (8)	– (–)[e]
Soft tissue	0	8.9[b] (5)	12.1[b] (3)	5.1[b] (32)	–[c]	–[c]	15.1[b] (9)	–[c]	– (–)[e]
Bone and soft tissue	–[c]	–[c]	–[c]	–[c]	–[c]	26.6[b] (11)	–[c]	–[c]	11.7[e] (–)

Melanoma	0.5 (1)	2.7[b] (7)	5.5[b] (7)	1.7[b] (52)	2.8[b] (8)	3.3[b] (7)	1.9 (5)	–[c]	1.6[e] (–)
Cervix	1.4 (2)	2.7 (6)	–[c]	2.0[b] (37)	1.5 (2)	–[c]	6.1[b] (10)	–[c]	2.2[f] (–)
Thyroid	2.3 (1)	5.7[b](3)	15.2[b] (4)	4.1[b] (47)	–[c]	5.6[b] (5)	13.7[b] (22)	36.4[b] (19)	3.1[g] (–)

NHL non-Hodgkin lymphoma, *Med. fup* median follow up, *Yrs of dx* years of diagnosis, ♂ male, ♀ female, *RR* relative risk, *n* number of second malignacies

[§]Chemo refers to patients treated with chemotherapy only; Ch + RT refers to patients treated with chemotherapy plus radiotherapy

[†]Only includes studies with ≥100 second malignancies; for cohorts included in several reports, only the paper with the longest follow-up is included

[a]Number of Hodgkin disease patients included in the study

[b]Significantly raised ($P < 0.05$)

[c]Data not published

[d]RRs are for males and females combined and for individuals diagnosed with HL at age 30 years and attained age range 40–60 years

[e]RR is for women diagnosed with HL at age 30 years and attained age 40 years

[f]RR is for all female genital second cancers

[g]RR is for individuals diagnosed with HL at age 30 years and all attained ages

Table 24.2 SIR, AER, and cumulative incidence of second malignancy among HL survivors in selected studies

	Van Leeuwen et al. [32]	Swerdlow et al. [43]		Dores et al. [44]	Foss Abrahamsen et al. [45]	Ng et al. [37][a]	Forrest et al. [49]	Hodgson et al. [27]
	Netherlands	Britain		International	Norway	International	Canada	International
	N = 1,253	*N* = 5,798[b]		*N* = 32,591[b]	*N* = 1,024[b]	*N* = 32,591[b]	*N* = 1,732	*N* = 18,862[b]
	<40 years	All ages		All ages	All ages	All ages	All ages	All ages
	Med. fup 14.1 year	Dx yrs 1963–2001		Med. fup <10 years	Med. fup 14 years	Med. fup 12 years	Med. fup 9.8 years	Med. fup 12.2 years
	Dx Yrs 1966–1986			Dx yrs 1935–1994	Dx yrs 1968–1985	Dx yrs 1935–1994	Dx yrs 1976–2001	Dx yrs 1970–1997
		Chemo	Ch + RT					
All cancers								
SIR	7.0	2.0	3.9	2.3	3.5	4.6	3.5	(–)
AER	72.3	32.9	65.3	47.2	10	89.3	(–)	(–)
CI	25 years = 27.7 %	20 year = 13 %	20 year = 18 %	(–)	28 years = 18.8 %	15 years = 13 %	15 years = 9 %	(–)
All solid								
SIR	6.1	(–)		2.0	(–)	3.5	2.8	4.6[b], 3.7[c]
AER	54.5	(–)		33.1	(–)	59.1	(–)	(–)
CI	25 years = 23.3 %	(–)		25 years = 21.9 %	28 years = 14.4 %	(–)	15 years = 7.2 %	30 years = 18.3 % (M)[d] and 26.1 % (F)[d]
Breast (females)								
SIR	5.2	0.5	2.4	2.0	3.8	6.7	(–)	6.1
AER	29.4	−1.8	5.1	10.5	27[e]	20.8	(–)	61[f]
CI	25 years = 16.3 %			25 years = 9.3 %	(–)	(–)	(–)	(–)

Acute leukemia								
SIR	37.5	18.4	22.7	9.9	13	82.5		(–)
AER	10.8	12.8	11.7	8.8	8[g]	14.3		(–)
CI	25 years = 3.3 %			(–)	28 years = 1.5 %	(–)		(–)

SIR standardized incidence ratio, *AER* absolute excess risk, *CI* cumulative incidence
[a]All patients received RT
[b]Supradiaphragmatic sites
[c]Infradiaphragmatic sites
[d]Diagnosed at age 30
[e]For women with 10–19 years of follow-up
[f]AER predicted for a 30 year old female attained age 50
[g]Applies to patients diagnosed ≤40 years of age

Table 24.3 SIR, AER, and cumulative incidence of second malignancy among pediatric HL survivors

	Castellino et al. [50]	Bhatia et al. [47]	Basu et al. and Constine et al. [51, 52]
	USA	USA	USA
	1,675	*N* = 1,380	*N* = 930
	Ages <21 year	Ages ≤16	Ages <19
	Med. fup 23.8 years	Med. fup 17 years	Med. fup 16.8 years
	Yrs of dx 1970–1986	Dx yrs 1955–1986	Dx yrs 1960–1990
All cancers			
SIR	8.7	18.5	14.2
AER	69.2	65[a]	62.6
CI	30 year = 10.9 % (M) and	30 year = 26.3 %	20 year = 8 % (M) and
	26.1 % (F)		23 % (F)
All solid			
SIR	(–)	18.5	(–)
AER	(–)	51[a]	(–)
CI	(–)	30 year = 23.5 %	(–)
Breast (females)			
SIR	17.0	55.5	37.3
AER	29.0	53[a]	18.6
CI	30 year = 18.3 %	30 year = 16.9 %	30 year = 24 %
Acute leukemia			
SIR	12.7	174.8	21.5
AER	3.4	1.3	5.7
CI	(–)	20 year = 2.1 %	(–)

SIR standardized incidence ratio, *EAR* excess absolute risk, *CI* cumulative incidence

[a]Results were published per 1,000 person-years. For consistency these have been multiplied by 10 (i.e., 10,000 P-Y)

breast cancer, thyroid cancer, and other solid tumors (Fig. 24.3). With increasing attained age, the relative risk of breast cancer declined among females diagnosed at a young age (modeled age 20 years), whereas this decline was much less pronounced among women treated at older ages (30 or 40 years at HL diagnosis) (Fig. 24.2). In contrast, the relative risk of other solid cancers remained stable with advancing attained age, with a small decline after attained age of 60 years (Fig. 24.1). The AER of breast cancer and non-breast solid cancers increased with increasing attained age for all age groups [27] (Figs. 24.1 and 24.2). These findings demonstrate the importance of considering both age at exposure and attained age in the evaluation of SMN risk, as well the potential importance of considering different solid cancers separately. Combining different age-at-treatment groups or all solid tumor types together may obscure significant variation in risks over time that can occur among different age groups or different SMN types. Also, the AER of SMNs changes over time differently than the SIR (Figs. 24.1 and 24.2). With increasing time since treatment, the major influence on the AER is the increasing background (i.e., "expected") rate of cancer, which rises rapidly with increasing age. As these baseline risks increase with advancing age, even stable elevations in SIRs translate into rising AER over time (Fig. 24.1).

24.4 Contributors to Second Cancer Risk

24.4.1 Radiation Therapy

Increased risks of second cancers following RT for HL have been reported for over two decades [29]. These reports add to a substantial body of evidence demonstrating that radiation is carcinogenic over a broad range of doses and can increase the risk of a variety of different tumor types [57–61]. Certain tissues, such as the female breast, and thyroid appear to be particularly susceptible to radiation-induced malignancy.

Among HL patients, treatment with mantle RT (involving the axillary, mediastinal, and neck nodes) to doses of 35–45 Gy is associated with a 2- to 20-fold increased relative risk of breast cancer, with a strong influence of age at exposure, as discussed in detail below [24, 27, 32, 37, 46, 47, 62]. Mantle RT is also associated with an increased relative risk of lung cancer, although

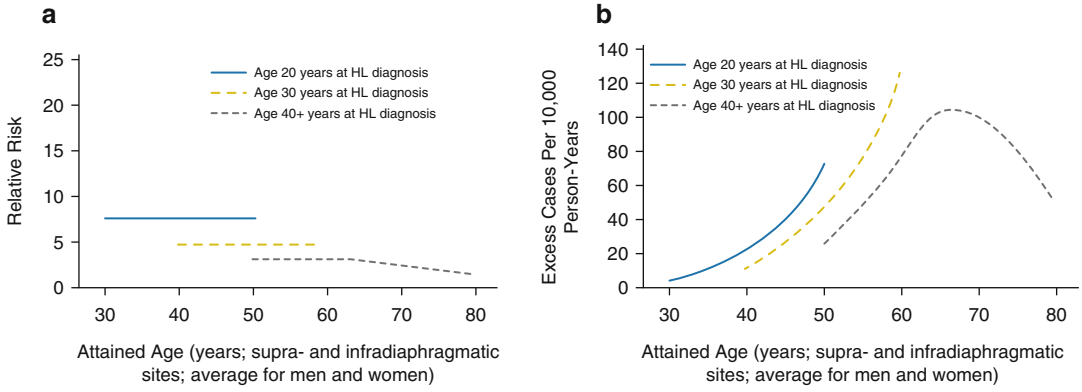


Fig. 24.1 Relative risk (*RR*) and absolute excess risk of supra- and infradiaphragmatic solid cancers according to age at HL diagnosis and attained age. (**a**) RR of supra- and infradiaphragmatic solid cancers. (**b**) AER of supra- and infradiaphragmatic solid cancers (From: Hodgson et al. [27])

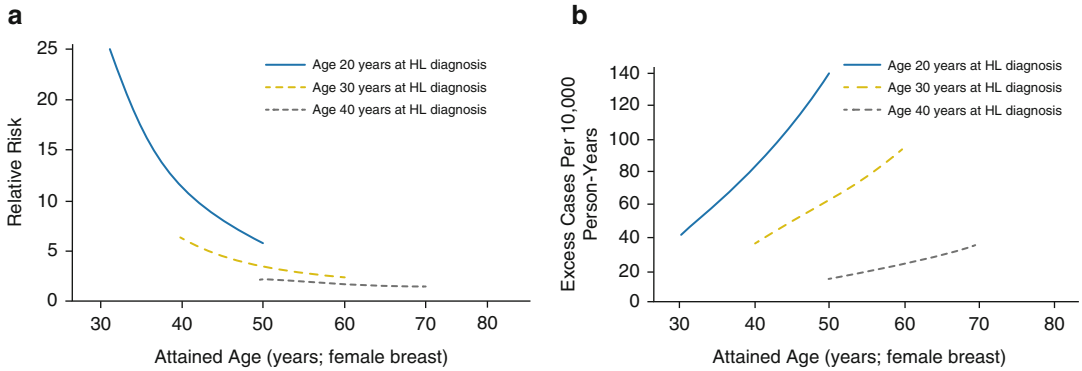


Fig. 24.2 Relative risk (*RR*) and absolute excess of female breast cancer according to age at HL diagnosis and attained age. (**a**) RR of female breast cancer. (**b**) AER of female breast cancer (From: Hodgson et al. [27])

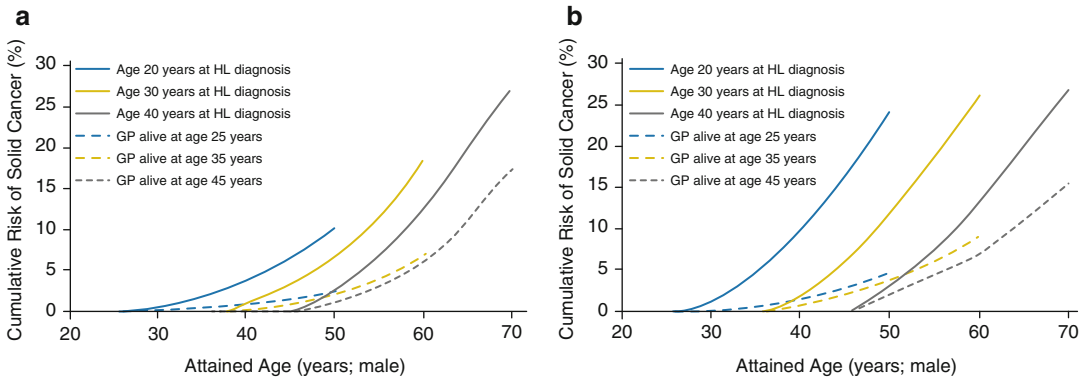


Fig. 24.3 (**a**) Cumulative incidence of all solid cancers among 10,619 male 5-year survivors of Hodgkin lymphoma (HL) compared with men of the same age in the general population (GP). (**b**) Cumulative incidence for 8,243 female 5-year survivors compared with women of the same age in the GP (From: Hodgson et al. [27])

the absolute excess risk is in fact small in the first 10–20 years after exposure, particularly among those treated at young ages (e.g., ≤0.2 per 10,000 person-years among those treated before age 20 years) [47, 48]. The risks of other solid cancers, especially stomach cancer, have also been shown to be elevated after RT [40].

Much of our current understanding of the relationship between radiation dose and cancer risk has been derived from cohort studies of individuals exposed to low levels of radiation, such as atomic bomb survivors [60, 63–65]. However, extrapolation of the dose–risk relationships seen at low total body doses into the 15–40 Gy ranges used for HL RT cannot be done with certainty, due to differences relating to dose rate, neutron exposure, and the possibility of cell killing at high doses. More recently, studies of SMN risk have evaluated the dose–risk relationship in the radiation dose range commonly used in the treatment of HL.

There appears to be an approximately linear increase in the risk of leukemia with increasing radiation dose to the bone marrow, up to approximately 2–4 Gy [66–68]. At doses above this, the risk of leukemia per unit radiation dose to the bone marrow appears to decline [66–68], a finding generally attributed to killing or inactivation of preleukemic cells at the higher radiation doses [66, 69]. One study of leukemia risk in survivors of uterine cancer, however, showed little evidence for such a clear downturn in risk [67].

The "bell-shaped" dose–risk curve for leukemia, with a peak at 2–4 Gy, does not seem to apply to the risk of most solid tumors. Most studies examining the dose–risk relationship for solid tumors suggest a continued increase in risk with doses up to approximately 40 Gy [41, 42, 70, 71]. Two studies have evaluated the relationship between radiation dose and breast cancer risk among adult females treated for HL with mantle RT [41, 42]. The RT dose to the area of the breast where the case's tumor had developed was estimated for each case-control set based on simulation films of the original HL radiotherapy and mammograms indicating the position of the breast tumor. Both studies showed increasing risk of breast cancer over the dose range commonly used in the treatment of HL. For example, in a large international collaborative case-control study of women treated for HL at age 30 years or less [42] (105 patients with breast cancer after HL and 266 controls without breast cancer), the risk was eightfold increased (95 % CI, 2.6–26.4) for the highest dose category (median dose of 42 Gy) compared to the lowest one (<4 Gy) (p trend <0.001, Table 24.4) [42]. Similarly, Inskip et al. conducted a case-control study of breast cancer in a cohort of 6,647 female survivors of childhood cancer participating in the US Childhood Cancer Survivors Study (CCSS) [70]. Radiation dose was estimated to the site of breast cancer for 120 cases (65 % treated for HL) and 464 controls (40.5 % treated for HL). They reported a linear increase in breast cancer risk with increasing dose, such that, compared to those with no radiation dose to the breast, the odds ratio of breast cancer was 11-fold higher among those with breast exposures of 40 Gy. This dose–risk relationship was modified by ovarian radiation exposure: the slope of the dose–risk curve was significantly less steep among those with ovarian radiation (>5 Gy), presumably due to the impact of hormonal influences on breast cancer risk (Fig. 24.4) [70].

The risk of lung cancer also rises with increasing radiation dose up to 40 Gy and with an increasing volume of lung irradiated (Table 24.4) [72, 73]. A study in breast cancer survivors showed that risk of esophageal cancer increases with higher radiation doses up to 45 Gy [74]. Furthermore, two studies in survivors of childhood cancer [75, 76] suggest that the risk of bone sarcoma increases rapidly with increasing dose above 10 Gy [77]. An international case-control study of stomach cancer nested in a cohort of 19,882 HL survivors found that stomach doses ≥25 Gy were associated with a significantly elevated risk of gastric cancer particularly when also given procarbazine-containing chemotherapy [40]. Risk increased with larger radiation doses to stomach up to 40–44 Gy (Table 24.4). Similarly, van den Belt reported that the risk of stomach cancer increases linearly with radiation dose to the stomach, with tenfold increased risk for mean stomach doses of >20 Gy compared to less than

Table 24.4 Relative risks of breast, lung, and stomach cancers after Hodgkin lymphoma, according to radiation dose to affected site in breast/lung/stomach and number of cycles of alkylating chemotherapy[a, b]

Breast cancer[a]			Lung cancer[b]			Stomach cancer[c]		
Radiation dose to affected site in breast	Relative risk	95 % CI	Radiation dose to affected site in lung	Relative risk	95 % CI	Radiation dose to affected site in stomach	Relative risk	95 % CI
0–3.9 Gy	1.0	(Referent)	0	1.0	(Referent)	0	1.0	(Referent)
4.0–6.9 Gy	1.8	0.7–4.5	>0–4.9 Gy	1.6	0.5–5.2	>0.1–0.9 Gy	1.3	0.4–4.1
7.0–23.1 Gy	4.1	1.4–12.3	5–14.9 Gy	4.2	0.7–21	1.0–4.9 Gy	1.0	0.3–3.5
23.2–27.9 Gy	2.0	0.7–5.9	15.0–29.9 Gy	2.7	0.2–15	5.0–24.9 Gy	0.5	0.1–2.7
28.0–37.1 Gy	6.8	2.3–22.3	30.0–39.9 Gy	8.5	3.3–24	25.0–34.9 Gy	4.6	1.2–20.5
37.2–40.4 Gy	4.0	1.3–13.4	≥40.0 Gy	6.3	2.2–19	35.0–39.9 Gy	8.2	2.6–29.7
40.5–61.3 Gy	8.0	2.6–26.4				≥40.0 Gy	4.2	1.2–15.6
No. of cycles of alkylating agents			No. of cycles of alkylating agents			No. of cycles of alkylating agents		
0	1.0	(Referent)	0	1.0	(Referent)	0	1.0	(Referent)
1–4	0.7	0.3–1.7	1–4	4.0	1.3–12.5	1–5	1.0	0.5–2.4
5–8	0.6	0.3–1.1	5–8	6.2	2.6–17.1	6	1.7	0.7–4.4
≥9	0.2	0.1–0.7	≥9	13.0	4.3–45	7–10	1.9	0.7–4.9
						≥11	3.0	1.2–7.7

[a]Adapted from results by Travis et al. [42]
[b]Adapted from results by Gilbert et al. [72]
[c]Adapted from results by Morton et al. [40]

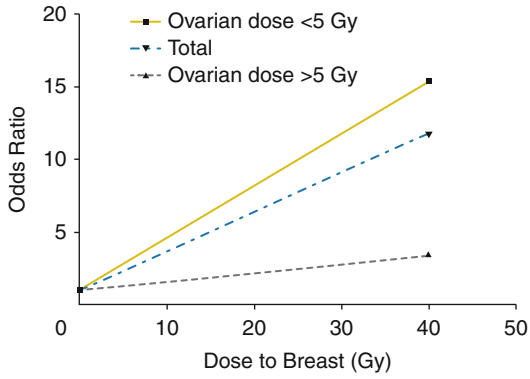


Fig. 24.4 An example of interaction between treatments. Fitted breast cancer risk by radiation dose to the breast and ovary; results from the Childhood Cancer Survivor Study, based on 120 breast cancer cases and 464 controls (From: Inskip et al. [70])

11 Gy [78]. Radiation-induced thyroid cancer may be an exception to these general findings for other solid cancers: dose–risk studies have suggested a leveling or decrease in thyroid cancer risk with doses above 10–30 Gy [61, 79, 80] although one study reported increasing risk of thyroid cancer with increasing dose up to 60 Gy [81].

These dose–risk studies provide a critical component to understanding the potential risk of second cancers associated with contemporary involved field RT (IFRT) or involved node/site RT (INRT/ISRT for HL). Specifically, they suggest that reduction in normal tissue dose associated with reducing the prescribed dose from 36–40 Gy to 20–30 Gy should produce a lower risk of breast, lung, and (when infradiaphragmatic RT is used) stomach cancers. The risk of thyroid cancer, however, may not be reduced.

The treatment of large volumes of normal tissues in pediatric patients, even with lower prescribed doses of 15–36 Gy, was still associated with substantially increased risks of second malignancy in one study [82], illustrating the importance of not only limiting the prescribed dose but also reducing the volume of normal tissue irradiated (and hence the normal tissue dose) compared to historic mantle or extended-field RT. One study found that for patients with mediastinal disease, the transition from mantle fields to mediastinal IFRT resulted in an approximately 65 % reduction in breast tissue exposure, largely due to the exclusion of the axillae [83]. Clinical studies provide evidence that this volume-related reduction in breast exposure appears to translate into a reduced risk of subsequent breast cancer. A recent large Dutch study, including 1,122 female 5-year survivors of HL, examined the effect of radiation fields (volume) on the risk of breast cancer up to more than 30 years after treatment of HL [24]. Mantle field irradiation was associated with a 2.7-fold (95 % CI, 1.1–6.9) increased risk of breast cancer compared to similarly dosed (36–44 Gy) radiation to the mediastinum alone (Fig. 24.5) [24]. This finding is reassuring since present-day radiotherapy for HL employs smaller radiation volumes which have been shown to reduce normal tissue doses [24, 84, 85].

24.4.2 Chemotherapy

There is a well-established association between exposure to alkylating chemotherapy agents and an increased risk of acute myeloid leukemia (AML) in HL survivors. The MOPP chemotherapy regimen (mechlorethamine, vincristine, procarbazine, and prednisone) was widely employed in the 1970s, as it became evident that it was superior to RT alone in curing high-risk HL. However, it was associated with an increased relative risk of AML of 20–50-fold [11, 54, 86–90]. As described below, there is no consistent evidence that the addition of extended-field RT to MOPP increases AML risk further [33, 91]. Since chemotherapy agents are given in combination, it is challenging to disentangle the effects of individual agents and the impact of cumulative dose, duration of use, and dose intensity on the risk of AML. In general, the cumulative dose of alkylating agents appears to be the strongest determinant of risk [14, 86, 92, 93].

Most cases of alkylating agent-induced AML are preceded by myelodysplasia (MDS), which generally progresses to AML within a year [54, 93–95]. Cytogenetic studies of alkylator-induced AML/MDS have shown unbalanced chromosome aberrations, primarily with loss of whole chromosomes 5 and/or 7 or various parts of the long arms of these chromosomes [93, 95, 96].

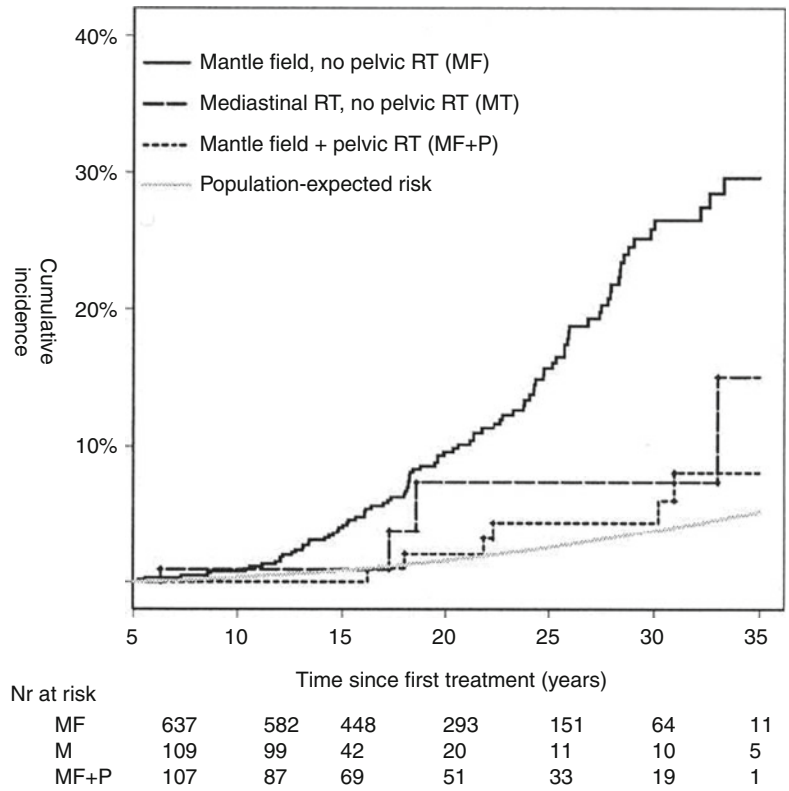


Fig. 24.5 The cumulative incidence of breast cancer after HL. Cumulative incidence of invasive breast cancer according to radiation fields and population-expected risk. (*RT* Radiotherapy) (From: De Bruin et al. [24])

More recently, another class of drugs used in the treatment of HL, topoisomerase II inhibitors, has also been associated with elevated risks of AML [14, 93]. Examples of these drugs used in HL treatment include etoposide and doxorubicin. Early evidence suggests that doxorubicin and 4-epidoxorubicin (epirubicin) may be associated with increased risks of AML [33, 96, 97], but this association is not nearly as well established as it is for alkylating agents and requires further study. Certainly, ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine) is associated with a lesser risk of AML than MOPP chemotherapy, although it is not clear that this risk is eliminated altogether [43, 54, 98]. Etoposide, used in newer HL chemotherapy regimens such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and OEPA (vincristine, etoposide, prednisolone, doxorubicin), is also leukemogenic [99]. As compared with "classical" alkylating agent–induced AML, etoposide-related AML typically occurs sooner after exposure, generally lacks a preceding myelodysplastic phase, and is characterized by balanced translocations involving chromosome bands 11q23 and 21q22 [14, 93, 100–102].

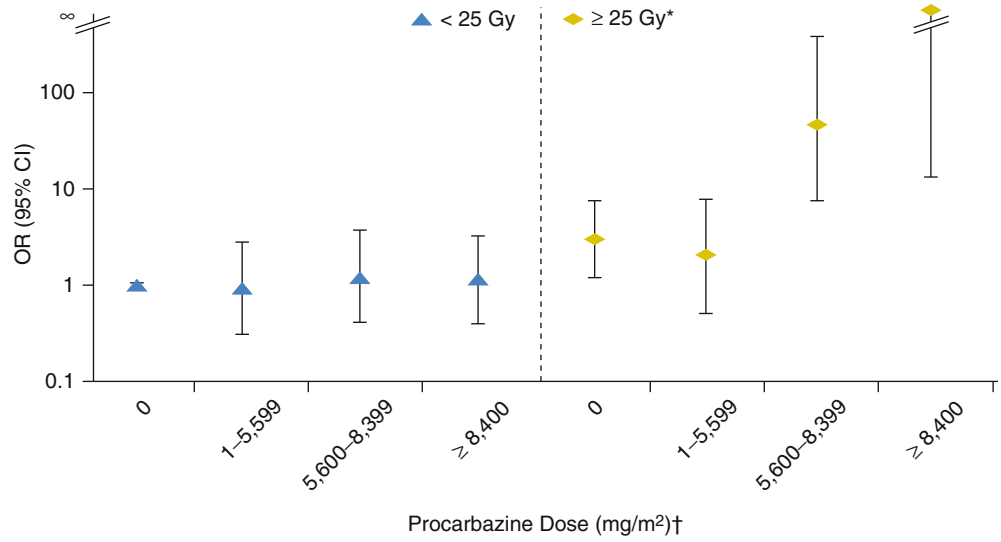
Evidence increasingly suggests that chemotherapy also may play a role in the development of non-hematologic SMNs, which typically occur >10 years after exposure [14, 103]. Alkylating agents have been reported to increase risks for lung, thyroid, gastrointestinal, and bladder cancers as well as sarcoma. For example, lung cancer risk after HL is increased 2–4-fold with increasing number of cycles of alkylating agent-containing chemotherapy, particularly MOPP [39, 43, 48, 73, 104, 105]. Among childhood cancer survivors, receipt of any alkylating agent has been associated with 2.4-fold increased risk for thyroid cancer; receipt of procarbazine and platinum has been associated with 3.2- and 8.6-fold increased risk,

respectively, of gastrointestinal cancer, and both alkylating agents and anthracyclines have been associated with sarcoma risk [76, 106–108].

The causal link between cyclophosphamide and bladder cancer represents one of the few established relationships between a specific alkylating agent and carcinogenesis at a specific site, likely as a result of direct genotoxic exposure of bladder epithelium from cyclophosphamide metabolites [109, 110]. Procarbazine-related risks for the gastrointestinal tract also may be related to direct exposure [40, 107, 111]. For procarbazine and risk of stomach cancer, a dose-dependent effect has recently been found in survivors of HL [40, 78]. Furthermore, patients who received both radiation to the stomach ≥25 Gy and high-dose procarbazine (≥5,600 mg/m^2) had strikingly elevated stomach cancer risk (RR, 77.5; 95 % CI, 14.7–1452) compared with those who received radiation <25 Gy and procarbazine <5,600 mg/m^2. Risk was also elevated (RR, 2.8; 95 % CI, 1.3–6.4) among patients who received radiation to the stomach ≥25 Gy but procarbazine <5,600 mg/m^2; however, no procarbazine-related risk was evident with radiation <25 Gy (Fig. 24.6). Treatment with dacarbazine also increased stomach cancer risk (RR, 8.8; 95 % CI, 2.1–46.6), after adjustment for radiation and procarbazine doses [40].

24.4.3 Genetic Factors

There is increasing interest in identifying the molecular and cellular basis underlying the development of SMNs in HL survivors and other cancer survivors. Germline mutations in the RB1 tumor suppressor gene, associated with hereditary retinoblastoma, constitute a well-described example of a rare mutation with high penetrance that confers a large risk of developing radiation-related second cancer [112–114]. Although there



Patients	n	18	7	6	8	18	5	15	10
	%	21	8	7	9	21	6	17	11
Controls	n	70	24	25	19	28	13	2	0
	%	39	13	14	10	15	7	1	0
	OR‡	1.0	0.9	1.2	1.1	2.9	2.0	43.8	∞
	95% CI	referent	0.3 to 2.7	0.4 to 3.6	0.4 to 3.2	1.2 to 7.6	0.5 to 8.0	7.4 to 861.9	12.9 to ∞

Fig. 24.6 Risk of stomach cancer after Hodgkin lymphoma in relation to radiation dose to stomach and procarbazine dose (From: Morton et al. [40])

is evidence that patients with a family history of cancer are more likely to develop radiation-related SMNs [115–120], it is unlikely that a single candidate gene abnormality will account for a significant component of the SMN risk following HL treatment. Currently, there is no uniform evidence that BRCA1 or BRCA2 gene mutations mediate the development of radiation-related breast cancers. Two studies have reported that mammographic radiation exposure does not significantly contribute to the risk seen in BRCA1/2 mutation carriers [121, 122], though three other studies found that young BRCA1/2 mutation carriers had an increased risk of breast cancer if exposed to a significant number of chest X-rays [123–125]. There have been no studies examining whether carriers of BRCA mutations with HL have an increased risk of RT-associated cancers. Homozygous mutations in the ataxia-telangiectasia (ATM) gene are associated with significant radiation toxicity, although two studies have reported that no ATM mutations were found in women who had developed breast cancer after RT for HL [119, 126]. Moreover, while P53 gene mutations are associated with an increased risk of primary malignancy [127], and increased radiation sensitivity in vitro [128, 129], there is currently no evidence that P53 mutations modify the risk of treatment-related SMN in HL patients.

Outside of the context of cancer predisposition syndromes, most studies have investigated SMN risks in relation to specific genes, selected based on understanding the biologic pathways of drug metabolism and carcinogenesis. These studies have reported associations for variants in oxidative stress, DNA detoxification, and DNA repair genes with treatment-related leukemia [130–136] and *FGFR2* with breast cancer after supradiaphragmatic radiotherapy for HL [137].

Methylating agents (e.g., dacarbazine) produce DNA damage, the repair of which is mediated in part by the MLH1 gene. Worrillow et al. examined the frequency of a common MLH1-93 polymorphism among patients who developed cancer following chemotherapy and/or radiotherapy, or were diagnosed with de novo myeloid leukemia or HL, and healthy controls [132]. Carrier frequency of the MLH1-93 variant was higher in patients who developed therapy-related AML or breast cancer after methylating chemotherapy for HL compared to patients without previous methylating exposure.

Recently, genome-wide association studies (GWAS), which agnostically interrogate hundreds of thousands to millions of variants across the genome [138], have revealed genomic regions associated with treatment-related leukemia [139] and with SMNs occurring among HL survivors initially treated with radiotherapy [140], supporting the idea of genetic susceptibility to treatment-related SMNs. A key limitation of previous studies has been a lack of detailed treatment data and/or sufficient sample size to quantify the effect of specific variants in individuals with differing treatment exposures. Because of the large sample sizes for such studies, international collaboration will be essential. Lending further support to the importance of this research area, several GWAS have identified genomic regions associated with toxicity after radiotherapy [141, 142].

24.5 Risk of Selected Second Malignancies

24.5.1 Risk Factors for Leukemia

Leukemia following HL is certainly the most studied treatment-induced malignancy, and thus, extensive knowledge of its risk factors has emerged [14, 91, 143]. Leukemia was the first malignancy for which elevated risk after treatment for HL was observed, probably because of the relatively short latency period, the rarity of acute leukemia in the general population, and the large SIR.

Overall, in patients treated in the 1960s–1980s, risks compared with the general population have been reported to be 10- to over 80-fold increased (Table 24.1). Nearly all studies show that the SIR of leukemia is higher than that of NHL and much greater than that of solid tumors overall (Table 24.1). Because the background risk of leukemia in the population is low, however, this strongly increased SIR translates into a relatively

low cumulative risk, ranging between 1.4 and 4.1 % at 15 years [11, 32, 43, 47, 48, 55, 86, 98]. Overall, the AER has varied between 8 and 30 excess cases per 10,000 patients per year (Tables 24.2 and 24.3) [43, 44, 48, 144].

Radiotherapy alone is associated with a small, or no, increased risk of leukemia compared with the risk in the general population [11, 32, 48, 55, 86], while alkylating agent CT, as widely used up to the 1990s, is linked with greatly elevated risk. In cohort analysis of CT-treated patients, the SIRs of leukemia overall tend to be over 20-fold increased compared to the general population, while for AML over 50-fold risk increases are reported [11, 43, 47, 54, 86, 88–90].

Several studies have compared the leukemogenicity of different CT regimens. Where exposure has been quantified, risk appears to be most related to total dose of alkylating agents or nitrosoureas [11, 33, 76, 86, 90, 145]. Risk of AML rises sharply with an increasing number of MOPP (mechlorethamine, vincristine, procarbazine, prednisone) (or MOPP-like) cycles [33, 86]. The risk associated with 10–12 MOPP cycles appears to be approximately three to five times higher than the risk following 6 MOPP cycles [33, 86]. Total dose of alkylators and nitrosoureas is likely the explanation of the reports of higher risk associated with salvage CT or maintenance CT [55, 86, 146], but there is evidence that retreatment may be a factor in risk [52, 86, 145, 147]. Among those treated with variations of MOPP that substitute cyclophosphamide for mechlorethamine, the risks are lower [11, 86, 90, 148, 149]. Mechlorethamine and procarbazine are usually given in combination, so it is difficult to disentangle the effects of each. One study showed that mechlorethamine rather than procarbazine had the strongest effect on leukemia risk [86].

In the 1980s, MOPP-only CT has been gradually replaced by ABV(D) (doxorubicin, bleomycin, vinblastine, and dacarbazine)-containing regimens in many centers. There are only a few reports on AML occurrence following ABV(D) alone. Patients treated with ABVD in the Milan Cancer Institute, where this regimen was designed, were shown to have a significantly lower risk of AML than MOPP-treated patients (15-year cumulative risks of 0.7 and 9.5 %, respectively) [98]. Another study showed that HL patients treated with MOPP/ABV(D)-containing regimens in the 1980s had substantially lower risk of AML/MDS than patients treated in the 1970s with MOPP alone (10-year cumulative risks of 2.1 and 6.4 %, respectively, $P=0.07$) [54]. An international collaborative study showed that the AER of AML declined significantly after 1984, from 7.0 to 4.2 per 10,000 patients per year in those diagnosed before age 35 years and from 16.4 to 9.9 per 10,000 patient-years in the ≥35 age group [144]. Also, AML risk was recently assessed in three generations of Stanford clinical trials for HL patients. The incidence of AML/MDS was significantly lower in patients treated (1989–2003), especially with the Stanford V regimens (0.3 % at 10 years) [150].

There is, however, concern about the role of anthracyclines and epipodophyllotoxins (both of which are topoisomerase II inhibitors) in the risk of leukemia. Limited evidence suggests that doxorubicin in combination with higher doses of alkylating agents and/or epipodophyllotoxins may have a synergistic effect on the risk of AML. Analyses of the German Hodgkin Lymphoma Study Group also show low risks of AML after COPP-ABVD (mechlorethamine replaced by cyclophosphamide) and standard BEACOPP (bleomycin, etoposide, doxorubicin combined with COPP), while substantially increased risk of AML was observed for the escalated BEACOPP regimen (actuarial risk at 5 years of 2.5 %) [34, 151].

Some studies suggest that RT adds to the leukemia risk associated with CT [91, 152], whereas other large series indicate that the risk of AML after combined treatment is comparable to that after CT alone [33, 43, 48, 86]. The interaction between RT and CT could be evaluated most rigorously in the large case-control study by Kaldor et al. [33] which included 163 cases of leukemia following HL. For each category of radiation dose (<10, 10–20, >20 Gy to the active bone marrow), leukemia risk clearly increased with the number of CT cycles. In contrast, among patients with a given number of CT cycles, risk of leukemia did not consistently increase with higher

radiation dose. Taken together, the preponderance of available data does not support the hypothesis that the combination of CT and RT confers a higher risk of leukemia than CT alone.

Therapeutic intensification with autologous stem cell transplantation (ASCT) is increasingly used for lymphoma patients who relapse. In some series relatively high actuarial risks (4–15 % at 5 years) of AML and myelodysplasia (MDS) have been observed after ASCT for HL [91]. Evidence suggests that much of the risk is related to intensive pre-transplant CT. Forrest and colleagues compared the risk of AML/MDS between 202 patients who had undergone ASCT and 1,530 patients who underwent conventional therapy for HL [49]. The 15-year cumulative incidence of developing AML/MDS was 1.1 % (95 % confidence interval (CI), 0.6–1.8) for those treated with conventional therapy alone and 3.6 % (95 % CI, 0.9–9.6) for those undergoing ASCT ($P=0.22$). In multivariate analysis, leukemia risk was also not influenced by ASCT [49].

The risk of AML in relation to treatment-associated acute and chronic bone marrow toxicity has been examined in only two studies to date [86, 153]. Significantly increased risks of leukemia were found among patients who developed thrombocytopenia, either in response to initial therapy or during follow-up. After adjustment for type and amount of CT, patients who showed a ≥70 % decrease in platelet counts after initial treatment had an approximately fivefold higher risk of developing leukemia than patients who showed a decrease of 50 % or less [86]. Severe acute thrombocytopenia may indicate greater bioavailability of cytotoxic drugs, which would likely contribute to the development of leukemia. In support of these findings, a study of leukemia risk after autologous bone marrow transplantation found that low platelet counts at the time of transplant were predictive for MDS/AML development in NHL patients who had received intensive pretransplant CT [153].

The prognosis of AML/MDS after HL treatment is extremely poor, with only 15 % of patients surviving more than 1 year and no apparent survival benefit from allogenic stem cell transplantation [91, 150, 154].

24.5.2 Risk Factors of Non-Hodgkin Lymphoma (NHL)

Krikorian and colleagues were the first to demonstrate a clearly elevated cumulative risk of NHL after HL, which amounted to 4.4 % at 10 years in patients given both irradiation and CT [155]. Other investigators have confirmed the increased risk of NHL in HL survivors [11, 32, 37, 43–45, 47, 48, 53, 55, 86]. In most studies the SIR for NHL ranges between 6 and 36 compared to the risk in the general population (Table 24.1). Because the background risk of NHL in the general population is low, this rather high SIR translates into a relatively low cumulative risk, ranging between 2 and 4 % at 20 years [32, 48, 156] in the larger studies. AER in these studies has varied between 5 and 13 excess NHL cases per 10,000 patients per year [43, 44, 48]. The majority of cases of second NHL diagnosed after HL are intermediate or aggressive histology B-cell lymphomas [156–158] and more often arise in extranodal sites than primary NHL [156, 159] (79 % of cases [158]).

The causes of the excess risk are not well understood. The results of older studies may in part reflect misclassification of the primary lymphoma in the absence of modern lymphoma immunophenotyping protocols (i.e., NHL misdiagnosed as HL) [156]. Rueffer et al. [156] reported that an expert panel of pathologists reviewing the histology of 4,104 HL patients (German Hodgkin Lymphoma Study Group) rejected 114 cases (2.1 %) initially diagnosed as HL and rediagnosed them as primary NHL. Only very few studies included a review of diagnostic pathology slides of the second NHL and original HL in order to avoid such misclassification [53, 86, 156].

Other investigators argued that the clinical, histologic, and immunophenotypic findings of NHL among HL survivors were analogous to those of NHL arising in immunosuppressed patients, suggesting that immunodeficiency plays a role in the pathogenesis of second NHL in these patients [158]. This view is supported by several studies in which risk did not vary appreciably between treatments [11, 48, 88]. However, in

other studies, the risk of NHL was found to be lowest among patients treated with RT alone and highest among patients who received intensive combined modality treatment, both initially and for relapse [55, 86, 155, 156, 160].

There exists some evidence indicating that transformation to NHL may be part of the natural history of the lymphocyte predominant subtype of HL [159, 161], which might explain the association between lymphocyte predominant HL and NHL risk observed in the International Database on HL [55] and the British National Lymphoma Investigation [162]. It may be that more than one of the above mechanisms operates in the development of NHL following treatment for HL. Although transformation to NHL may be part of the natural history of some types of HL, the role of intensive combined modality treatment and its associated immunosuppression should be explored further. Future studies should incorporate a review of all slides of the second NHL and the original HL diagnosis by an expert pathologist.

24.5.3 Risk Factors for Breast Cancer

For female HL survivors, the strongly elevated risk of breast cancer following radiotherapy has become a major concern [24, 32, 44, 163–167]. In several studies breast cancer contributes most to the AER of second malignancy in female survivors [27, 32, 37, 47, 168]. The magnitude of the risk of breast cancer after HL and risk factors for its development have been discussed in several review papers [59, 169–171]. The risk of breast cancer after HL greatly depends on age at treatment, time since treatment, therapies given for HL, and hormonal factors.

The overall SIR of breast cancer in female HL survivors has been only modestly elevated in studies which included all age groups (about 1.5–2.2-fold risk increases compared to the general population) (Table 24.1) [27, 29, 44, 48, 54, 55, 149]. Larger SIRs (four- to sevenfold) were observed in studies with predominantly young adults or a large proportion of long-term survivors [24, 32, 37, 38, 45, 62]. AERs for all ages have been around 2–10 per 10,000 HL patients per year (Tables 24.2 and 24.3) [44, 48, 54], again with a greater risk (20–60 per 10,000 per year) in studies with predominantly young adults and/or a large proportion of long-term survivors [24, 32, 37, 45, 62]. Several studies covering the whole age range have shown that the SIR of developing breast cancer increases dramatically with younger age at first irradiation (or start of treatment) (Fig. 24.2) [24, 27, 32, 37, 44, 45, 48, 62, 172]. A strong trend of increasing SIR of breast cancer with decreasing age at exposure has also been observed in other radiation-exposed cohorts [65, 173–175]. In a Dutch study, survivors who had radiation treatment before 21 years of age had an 18-fold increased risk of breast cancer compared with the general female population of the same age; women irradiated at ages 21–30 had a sevenfold increased risk, women irradiated at ages 31–40 had a 3.2-fold increased risk, and a small, nonsignificant increase was observed for women irradiated at ages 41 or older (SIR, 1.4) [24]. Similar trends have been reported by others [37, 44, 48, 62, 176]. Most studies confirm that breast cancer risk is not elevated compared with the general population in women treated after age 35–30 [44]. In most studies the AER of breast cancer is also highest after treatment before age 20 (Fig. 24.2) [24, 27, 32, 37, 44, 62], but shows little variation between exposure at ages 20–35.

The SIR of breast cancer after HL treatment at ages under 16 has ranged from 17 to 458 [88, 89], with most studies showing SIRs around 50–100 [32, 37, 38, 47, 172, 177–179]. Three studies with long-term follow-up reported that, among women treated before age 20, the SIR compared with age-matched peers from the general population did not consistently vary by age at treatment [47, 70, 177]. This would imply that prepubertal radiation exposure increases the risk to the same extent as exposure during puberty. In the atomic bomb survivors and other radiation-exposed cohorts, the RR also did not vary by exposure age for ages under 20 [180]. However, a recent British study reported greatest SIRs for female HL survivors irradiated around age 14 [62] and a subsequent case-control study observed especially high risk when women were irradiated within

6 months of menarche [181] possibly associated with pubertal breast development.

The large variation in breast cancer risks across studies, especially in young patients, is not surprising in view of the large differences between series in important variables such as the proportion of patients irradiated, duration of follow-up, and completeness of follow-up. Studies with more complete follow-up have generally found lower risks of breast cancer [32, 44, 48, 62, 89, 179] than those in which follow-up was less complete or not addressed [87, 88, 172].

Incomplete follow-up may lead to overestimation of second malignancy risk if patients who remain well lose contact with clinical follow-up, while those with second cancer come to attention because of this. In a Dutch study, with (nearly) complete follow-up, the 30-year cumulative incidence of breast cancer (accounting for death as a competing risk) amounted to 26 % for women first treated before age 21 and 19 % for those treated at ages 20–30 [24]. In pediatric HL survivors, Bhatia and colleagues estimated a cumulative incidence of breast cancer of 13.9 % at age 40 years, reaching 20.1 % at age 45 years [47]. Castellino and colleagues [49] recently reported a cumulative incidence of breast cancer of 18.3 % at 30 years after treatment in the US Childhood Cancer Survivor Study. Travis and collaborators [182] estimated treatment-specific cumulative risks of breast cancer: for an HL survivor who was treated at age 25 with a chest radiation dose of at least 40 Gy without alkylating agents, the cumulative absolute risks of breast cancer by age 35, 45, and 55 years were 1.4 % (95 % CI, 0.9–2.1), 11.1 % (95 % CI, 7.4–16.3), and 29.0 % (95 % CI, 20.2–40.1), respectively [182]. Based on 373 breast cancer patients in a very large HL cohort ($n=5{,}002$ women), Swerdlow and colleagues [62] recently reported modeled cumulative risks by follow-up time, age at treatment, and treatment modalities. For women who received 40 Gy under age 20, and no alkylating chemotherapy (see below), the cumulative incidence of breast cancer at 40 years was 48 %.

The high risk of breast cancer after HL is largely attributable to chest radiotherapy. Since, in many cohort studies, 80 to over 90 % of patients received supradiaphragmatic RT, few studies could estimate RRs associated with such RT compared with no RT [24, 32, 37, 45, 47]. In the British cohort reported by Swerdlow and colleagues, a large proportion of patients had been treated with CT alone, and no increased risk of breast cancer was observed among them [43].

Elevated risk of breast cancer develops late and is typically observed from 15 or more years after first treatment (Fig. 24.7) [24, 32, 37, 44, 45, 48, 62]. This strong trend in breast cancer risk by time since treatment strongly indicates a radiogenic effect. Furthermore, in several cohort studies, almost all cases of breast cancer after HL have been in or at the margin of the radiation field, for instance, 16 of 16 cases [89], 22 of 26

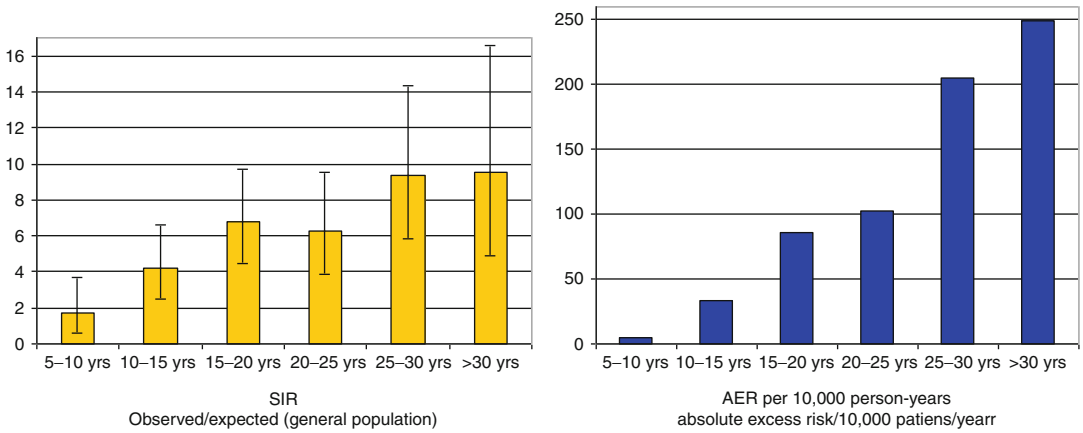


Fig. 24.7 Risk of breast cancer after HL by follow-up time (1122 Dutch HL patients) (From: De Bruin et al. [24])

[38], and all of 42 cases [47] in three publications. In the large, population-based study by Travis and colleagues [42], 49 % of 105 breast cancers occurred in the unblocked chest treatment field, 24 % under the lung blocks, 15 % at the blocked edge, 8 % in the field edge, and 3 % out of beam, with relative location not known for one patient.

Three case-control studies investigated the effects of RT dose and other treatment factors on breast cancer risk [41, 42, 70]. In all studies, the risk of breast cancer increased significantly with higher RT dose up to the highest dose levels (Table 24.4; see for details: section on 4.1). A large Dutch study examined the effect of radiation fields (volume) on the risk of breast cancer up to more than 30 years after treatment of HL [24]. Among 1,122 female 5-year survivors, treated for HL before age 51 (median follow-up time of 18 years), 120 cases of breast cancer were identified (overall SIR 5.6; AER 57 per 10,000 per year). Importantly, mantle field RT (involving the axillary, mediastinal, and neck nodes) was associated with a 2.7-fold (95 % CI, 1.1–6.9) increased risk of breast cancer compared to similarly dosed (36–44 Gy) radiation to the mediastinum alone (Fig. 24.5) [24].

In four studies, patients who received both CT and RT had significantly decreased risk (about halved) compared to those treated with RT alone, and the RT-related risks were attenuated by treatment with alkylating agents [24, 41, 42, 62]. Risk of breast cancer decreased with increasing number of alkylating agent cycles ($P=0.003$ for trend); the RR associated with nine or more cycles of alkylating CT compared with no alkylating CT was 0.2 (95 % CI, 0.1–0.7) (Table 24.4) [42]. In the large Dutch cohort study [24], chemotherapy regimens with higher cumulative procarbazine doses seemed to be associated with a greater reduction of breast cancer risk, with 40 and 60 % risk reductions for regimens with less than 8.4 g/m^2 procarbazine and more than 8.4 g/m^2 procarbazine, respectively. The substantial risk reduction associated with CT appears to be due to the high frequency of premature menopause in CT-treated patients [24, 41, 181] and the resulting reduction in the exposure to ovarian hormones. De Bruin et al. [24] reported that 30 % of all women reached menopause before age 41; such an early menopause was associated with a 60 % (95 % CI, 20–80 %) reduced risk of breast cancer (Table 24.5). A strong decrease in breast cancer risk (about 60 %) has also been observed among women who received a castrating dose of 5 Gy or more to the ovaries, compared with those who received lower doses (Fig. 24.4) [24, 41, 42, 70]. These results indicate that ovarian hormones are a crucial factor to promote tumorigenesis once RT has produced an initiating event.

In the Dutch study a long versus short duration of intact ovarian function after radiation was a strong predictor of subsequent breast cancer risk. Women with less than 10 years of intact ovarian function after radiotherapy had a 70 % (95 % CI, 40–80 %) decreased risk of breast cancer compared with women with 10–20 years of ovarian function after irradiation, while those with more than 20 years of intact ovarian function after radiotherapy had 5.3-fold (95 % CI, 2.9–9.9) increased risk of breast cancer (Table 24.5). These risk reductions were observed both among women treated before age 21 and among those treated between ages 21 and 30. Among women treated between ages 31 and 40, cumulative exposure to endogenous estrogens was not associated with risk for breast cancer, possibly because these women were closer to natural menopause at time of treatment [24]. A recent British study confirmed these findings and reported a 3.6-fold risk increase for women having 25 or more premenopausal years after start of RT [181].

It is not yet known whether current less gonadotoxic CT, such as ABVD, is also associated with reduced risk of RT-associated breast cancer risk. Furthermore, we do not yet know whether hormone replacement therapy (HRT) for CT-induced premature menopause affects RT-associated breast cancer risk. HRT is an established risk factor for breast cancer [183, 184] and might counteract the protective effect of CT. Remarkably, in the international case-control study by Travis et al. [42], the relation between alkylating agent treatment and breast cancer risk differed between North America and European

Table 24.5 Effects of fertile lifespan after irradiation to the breast on breast cancer risk (invasive and DCIS) according to age at first treatment[a]

	All ages <41	Age <21	Age 21–30	Age 31–40
No. of patients	715	201	323	191
No. of events	98	36	40	22
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
Model 3[b]				
Premature menopause[c]				
Menopause at age 41 or later	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Menopause before age 41	0.4 (0.2–0.8)	0.2 (0.0–0.8)	0.1 (0.0–0.5)	1.3 (0.4–3.6)
Model 4[b]				
Years intact ovarian function[c]				
<10 years	0.3 (0.2–0.6)	0.1 (0.0–0.6)	0.1 (0.0–0.3)	1.2 (0.4–3.5)
10–20 years	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
>20 years	5.3 (2.9–9.9)	11.9 (3.7–37.9)	6.0 (2.3–15.4)	3.2 (0.3–30.7)

BC breast cancer, *IBC* invasive breast cancer, *DCIS* ductal carcinoma in situ, *HR* hazard ratio, *Ref* referent, *RT* radiation therapy

[a]Adapted from de Bruin et al. [24]

[b]Adjusted for each other, radiation field-size, age at first RT to the breast and time since first RT to the breast, smoking, obesity, nulliparity, oral contraceptive use; calendar-time was used as the time scale

[c]Unknown age at menopause was modeled as a separate category

centers. Within Europe, significant reductions in risk were observed (for six cycles: RR = 0.33; 95 % CI, 0.15–0.65), while in North America the RR associated with six cycles of alkylating agent therapy was close to unity. These discrepant results may be due to the much higher prevalence of HRT in North America compared with Europe.

A few recent studies investigated whether the clinicopathological characteristics of radiation-induced breast cancers differ from those of sporadic breast cancers [185–188]. Remarkably, one study found that breast cancers following RT for HL have a molecular profile distinct from idiopathic breast cancers from age-matched women. Another study reported more estrogen-negative breast cancers after RT for HL [187]. However, two other studies did not find much difference in breast cancer–specific survival between women with breast cancer after HL and other age-matched breast cancer patients [186, 188].

In summary, chest RT at young ages is associated with a very high risk of breast cancer after 15 years and later, and this hazard needs to be borne in mind both when selecting treatment for girls and young women with HL and when following up patients treated in this way. Reductions of radiation dose and field size (replacement of mantle RT by involved field/involved node RT) in current treatment protocols are expected to result in lower breast cancer risk. Gonadotoxic chemotherapy such as the MOPP regimen appears to reduce the increased risk of breast cancer from RT through the induction of premature menopause. The use of hormone replacement therapy may negate this favorable effect of CT, but direct information about this is lacking.

24.5.4 Risk Factors for Lung Cancer

Next to breast cancer, lung cancer accounts in many studies for the largest absolute excess of solid malignancy after HL [44, 48]. An excellent review of risk factors for lung cancer after HL has been published [189]. The risk of lung cancer after HL depends on time since treatment, age at treatment, treatments administered for HL, and smoking.

The SIR of lung cancer is hardly increased in the first 5 years after treatment, with larger SIRs (five or greater), thereafter until at least 25 years [32, 37, 39, 44, 48, 190].

A meta-analysis of 21 observational studies reported that the relative risk of lung cancer varied little with age at HL treatment and was highest among those aged 15–24 years (RR = 8.6) and lowest among aged >55 years at first treatment (RR = 2.88) [190]. Dores et al. [44] reported that the SIR of lung cancer decreased from a 5.5-fold increase (compared with the general population) for patients diagnosed before age 21 to a 1.5-fold excess for patients diagnosed at age 61 or above. In the UK study [48], the SIRs for lung cancer

decreased from 20-fold among those diagnosed before age 25 to a 2.2-fold excess for patients diagnosed at age 55 or above.

A large international collaborative case-control study examined lung cancer risk in relation to the radiation dose to the specific location in the lung in which cancer later developed [39]. This study included 222 lung cancer patients and 444 matched controls (patients with HL in whom lung cancer had not been diagnosed) [39, 72]. Case patients developed lung cancer after an average of 10.8 years. The risk increased with increasing radiation dose to the area of the lung in which cancer later developed (P for trend <0.001; see also Table 24.4). The risk estimates for the highest dose categories of 30.0–39.9 Gy and ≥40 Gy compared with no RT were 8.5 (95 % CI, 3.3–24) and 6.3 (95 % CI, 2.2–19), respectively, suggesting that the risk might level off at very high doses [72]. This study also addressed the modifying effects of the patient's smoking habits on RT-associated risks. The increased RRs from smoking appeared to multiply the elevated risks from radiation (Table 24.6). This implies that there are very large AERs for lung cancer among irradiated patients who smoke.

Chemotherapy for HL can also increase the risk of lung cancer [39, 43, 48, 53, 189, 191]. The British National Lymphoma Investigation cohort study of 5,519 patients [43, 48] showed a significantly elevated risk of lung cancer following CT alone, with the SIR (3.3; 95 % CI, 2.2–4.7) compared with the general population being of similar magnitude to that observed in patients treated with either RT (SIR = 2.9; 95 % CI, 1.9–4.1) or mixed modality treatment (SIR = 4.3; 95 % CI, 2.9–6.2).

Two large case-control studies have investigated the separate and joint roles of CT, radiation, and smoking in detail [39, 73]. In both reports, there was a clear trend of increasing lung cancer risk with greater number of cycles of alkylating CT (P trend < 0.001; (Table 24.4) [39]) or MOPP-CT (P trend = 0.07 [73]). In the study by Travis and colleagues [39], data were also collected on cumulative dose of individual cytotoxic drugs. Among patients treated with MOPP, increasing total dose of mechlorethamine or procarbazine was strongly associated with increasing lung cancer risk when evaluated separately (P trend for dose for each <0.001) [39]. Risk of lung cancer after treatment with alkylating agents and radiation together was as expected if individual excess RRs were summed: RRs of 4.2 (95 % CI, 2.1–8.8) were observed for patients given alkylating agents alone, 5.9 (95 % CI, 2.7–13.5) for patients treated with RT alone (>5 Gy), and 8.0 (95 % CI, 3.6–18.5) for those who received combined modality treatment, compared with the reference group of patients who received no alkylating agents and had less than 5 Gy of radiation [39]. As was observed for the joint effects of smoking and RT, the risks from smoking appeared to at least multiply risks from alkylating CT (Table 24.6) [39].

Smoking remains a major cause of lung cancer in patients treated for HL, as is evident from the observation that only 7 out of 222 cases included in the study by Travis and colleagues

Table 24.6 Risk of lung cancer in patients with HL according to type of treatment and smoking category

Treatment for Hodgkin lymphoma		RR (95 % CI) by smoking category (no. of case patients; control patients)[a]	
Radiation ≥5 Gy	Alkylating agents	Nonsmoker, light, other[b]	Moderate-heavy[c]
No	No	1.0[d]	6.0 (1.9–20.4)
Yes	No	7.2 (2.9–21.2)	20.2 (6.8–68)
No	Yes	4.3 (1.8–11.7)	16.8 (6.2–53)
Yes	Yes	7.2 (2.8–21.6)	49.1 (15.1–187)

Adapted from Travis et al. and Swerdlow et al. [39, 43]
RR relative risk, *95 % CI* 95 % confidence interval
[a]Represents estimated tobacco smoking habit 5 years before diagnosis date of lung cancer and corresponding date in control patients, with the use of information recorded up to 1 year before these dates
[b]This group includes nonsmokers, light current cigarette smokers (less than one pack per day), former cigarette smokers, smokers of cigar and pipes only, and patients for whom tobacco smoking habit was not stated
[c]Moderate (one to two packs per day) and heavy (two or more packs per day) current cigarette smokers
[d]Reference group

[39] occurred in patients who had never smoked. Further, it was estimated that 9.6 % of all lung cancers were due to treatment, 24 % were due to smoking, but 63 % were due to treatment and smoking in combination; the remainder (3 %) represented tumors in which neither smoking nor treatment played a role.

In summary, both supradiaphragmatic RT and CT contribute to the elevated risk of lung cancer after HL. In addition, the above data suggest that patients with HL who smoke will have a considerably greater risk of lung cancer after chest RT and/or CT than those who do not smoke, and this is in accord with experience in other radiation-exposed groups [192]. As a consequence, smokers who have received chest RT should be particularly strongly advised to refrain from smoking. The evidence implicating specific chemotherapeutic agents as carcinogenic to the lung is less clear. It is not yet known whether modern CT regimens other than MOPP also increase the risk of lung cancer. The role of lung cancer screening in HL patients has not yet been assessed; international collaboration is needed to study the efficacy of screening with low-dose spiral computer tomography [36, 189].

24.6 Clinical Implications

Hodgkin lymphoma survivors who are at high risk of developing second cancers can be identified largely based on their prior treatment exposures, current age, and latency since treatment. Expert opinion-based recommendations have been published advocating the early onset of breast cancer screening starting 8 years following mediastinal RT, for women who are age 25–30 [193]. However, a large proportion of irradiated females do not perceive their risk of breast cancer to be much higher than that of the general population [194–197]. As a consequence, a large proportion of HL survivors do currently not undergo appropriate breast surveillance at young ages, when their risk is already high and comparable to that of carriers of BRCA1/2 mutations. A study among irradiated female childhood cancer survivors in the USA showed that 64 % of those aged 25–39 years and 24 % of those 40–50 years old had not had a mammography in the past 2 years, despite a guideline recommending annual screening [197]. Although early breast surveillance starting is recommended following mediastinal RT, the optimal screening modalities have yet to be determined. Two series found that mammography detected >90 % of breast cancers after HL [196, 198], and a British study of screening program for women previously treated with supradiaphragmatic RT found that none of the five invasive BCs diagnosed involved axillary lymph nodes, compared with 7 of 13 (54 %) diagnosed outside the program [199]. However, in one of these studies, after excluding two cases of incident BC on baseline mammogram, five of the secondary ten BCs were detected clinically [196], and in another series of female HL survivors undergoing mammographic screening, 7 of 12 breast cancers were palpable at the time of detection [200]. Because mammography is less sensitive in young women with dense breast tissue, magnetic resonance imaging (MRI) should be considered at younger ages.

Ng et al. reported the outcome of 148 women screened with breast MRI ≥8 years after mediastinal RT (given prior to age 35 years) and a median age at enrollment of 43 years. The sensitivity of mammogram alone, MRI alone, or both modalities was 68, 67, and 94 %. Specificity for each modality alone or in combination was not significantly different. One of 18 cancer cases detected had lymph node involvement [201]. A similar study of MRI breast screening among survivors of pediatric HL in which the median age at first screening was 30 years reported that the sensitivity for mammogram alone, MRI alone, and both modalities was 70, 80, and 100 %, respectively, with all detected cases being node negative. In both studies, mammography was more likely to miss invasive cancers than MRI [202]. These studies suggest that the addition of MRI to mammography will detect breast cancers at earlier stages than mammography alone.

Some have recommended that patients who have received para-aortic RT should undergo colorectal cancer screening starting 10–15 years

following treatment. Screening for secondary lung cancer is more controversial. As noted above, older HL survivors treated with alkylating agents or mantle RT are at significantly increased risk of developing lung cancer, particularly if they are smokers. One important consideration is that the absolute risk of lung cancer is low among nonsmoking patients treated before age 30 with contemporary chemotherapy (e.g., ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine), and it is unlikely that they would benefit from screening. Risk is highest among those treated with chest RT and alkylator-based chemotherapy at ages >40 years, particularly if they are smokers. The results of studies evaluating the efficacy of screening with spiral computer tomography in other high-risk patients may illuminate the potential benefit to HL survivors, but it currently remains investigational.

Physicians should make a special effort to dissuade HL patients from smoking. While most survivors will be aware that smoking increases their risk of lung cancer, they may not understand that their smoking-related risk may be significantly greater than that of others with whom they share the activity, and they are often not aware of the poor prognosis associated with lung cancer. Advice on smoking cessation during an office visit can improve quit rates, and pharmacotherapy improves the probability of success [203].

While retrospective studies describing the RT-related risk of SMNs have been useful in identifying groups of survivors for whom the early utilization of cancer screening may be worthwhile, and have been instrumental in motivating the development of clinical trials which are now much less reliant on the use of RT, it is important to recognize that they often have limited value in counseling contemporary patients about the risks of modern therapy. For example, most of the widely cited cohort studies of SMN risk among HL survivors include patients treated in the 1960s [44, 46–48, 54]. At that time, RT was often the sole primary treatment for early-stage HL, and the RT fields typically encompassed the whole neck, bilateral axillae, the entire length of the mediastinum, the spleen, and paraaortic nodes. Patients were often prescribed 40–45 Gy and treated without customized lung shielding [204, 205]. Since that time, several important improvements have occurred in the delivery of RT that reduce the normal tissue exposure: prescribed doses are typically 20–30 Gy for adults and 21 Gy for children. With the development of involved-field RT (IFRT), the omission of uninvolved axillary nodes from these historic fields significantly reduced the breast tissue dose compared to historic mantle RT fields, and follow-up studies of more limited field RT suggest that the associated reduction in irradiated breast volume translates into a clinically significant reduction in SMN risk [24, 34]. More recently, utilization of modern image guidance and the further reduction in target volumes limited to only the initially involved lymph nodes, referred to as involved-node RT (INRT) or involved-site RT (ISRT), further reduce the dose to normal tissues, with early results demonstrating excellent disease control [84, 85]. As our understanding of the relationship between radiation dose and SMN risk develops, it should be possible to create predictive models of the SMN risk associated with modern HL treatments based on epidemiologic observations and radiobiologic principles.

Obviously the best means of limiting radiation-related SMN is to avoid using RT when it does not contribute meaningfully to HL cure. Data are emerging that may facilitate the selection of a greater proportion of patients for treatment with chemotherapy alone based on clinical or biologic factors. As an increasing proportion of patients are treated with chemotherapy alone, an emerging issue will be the extent to which contemporary chemotherapy regimens contribute to the risk of solid tumors. Many patients in second cancer studies received MOPP chemotherapy, and the increased SMN risks associated with alkylator-based chemotherapy do not apply to patients receiving, for example, ABVD chemotherapy. Patients treated initially with chemotherapy alone, even in more recent years, have increased risks of solid cancers [27, 43, 48], though it is unknown what regimens or specific agents might account for this risk. A British National Lymphoma Investigation (BNLI) study

found that the relative risk of second cancer was raised among 2,366 HL survivors treated with chemotherapy alone (RR = 2.0), although the risk was not increased among the 257 patients treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) [43]. As noted above, genetic susceptibility likely plays a role in the development of treatment-related SMNs. It is unlikely that an abnormal allele in a single candidate gene will account for a significant proportion of SMNs. New cohorts should be assembled to create a resource of biologic samples that would facilitate study of the molecular biology of second cancers.

Finally, when interpreting results of second cancer studies, it must be kept in mind that the problem of treatment-induced malignancies has arisen by virtue of the successes of HL treatment. The SMN risk of treatment must be balanced against the potential benefit in terms of curing patients' HL. For example, 10-year follow-up of patients treated with "dose-escalated" BEACOPP demonstrated that this regimen increased the risk of secondary AML compared to COPP/ABVD (0.4 % vs. 3.0 %), but produced a significant improvement in overall survival (75 % vs. 86 %) [206]. These outcomes highlight both the challenges of improving the cure rate for high-risk patients without adding clinically significant toxicity and the importance of considering SMN risk in the context of the beneficial effects that the exposures under study may have on curing the primary HL.

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Cardiovascular and Pulmonary Late Effects

25

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Contents

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25.1 Cardiovascular Toxicity

Radiotherapy and chemotherapy for Hodgkin lymphoma may both cause cardiovascular toxicity. Cardiovascular toxicity following radiotherapy is not usually observed until more than 5 years after therapy, whereas anthracycline-related toxicity is observed at varying intervals after therapy. This chapter mainly focuses on late effects. Tables 25.1 and 25.2 show standardized mortality rates and standardized incidence rates of several cardiovascular diseases following treatment for Hodgkin lymphoma including the absolute excess risks.

25.1.1 Chemotherapy-Associated Cardiotoxicity

25.1.1.1 General Aspects of Chemotherapy-Associated Cardiotoxicity

The most relevant cardiotoxic chemotherapeutic agents used in treatment for patients with Hodgkin lymphoma are anthracyclines, specifically doxorubicin and epirubicin. Anthracycline-associated toxicity may occur at different intervals after therapy. Cardiotoxicity may present as electrocardiographic changes and arrhythmias or as cardiomyopathy leading to congestive heart failure. Anthracycline-associated cardiotoxicity is mainly caused by direct damage to the myocardium, but anthracyclines are also recognized to cause vascular endothelial

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_25, © Springer International Publishing 2015

Table 25.1 Risk of death from myocardial infarction in large cohorts of patients treated for Hodgkin lymphoma

Authors (years of treatment)	No. in cohort	Age range at treatment in years	Follow-up time in years (range)	Type of treatment	SMR[a]	(95 % CI) SMR[a]	AER[b]
Boivin [18] (1940–1985)	4,665	All ages[c]	Average 7 (–)	Mediastinal RT±CT	4.1	(1.5–10.9)	–
Hancock [19] and Hoppe [20] (1960–1991)	2,232	1–82 (average 29)	Average 9.5 (–)	89 % including mediastinal RT	3.2	(2.3–4.0)	17.8
King [21] (1954–1989)	326	5–72 (mean 25.6)	Mean 13.3 (3–37)	Mantle RT±CT	2.8	(0.7–4.9)	10.4[d]
Glanzmann [22] (1964–1992)	352	4.0–81 (mean 33.8)	Mean 11.2 (1.0–31.5)	Mediastinal RT±CT	4.2	(1.8–8.3)	–
Brierley [23] (1973–1984)	611	17–90 (median 31)	Median 11.0 (0.7–18.0)	97 % RT±CT	1.5	(0.7–3.0)	5.4
Aleman [24] (1965–1987)	1,261	Median 26	Median 17.8	97 % RT±CT; 84 % mediastinal RT	4	(2.3–6.5)	5.6
Swerdlow [6] (1967–2000)	7,033	All ages	Median 11.1	72 % RT±CT; 34 % including mediastinal RT	2.5	(2.1–2.9)	12.6

CT chemotherapy, *RT* radiotherapy, *SMR* standardized mortality ratio, *CI* confidence interval, *AER* absolute excess risk
[a]Standardized mortality ratio (SMR) as the ratio of the observed (O) and expected (E) numbers of cardiovascular events in the cohort. The expected numbers are calculated based on general population rates
[b]Absolute excess risk (AER) per 10,000 person-years as O minus E, divided by the number of person-years at risk, multiplied by 10,000
[c]62% <40 years
[d]Calculated from the data in the paper: (observed (7) – expected (2.5)/person-years at risk (4,335)) × 10,000

dysfunction which may increase cardiovascular risk. Several risk factors for anthracycline-associated cardiotoxicity have been identified (see Table 25.3). The occurrence of acute anthracycline-associated cardiotoxicity is exponentially dose dependent and increases dramatically with cumulative doses greater than 500 mg/m^2 doxorubicin [1]. Doses less than 300 mg/m^2 rarely cause substantial toxicity [2]. The total dose of anthracyclines during first-line therapy for Hodgkin lymphoma does not usually exceed this. The cumulative dose of six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is 300 mg/m^2 and of eight cycles of bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (escalated BEACOPP) is 280 mg/m^2. However, it is now recognized that there is no risk-free dose of anthracyclines and some, particularly younger, patients have experienced cardiac damage at doses of <250 mg/m^2 [3].

Whether toxicity following chemotherapy and radiotherapy is additive or synergistic remains unclear. Clinical studies have shown that anthracycline-containing therapy may further increase the radiation-related risk of congestive heart failure and valvular disorders by two- to threefold compared to radiotherapy alone [4]. This effect may be more than additive [5]. A British study also demonstrated that an increased risk of death from myocardial infarction was related to anthracycline and vincristine treatment as well as supradiaphragmatic radiotherapy; the risk of death from myocardial infarction was increased for patients who did not receive supradiaphragmatic radiotherapy but had received vincristine (standardized mortality ratio (SMR) = 2.2, 95 % CI = 1.6–3.0) and anthracyclines (SMR = 3.2, 95 % CI = 1.9–5.2), especially those who were treated with the ABVD regimen (SMR = 7.8, 95 % CI = 1.6–22.7) [6].

The potential role of genetic variability in the pathogenesis of chronic cardiotoxicity including congestive heart failure is beginning to be elucidated. A few studies in humans have provided

Table 25.2 Standardized incidence ratio and absolute excess risks of myocardial infarction, congestive heart failure, stroke, and transient ischemic attack by sex, age at start of treatment, follow-up interval, attained age, and treatment in patient treated for Hodgkin lymphoma

	MI		CHF		Stroke		TIA	
	SIR	AER	SIR	AER	SIR	AER	SIR	AER
Total cohort[a]	3.6	35.7	4.9	25.6	2.2	12	3.1	9
Sex								
Male	4.2	60.7	3.9	21.7	2.0	10	2.7	8
Female	2.1	9.4	6.4	29.8	2.4	14	3.8	11
Age at treatment (years)								
≤20	5.4	15.0	18.2	27.6	3.8	7	7.6	5
21–30	4.9	40.1	6.8	40.5	3.1	14	4.2	7
31–40	2.7	46.3	2.6	21.2	2.0	15	3.1	13
41–50	–	–	–	–	1.4[b]	11	2.1[b]	18
Follow-up period (years)								
5–9	1.7[b]	4.3	7.1	11.0	2.1[b]	5	2.3	3
10–14	4.4	33.9	3.4	8.7	2.3	10	3.3	8
15–19	4.0	46.4	8.5	47.3	2.6	18	4.4	17
20–24	4.7	84.0	2.4b	13.7	2.1[b]	17	2.5[b]	11
≥25	2.9	69.2	4.5	62.5	1.9[b]	26	2.8	23
Attained age (years)								
<51	4.1	24.8	6.9	13.8	2.5	7	3.2	4
≥51	3.1	93.0	3.9	55.9	2.0	29	3.1	30
Treatment								
Radiotherapy alone					2.0	11	3.4	12
Chemotherapy alone					0.4[b]	−6	–	–
Radiotherapy/chemotherapy					2.6	15	3.4	10
Treatment								
Initial RT only	3.9	49.9	4.8	27.1				
RT+CT, no anthracyclines	3.9	66.0	5.3	31.8				
RT+CT, anthracyclines	3.5	23.6	6.2	21.2				
Initial CT only	1.0[b]	7.4	0.0	−8.2				

MI myocardial infarction, *CHF* congestive heart failure, *TIA* transient ischemic attack, *SIR* standardized incidence ratio, *AER* absolute excess risk, *RT* radiotherapy, *CT* chemotherapy

[a]Adapted from Aleman and van den Belt-Dusebout et al. [4] and De Bruin and Dorresteijn et al. [25]. MI and CHF data from cohort of 1,474 survivors of Hodgkin lymphoma treated before the age of 41 between 1965 and 1995 and stroke and TIA data from cohort of 2,201 5-year survivors of Hodgkin lymphoma treated before the age of 51 between 1965 and 1995

[b]Not statistically significant

evidence that genetic susceptibility may play a role in the risk of anthracycline-associated cardiotoxicity [7, 8].

25.1.1.2 Prevention of Chemotherapy-Associated Cardiotoxicity

The obvious measure to prevent cardiotoxicity is to limit both cardiotoxic chemotherapy (especially anthracyclines) and radiation volume and dose as much as possible. The evidence on the effectiveness of other approaches to reduce or prevent anthracycline-associated cardiotoxicity is limited in quantity and quality [9]. Early studies suggested that limiting the peak serum concentration of anthracyclines by administering them by continuous infusion could limit cardiotoxicity [10], but this has not been confirmed by subsequent studies, mainly in children. Anthracyclines release free radicals that damage cardiac myocytes, which are especially

Table 25.3 Risk factors for anthracycline-associated cardiotoxicity

Risk factor	Features
Total cumulative dose	Most significant predictor for abnormal cardiac function
Age	For comparable cumulative doses, younger age predisposes to greater cardiotoxicity
Length of follow-up	Longer follow-up results in higher prevalence of myocardial impairment
Gender	Females more vulnerable than males for comparable doses perhaps due to a greater fat percentage of body mass [26]
Race	Those of black race possibly more susceptible [27]
Concomitant mediastinal irradiation	Enhanced toxicity; not clear whether additive or synergistic
Genetic susceptibility	Studies in childhood cancer have revealed mutations of the HFE and CBR3 genes confer increased risk. Those with trisomy 21 also at increased risk [8, 28]

Adapted from Table 10.4 of Chap. 10, Cardiovascular Effects of Cancer Therapy, by Adams, Constine, Duffy, and Lipshultz (and from Simbre et al. [29]) in *Survivors of Childhood and Adolescent Cancer* (second edition) published by Springer

susceptible to such damage because of their highly oxidative metabolism and poor antioxidant defenses. Dexrazoxane, a free-radical savaging, iron-chelating agent, has been demonstrated to reduce cardiotoxicity [11, 12], but there has been reluctance to adopt the agent into protocols due to, perhaps unfounded, concerns regarding second cancer risks and reduction in oncological efficacy [13]. More information is needed before this agent can be introduced in clinical practice. Small randomized trials in adults found that prophylactic treatment with carvedilol and nebivolol during anthracycline therapy resulted in better preserved cardiac function [14, 15]. Furthermore, there are some indications of a possible beneficial effect of angiotensin-converting enzyme (ACE) inhibitors after cardiotoxic chemotherapy [16]. Several other agents including L-carnitine have also been investigated [17] with some promising results. However, these studies have not, so far, been conclusive.

25.1.1.3 Management of Chemotherapy-Associated Cardiotoxicity

Currently there are no indications that the management of anthracycline-associated congestive heart failure should differ from that due to other causes. Treatment generally focuses on correcting underlying physiological abnormalities such as increased afterload and decreased contractility and frequently includes treatment with ACE inhibitors and/or beta-blockers [34]. Several guidelines developed for treating patients with asymptomatic left ventricular dysfunction or heart failure (not specifically after cancer treatment) include beta-blockers, ACE inhibitors, diuretics, and others [35, 36].

25.1.2 Radiation-Associated Cardiotoxicity

25.1.2.1 General Aspects of Radiation-Associated Cardiotoxicity

Radiation-associated heart disease in cancer survivors includes a wide spectrum of cardiac pathologies, such as coronary artery disease, myocardial dysfunction, valvular heart disease, pericardial disease, and electrical conduction abnormalities [37, 38] (see Fig. 25.1). Pericarditis is sometimes observed early after radiation, although not commonly with modern doses and techniques of Hodgkin lymphoma radiotherapy. Delayed pericarditis may occur months to years after radiation and usually resolves spontaneously although it may develop into chronic and/or constrictive pericarditis [31, 32]. Radiation-associated heart diseases, other than pericarditis, usually present 10–15 years after exposure, although recently, a significantly increased risk of ischemic heart disease has been reported within 5 years following radiotherapy for breast cancer [39]. Non-symptomatic abnormalities may develop much earlier on cardiac imaging.

Radiation causes both increased mortality (mainly fatal myocardial infarction) and increased morbidity (see Tables 25.1 and 25.2). Epidemiological studies on Hodgkin lymphoma survivors show relative risk estimates for cardiac

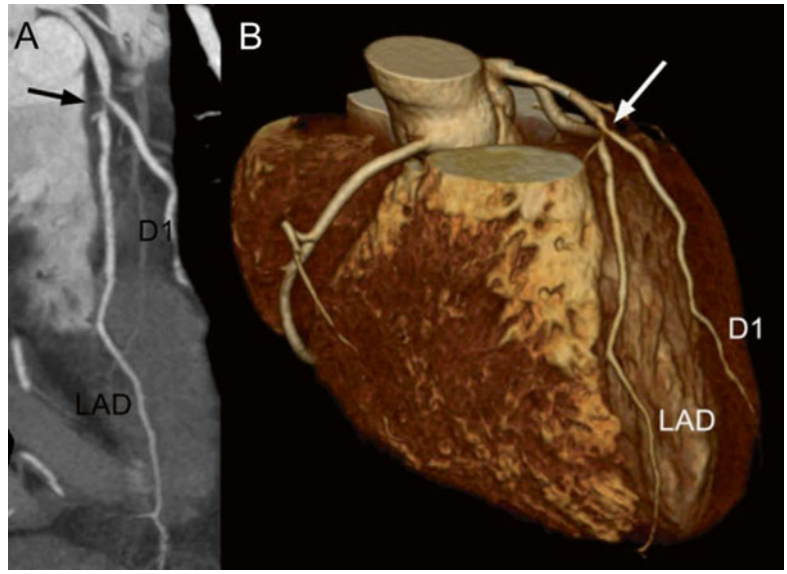

Fig. 25.1 Cardiac CT. Coronary artery disease: a 41-year-old man with severe obstructive coronary disease of the left anterior—diagonal bifurcation (*arrow*) only a few years after mediastinal radiation therapy because of Hodgkin lymphoma by angiographic (*A*) and cardiac CT (*B*) imaging (From Lancellotti et al. [58])

death in the range of two- to sevenfold, depending on age at treatment (increased relative risks for irradiation at a young age), the radiation therapy methods used, and the follow-up time [37, 38, 40]. In a Dutch study of Hodgkin lymphoma patients treated before the age of 41 years, three- to fivefold increased standardized incidence ratios (SIR) for various heart diseases were observed, even after a follow-up of more than 20 years [4]. The persistence of increased relative risk over prolonged follow-up is of concern because this implies an increase in absolute excess risks over time, due to the rising incidence of cardiovascular disease with age.

Prospective screening studies demonstrate that clinically significant cardiovascular abnormalities, like coronary artery stenosis [41], reduced left ventricular dimensions, and valvular and conduction defects, are very common, even in asymptomatic Hodgkin survivors [42]. Hodgkin lymphoma patients also have a significantly higher risk (SIR 8.4) of requiring valve surgery or revascularization procedures 15–20 years after radiotherapy [43]. Furthermore, an increased risk of restenosis after coronary artery stenting has been reported in patients treated with thoracic radiation for lymphoma [44].

There are several risk factors for radiation-associated cardiotoxicity (see Table 25.4). Cardiotoxicity is evidently related to both total radiation dose and dose per fraction to the heart [32]. Large doses per fraction are thought more damaging to the heart than low doses per fraction. In support of this, increased complication rates were reported for Hodgkin lymphoma patients treated with 3×3.3 Gy per week, compared with patients treated with 4×2.5 Gy per week to the same total dose [45].

The heart volume included in the radiation field influences the risk of cardiotoxicity [32, 46], although there are still uncertainties regarding dose-effect and volume-effect relationships. A reduction in the increased risk of death from cardiovascular diseases other than myocardial infarction was reported 30 years ago in Hodgkin lymphoma patients treated after partial shielding of the heart and restriction of the total, fractionated, mediastinal dose to less than 30 Gy [47]. More recently, relationships between mean heart dose and several radiation-related heart diseases have been demonstrated following treatment for childhood cancer [46], breast cancer [39], and Hodgkin lymphoma [48]. More data are needed to determine these dose-effect relationships more precisely and to disentangle radiation and chemotherapy effects.

Several studies, mainly in breast cancer, using single positron emission computed tomography

Table 25.4 Risk factors for the different manifestations of radiation-associated cardiotoxicity

Risk factor	Pericarditis	CM	CAD	Arrhythmia	Valvular disease	All causes of CD	References
Total dose (>30–35 Gy)	X	X	X	X	X	X	[30–32]
Dose per fraction (≥2.0 Gy/day)	X	X	X	Likely	Likely	X	[32]
Volume of heart exposed	X	X	X	Likely	Likely	X	[19, 31]
Younger age at exposure	–	X	X	Likely	Likely	X	[4, 19]
Increased time since exposure	–	X	X	X	X	X	[4]
Use of adjuvant cardiotoxic chemotherapy	–	X	–	X	X	X	[4, 5, 33]
The presence of other known risk factors in each individual such as current age, weight, lipid profile, and habits such as smoking	–	–	X	–	–	X	[4, 22]

Adapted with permission from Table 10.5 of Chap. 10, Cardiovascular Effects of Cancer Therapy, by Adams, Constine, Duffy, and Lipshultz (and from Simbre et al. [29]) in *Survivors of Childhood and Adolescent Cancer* (second edition) published by Springer
CM cardiomyopathy, *CAD* coronary artery disease, *CD* cardiac death

and Doppler echocardiography have revealed subclinical abnormalities [49] less than 2 years after radiotherapy. There is some evidence of a volume effect with such studies demonstrating that the extent of the left ventricle irradiated is predictive of observed imaging abnormalities [50, 51]. Although a relationship between these subclinical abnormalities and subsequent clinical heart disease may be expected, this has not yet been proven [32, 50–52]. However, one study in Hodgkin lymphoma survivors did demonstrate that diastolic dysfunction detected by Doppler echocardiography in asymptomatic patients was associated with stress-induced myocardial ischemia and an increased risk of subsequent cardiac events [53].

Radiotherapy techniques have greatly improved over the past 20 years [54], leading to more homogeneous dose distributions and reduced risks of toxicity [55–57].

25.1.2.2 Other Risk Factors for Cardiotoxicity

The risk for cardiovascular disease may also increase through indirect effects of radiotherapy; irradiation of the left kidney during para-aortic and spleen radiotherapy, for example, may lead to hypertension [59].

General risk factors for cardiovascular diseases, such as hypertension, diabetes, hypercholesterolemia, obesity, and smoking [60–62], will also contribute to the risk for cardiovascular diseases in patients treated for Hodgkin lymphoma [4, 63, 64]. Whether the cardiovascular risk factor profile in these patients differs from that of the general population is unknown.

25.1.2.3 Prevention of Radiation-Associated Cardiotoxicity

With respect to radiation it is important to use conventionally fractionated radiation and to limit both radiation dose and volume [54]. Modern radiation techniques like intensity-modified radiotherapy allow radiation with lower exposure of the heart without compromising the radiation dose in the target volume [56]. Ongoing research is expected to provide more information regarding which structures are most critical and whether it is less harmful to expose a slightly larger volume to a low dose or a smaller volume to a slightly higher dose. Optimization of treatment choice is still an important subject of study. In the future, we hope to be able to identify survivor groups at high risk of late adverse effects (based on treatment and/or genotype) for which

screening should be recommended and/or intervention trials could be designed.

25.1.2.4 Management of Radiation-Associated Cardiotoxicity

There are currently no indications that radiation-associated ischemic heart disease needs a special approach. Screening for cardiovascular diseases following thoracic radiotherapy is still a matter of debate [65]. There are uncertainties about the screening modalities. Stress testing may identify asymptomatic individuals at high risk for acute myocardial infarction or sudden cardiac death [66], but this is not yet common practice. Furthermore, there is no evidence for treatment other than management of general risk factors for cardiovascular disease. It is quite likely that among patients treated for Hodgkin lymphoma, subgroups can be identified that have risks similar to patients with recognized risk factors like diabetes. In many countries, guidelines have been developed for primary and secondary prevention of cardiovascular diseases [67–69].

Lifestyle advice should be given. Patients should be advised to refrain from smoking from the start of treatment of Hodgkin lymphoma, maintain a healthy body weight, and exercise regularly. If cardiovascular surgery is needed, operating surgeons should be aware of increased risks due to radiation-induced fibrosis [70].

25.1.3 Radiation Damage to Major Arteries

25.1.3.1 General Aspects of Radiation Damage to Major Arteries

As well as cardiac toxicity, other blood vessels may be damaged by radiation treatment for Hodgkin lymphoma. Damage to the carotid arteries is of particular importance. Significantly increased risks of transient ischemic attack (TIA) and stroke have been described in patients previously treated with radiotherapy for Hodgkin lymphoma [25, 63].

The Childhood Cancer Survivor Study (CCSS) published on self-reported incidence and risk factors for stroke among childhood Hodgkin lymphoma survivors [63]. Twenty-four late-occurring strokes were observed in a cohort of 1,926 survivors of childhood Hodgkin lymphoma (RR = 4.32; 95 % CI = 2.01–9.29). A Dutch retrospective cohort study among 2,201 5-year Hodgkin lymphoma survivors treated before the age of 51 between 1965 and 1995 showed a substantially increased risk for stroke and TIA that was associated with radiation to the neck and mediastinum [25]. The standardized incidence ratio for stroke was 2.2 (95 % CI = 1.7–2.8) and 3.1 for TIA (95 % CI = 2.2–4.2). Compared with the general population, these risks remained elevated after prolonged follow-up. The cumulative incidence of ischemic stroke or TIA 30 years after Hodgkin lymphoma treatment was 7 % (95 % CI = 5–8 %). Other major arteries are also susceptible to damage from doses of radiation above 30 Gy, including the subclavian and iliac vessels [43, 71].

25.1.3.2 Prevention of and Screening for Radiation Damage to Major Arteries

Limitation of radiation dose and volume and the use of radiation techniques that allow homogeneous dose distributions are important. With current concepts used in radiation therapy for patients with Hodgkin lymphoma (involved-node or involved-site radiation rather than involved-field radiation) [54], it is predicted that the risk of radiation-related damage to the carotids in patients treated for Hodgkin lymphoma will diminish [72].

As there is no proof for the value of screening for radiation effects on the carotid arteries, screening is not generally recommended. Intervention studies are difficult to perform because of the relatively low number of patients treated for Hodgkin lymphoma and the long interval between treatment and clinical event. Surrogate endpoints like measurement of intima-media thickness of the carotid arteries could be used.

As for cardiotoxicity, general risk factors for cardiovascular disease should be monitored and treated as necessary. Lifestyle advice should also

be given, i.e., patients should be advised to refrain from smoking (from the start of treatment of Hodgkin lymphoma), maintain a healthy body weight, and exercise regularly [73].

25.1.3.3 Management of Radiation Damage to Major Arteries

The management of radiation-associated cerebrovascular disease should be as for that due to other causes. Experience has demonstrated that intervention for carotid artery stenosis as for indications in non-radiation-related disease can be successful. Both open endarterectomy [74] and angioplasty with stenting [75] have been used. There may be particular challenges with an open surgical approach following radiotherapy including fibrosis and poor healing of irradiated tissue. Additionally, the disease may be situated more proximally in the carotid artery, and restenosis has been reported to be more common [76]. As such it could be recommended that radiation-associated disease is managed by vascular surgeons with experience of the condition.

25.2 Late Pulmonary Toxicity

Several chemotherapeutic agents and radiation may lead to pulmonary morbidity and mortality. Significant mortality may be seen in the first months up to 1 year after chemotherapy [77]. During long-term follow-up, the mortality from second pulmonary neoplasms is significantly increased (see Chap. 24, Hodgson DC, van Leeuwen FE), but not from other pulmonary diseases [24, 78]. Furthermore, higher morbidity may also be seen with longer follow-up.

25.2.1 Chemotherapy-Associated Pulmonary Toxicity

25.2.1.1 General Aspects of Chemotherapy-Associated Pulmonary Toxicity

Several frequently used chemotherapeutic agents may cause pulmonary toxicity. Bleomycin is the most frequently used agent in treatment of patients with Hodgkin lymphoma that causes pulmonary toxicity.

25.2.1.2 Bleomycin

The pulmonary toxicity of bleomycin has been recognized since it was used in clinical trials in the 1960s for testicular cancer. Acute pulmonary toxicity following bleomycin-containing chemotherapy usually presents with dyspnea, dry cough, and fever. Long-term pulmonary toxicity is predominantly fibrotic and may be associated with pulmonary impairment and a dry cough. The classic radiographic pattern of bleomycin-induced interstitial fibrosis on chest X-ray is bibasilar reticular or fine nodular infiltrates. On CT scans, infiltrative changes, nodules, and patchy ground-glass opacities may be seen (see Fig. 25.2). Nowadays, FDG-PET can identify early bleomycin-related pulmonary toxicity, and it may also be used for follow-up of this toxicity. Conventional CT scanning is not able to distinguish between residual changes and active inflammation. Thus, PET represents a useful diagnostic tool and, independently of CT, indicates the resolution of disease activity, even in the presence of residual pulmonary scarring [79].

The severity of bleomycin toxicity may vary. Martin et al. [77] reported a bleomycin pulmonary toxicity incidence rate of 18 % in patients treated with ABVD (25 of 141 patients), and one quarter of the patients with bleomycin pulmonary toxicity died from pulmonary toxicity within 9 months of

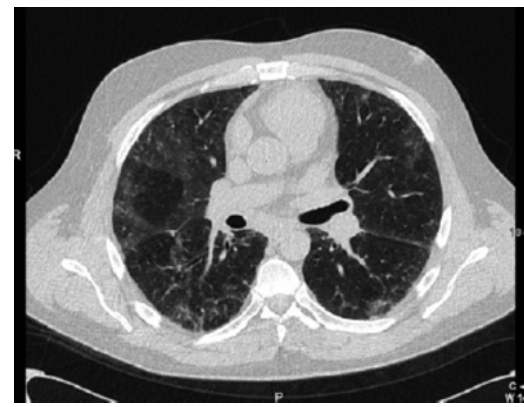

Fig. 25.2 CT scan of the chest showing interstitial pulmonary changes attributed to bleomycin

their Hodgkin lymphoma diagnosis. Risk factors for bleomycin toxicity included age >40 years, smoking, previous lung or renal impairment, thoracic radiotherapy, and G-CSF treatment. A detrimental impact on 5-year overall survival rates in Hodgkin lymphoma patients who developed bleomycin pulmonary toxicity was observed; the 5-year overall survival was 90 % in unaffected patients and 63 % in patients with bleomycin pulmonary toxicity ($p=0.001$). In patients who survived the pulmonary toxicity, bleomycin pulmonary toxicity had no effect on outcome.

The BEACOPP regimen, which contains lower doses of bleomycin and higher steroid doses, has a lower incidence of pulmonary toxicity [80]. Several clinical trials are investigating whether bleomycin dose can be lowered or omitted during Hodgkin lymphoma treatment, to reduce toxicity without reducing treatment efficacy [81].

25.2.1.3 Other Agents Leading to Pulmonary Toxicity

Carmustine is used in high-dose regimen such as carmustine, etoposide, cytarabine, and melphalan (BEAM) and may also induce pulmonary toxicity. The toxic reaction in the lung caused by carmustine usually manifests as chronic interstitial fibrosis that occurs after prolonged treatment and high cumulative doses.

The substitution of etoposide for gemcitabine in the escalated BEACOPP regimen was reported as non-feasible due to severe acute pulmonary toxicity. This increased toxicity was probably related to the concomitant application of gemcitabine and bleomycin [82]. No long-term follow-up is available for this treatment yet. In the same patient population [83], no increased toxicity was observed following radiation treatment. The authors therefore concluded that integration of radiotherapy in gemcitabine-containing regimens for Hodgkin lymphoma is feasible provided there is an interval of at least 4 weeks between the two modalities and that radiotherapy follows chemotherapy.

Brentuximab vedotin, an antibody-drug conjugate composed of a CD30-targeted chimeric monoclonal antibody covalently linked to the microtubule disrupting agent monomethyl auristatin E (MMAE), has shown very promising results in the treatment of patients with relapsed Hodgkin lymphoma [81] and is currently being tested in first-line treatment. Brentuximab vedotin should, however, not be given in combination with bleomycin because this leads to a high risk of pulmonary toxicity [84].

25.2.1.4 Prevention of Chemotherapy-Associated Pulmonary Toxicity

Information on how to prevent long-term toxicity is scarce. High inspired concentrations of oxygen after prior treatment with bleomycin have been reported to be toxic [85].

25.2.1.5 Management of Chemotherapy-Associated Pulmonary Toxicity

There is no accepted standard treatment for acute bleomycin toxicity. Corticosteroids, withholding bleomycin from subsequent chemotherapy, and proceeding with a regimen not containing bleomycin, if possible, are the most common approach [77]. Long-term corticosteroid treatment may be necessary to avoid recall pneumonitis.

25.2.2 Radiation-Associated Pulmonary Toxicity

25.2.2.1 General Aspects of Radiation-Associated Pulmonary Toxicity

Radiation may damage both the lung and the pleura leading to different clinical symptoms. Lung irradiation can cause subacute pneumonitis resulting in a dry cough and shortness of breath 2–3 months following treatment. Corresponding changes on chest X-rays and CT scans of the thorax may be observed (see Fig. 25.3). In the longer term, this may progress to chronic pulmonary fibrosis. Splenic radiation may lead to limited radiation pneumonitis of the left lung base, followed by pleural thickening, often without any clinical symptoms [86].

The risk for radiation-induced pneumonitis is related to both the radiation dose and irradiated volume. Generally accepted clinical parameters

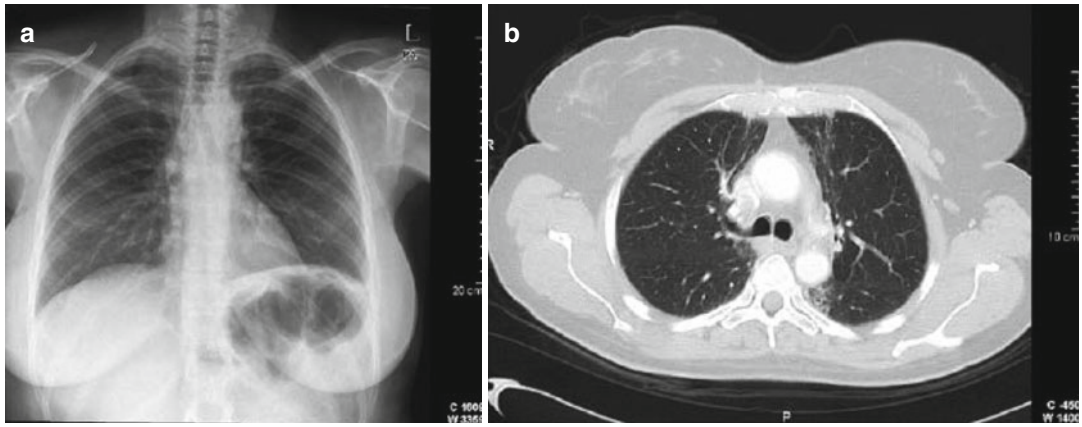

Fig. 25.3 (**a**) Chest X-ray 11 years after mediastinal radiation showing paramediastinal radiation fibrosis. (**b**) CT scan of the chest of the same patient also 11 years after mediastinal radiation showing interstitial pulmonary changes limited to the mediastinal radiation field

related to radiation pneumonitis within 1 year after treatment include mean lung dose (MLD) and the volume of lung tissue receiving at least 20 Gy (=V20). Koh et al. reported in their study performed to quantify the incidence of radiation pneumonitis in a modern Hodgkin lymphoma cohort that a V20 ≥36 % and a mean lung dose range of ≥14.2 Gy predicted a risk of RTOG grade 2 or greater pneumonitis would be considered clinically significant (10–25 % vs. 3 % overall) [87]. Fox et al. reported similar cutoffs (V20 ≥33.5 % and MLD ≥13.5 Gy) and also noted that those treated with mediastinal radiotherapy for relapsed Hodgkin lymphoma pre-transplant had a higher risk of radiation pneumonitis than those treated post-transplant (57 % vs. 0 %, $p=0.015$) [88].

A Dutch study on breast cancer and Hodgkin lymphoma patients reported a partial recovery from early local perfusion, ventilation, and density changes that were seen between 3 and 18 months after radiotherapy. In lymphoma patients, local lung function did not further improve after 18 months [89].

Although minor radiological and pulmonary function abnormalities may be seen regularly following radiation therapy for Hodgkin lymphoma, clinically significant symptoms are rare.

25.2.2.2 Prevention of Radiation-Associated Pulmonary Toxicity

During treatment the mean lung dose and V20 should be kept as low as possible by utilizing modern concepts of target volume definition and advanced treatment planning and delivery techniques where appropriate. Patients should be advised to refrain from smoking.

25.2.2.3 Management of Radiation-Associated Pulmonary Toxicity

Treatment of symptomatic radiation pneumonitis, occurring within the first year following treatment, generally consists of high-dose corticosteroids given for at least 2 weeks and then tapered over 3–12 weeks dependent on response. In the long term, no specific treatment is currently available, and pulmonary fibrosis following radiation is generally irreversible.

25.2.2.4 Combined Toxicity

Combined modality treatment is frequently used in patients with Hodgkin lymphoma. As the pulmonary toxicity of bleomycin and radiotherapy may interact, bleomycin dose modification may

be required [90], and radiotherapy may have to be similarly adapted.

Conclusion

The cure rate of Hodgkin lymphoma patients today exceeds 80 % with risk-adapted treatment using modern chemotherapy and radiotherapy regimens. Effective chemotherapy combinations have been developed and ability to manage acute toxicities has improved significantly. Much of the knowledge regarding long-term cardiovascular and pulmonary toxicities relates to historical treatment regimens that are no longer applied. By utilizing the data available on toxicity and delivering patient-tailored treatment, we expect to observe lower risks of cardiovascular and pulmonary toxicity in the future for patients being treated today. However, it is important that treating physicians and patients remain aware of these possible late effects following cure.

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Gonadal Dysfunction and Fertility Preservation in Hodgkin Lymphoma Patients

26

Karolin Behringer and Michael von Wolff

Contents

26.1 Introduction

Patients with Hodgkin lymphoma (HL) are generally young, and high cure rates can be achieved. Thus, HL diagnosis and therapy frequently occur at a time of life when family planning plays an important role. It is therefore of major importance for the patients to discuss this subject and to consider fertility preservation techniques as early as possible after diagnosis.

26.2 Gonadal Dysfunction in Men

26.2.1 Male Reproductive Physiology

Sperm production in males is stimulated via secretion of follicle-stimulating hormone (FSH) by the pituitary gland, regulated by a negative feedback mechanism via inhibin produced from the Sertoli cells and/or seminiferous tubules. Impaired or absent sperm production can be anticipated based on progressive elevation of FSH levels. Testicular androgen production is regulated by pituitary secretion

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma: A Comprehensive Overview*, Hematologic Malignancies,
DOI 10.1007/978-3-319-12505-3_26,

of luteinizing hormone (LH) and controlled by a comparable feedback mechanism via testosterone production of the testicular Leydig cells.

Gonadal function can be evaluated by measuring FSH and LH together with the morning testosterone level. A semen analysis is a more definitive test of fertility, with normal values of $>15 \times 10^6$/mL, a total sperm motility of >40 %, and with >3 % of normal forms.

26.2.2 Hodgkin Lymphoma and Male Gonadal Dysfunction

Seventy to eighty percent of male HL patients have inadequate pretreatment semen quality due to the lymphoma itself [1–4]. The mechanisms involved are still unknown; however, possible factors include damage to the germinal epithelium, disturbances in the hypothalamic–hypophysial axis, immunological processes associated with cancer that impair spermatogenesis, and the impact of cytokines [2, 5–9]. In a study by the German Hodgkin Study Group (GHSG), male fertility was assessed in a total of 243 patients. In pretreatment semen analysis, only 20 % of patients had normal sperms. Azoospermia was observed in 11 % of patients and dysspermia in 69 % [3].

26.2.3 Treatment-Related Gonadal Dysfunction

Post-treatment gonadal damage is most often associated with chemotherapy regimens that include alkylating agents such as cyclophosphamide and procarbazine. The degree of damage and recovery of spermatogenesis depends on the choice of drugs and the dose given. In multiple analyses, the rate of azoospermia after cyclophosphamide, vincristine, procarbazine, and prednisone (COPP); Mustargen, vincristine, procarbazine, and prednisone (MOPP); or cyclophosphamide, vincristine, procarbazine, prednisone, Adriamycin, bleomycin, vinblastine, and dacarbazine (COPP/ABVD) is high, ranging from 80 to 100 % [4, 10–14]. Recovery of spermatogenesis can occur and has been recorded in 11–14 % of males after these regimens [4, 13–15]. This rate was 40 % when dysspermia was included [4]. Da Cunha and colleagues assessed MOPP-induced gonadotoxicity, demonstrating a significantly higher rate of azoospermia in patients treated with more than five cycles of MOPP compared to those receiving three or fewer cycles [16]. Newer and more intensive alkylating agent–based combinations such as bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) are highly gonadotoxic in males. A study of the GHSG performing post-treatment sperm analyses at a median of 17.4 months after the end of therapy revealed azoospermia in 64 % of patients, other forms of dysspermia in 30 %, and normal sperm analysis results in only 6 % of cases [3]. Thirty-eight patients with advanced-stage disease were examined, and 89 % were azoospermic after treatment. None of these patients had a normal sperm status. There was no statistically significant difference in the post-treatment fertility status between a group of patients treated with eight cycles of BEACOPP baseline (with a cumulative cyclophosphamide dose of 5,200 mg/m^2) and a group treated with eight cycles of BEACOPP escalated regimens (with a cumulative cyclophosphamide dose of 10,000 mg/m^2) [3].

In contrast, ABVD is less gonadotoxic, with gonadal damage that might be only transient [13, 17, 18]. However, more detailed data in advanced-stage patients receiving eight cycles of ABVD is needed.

Pelvic radiotherapy is now infrequently used in the management of HL. The testes are highly sensitive to irradiation in a dose-dependent manner. Doses above 4–6 Gy can result in permanent azoospermia, and doses of more than 6 Gy have a significant risk of this complication. Direct testicular radiation is usually not necessary in HL patients, and scattered radiation can be reduced by shielding the testes.

26.2.4 Predictive Factors for Gonadal Dysfunction and Damage

In a multivariate analysis of HL patients at initial diagnosis, Rueffer and colleagues described an

elevated erythrocyte sedimentation rate (ESR) and poor prognostic risk groups as predictive for severe dysspermia [2]. A comparable study by Gandini and colleagues evaluated the semen quality in 106 untreated HL patients and showed a significant decrease in sperm concentration, total sperm count, and forward motility in the later stages of HL (stage III–IV) compared to early stages (stage I–II). Interestingly, of 53 patients with elevated ESR, 79.2 % had a normal sperm count, suggesting this parameter was not predictive for semen quality or potential infertility [19]. In an analysis of the GHSG, risk groups, extranodal involvement, and treatment with chemotherapy and BEACOPP were predictive factors for post-treatment azoospermia only in a univariate model. The fertility status prior to therapy was not predictive for post-treatment fertility [4, 20].

26.2.5 Hormonal Analyses to Assess Testicular Function After Therapy

Achievement of paternity and sperm counts provide the strongest evidence of male fertility; however, gonadotropin measurement can also provide useful surrogate information. Most studies in male patients show that the FSH levels correlate with testicular function after treatment [3, 4, 11, 18, 21]. In a study by van der Kaaij and colleagues, FSH was measured in a total of 355 patients with early-stage disease at least 12 months after the end of treatment. FSH was elevated in 35 % of all patients and in 3 % of those receiving radiotherapy only. In contrast, 60 % of patients treated with alkylating agents had elevated FSH levels, whereas this was observed in only 8 % of patients receiving chemotherapy without alkylators. Recovery of fertility was also poorer in patients treated with alkylating agent–containing chemotherapy [21]. Kreuser and colleagues reported increased FSH levels in 80 % of patients after treatment with COPP/ABVD [11]. In a retrospective GHSG analysis, abnormal FSH levels after chemotherapy were found in 79 %. In this group, the majority of patients were azoospermic (78 %; $p = 0.001$), suggesting an indirect correlation between FSH level and testicular dysfunction after therapy [3]. In contrast, normal levels of LH and testosterone were found in 86 and 63 % of patients after treatment. This underlines the hypothesis that spermatogonia cells are sensitive, whereas Leydig cells are more resistant to the toxic effects of cytostatic drugs [3, 11, 14]. Another important hormone in the assessment of infertility in men is inhibin B, which is produced by the Sertoli cells. Some studies support the use of inhibin B and inhibin B/FSH ratios as markers of male infertility [22, 23]. According to the results of a study by van Casteren and colleagues, 65 % of male cancer survivors had low inhibin B values as compared to 26 % in the control group [24]. Inhibin B levels significantly correlated with sperm concentration [24–26]. In a recent GHSG study, fertility status in men was assessed using hormonal levels of FSH and inhibin B. A total of 761 male survivors younger than 50 years at diagnosis were analyzed after a mean observation time of 48 months. Inhibin B and FSH values significantly correlated with chemotherapy intensity. Half of the survivors after early-stage treatment (2-4xABVD or 2xBEACOPPescalated + 2xABVD) had FSH and inhibin B levels corresponding to proven fertile men, whereas 88.8 % of survivors after advanced-stage treatment had levels indicating oligospermia. An effect of follow-up time on inhibin B and FSH levels was found in men after 2xBEACOPPescalated + 2x ABVD, suggesting a recovery up to 4 years after intermediate aggressive treatment. In contrast to the dose-dependent effect of chemotherapy on spermatogenesis, mean testosterone levels were within the normal range [27].

26.2.6 Endocrine Hypogonadism After Chemotherapy in Men

Little is known on the endocrine status of men after chemotherapy for HL. A recent study by Kiserud and colleagues investigated post-treatment exocrine and endocrine gonadal function in 165 HL and 129 non-Hodgkin lymphoma

(NHL) patients. In almost one-third of the patients, the hormone levels were compatible with endocrine hypogonadism, defined as low testosterone with or without elevated LH or elevated LH and normal testosterone. Interestingly, only three patients were receiving testosterone replacement at the time of analysis [28]. Comparable findings after chemotherapy for testicular cancer in young males were linked with a subsequent risk of developing metabolic syndrome [29].

According to the results of the GHSG study, aging male symptoms were not different between patients in the trials and reference values [27].

26.2.7 Fertility Preservation in Men: Preventative Pretreatment Strategies and Management After Chemotherapy

Sperm banking is a widely available and successful pretreatment preventative strategy [30]. All postpubertal males should thus be offered sperm banking prior to potentially gonadotoxic chemotherapy. This also needs to include patients planned for ABVD, although this regimen has a lower risk of treatment-related infertility. The reason for this is that in the event of early relapse, sperm quality and quantity might not have recovered, rendering banking impossible prior to gonadotoxic salvage treatment. Sperm should be banked regardless of count as intracytoplasmic sperm injection can be successfully used as part of in vitro fertilization (IVF) where counts are low. If azoospermia is present and time permits, testicular sperm retrieval can be successful, particularly in the presence of a normal or only modestly elevated FSH level.

Cryopreservation of testicular tissue in prepubertal boys is still highly experimental, and pregnancies in humans have not been achieved. However, due to recent success in animal models [31], this technique is already offered in specialized centers to boys, expecting that the scientific progress will allow using the tissue to generate sperm or to reactivate the testes in the future.

26.3 Gonadal Dysfunction in Women

26.3.1 Female Reproductive Physiology

In premenopausal menstruating women, ovarian function is controlled by pituitary secretion of FSH and LH. FSH activates the granulosa cells of growing ovarian follicles which in turn begin to proliferate and to produce estradiol. This reduces the FSH levels by feedback inhibition, maintaining them at low levels. A mid-cycle LH surge induces ovulation following the formation of the luteal body that produces progesterone. Follicle development takes place over several months prior to ovulation. The growing follicles produce not only estradiol but also inhibin, which prevents the growth of too many follicles by down-regulating FSH.

At puberty, approximately 300,000 follicles are present in the ovary. This number declines with age to around 1,000 at menopause (around 50–52 years of age), when FSH levels are insufficiently suppressed due to declining estrogen levels and therefore rise. The decline accelerates after the age of 35.

The number of follicles present in the ovary is known as the ovarian reserve and reflects reproductive capacity. Anti-Müllerian hormone (AMH) is produced by early, developing follicles, and its levels vary slightly during the menstrual cycle. It acts directly on other follicles in the ovary and inhibits the growth of too many follicles. The levels of this hormone are increasingly used in clinical studies to assess long-term gonadal damage and ovarian reserve.

26.3.2 Treatment-Related Infertility

While the mechanisms underlying the ovariotoxic effects of cytostatic drugs are still largely unknown, it is clear that the development of primary ovarian failure after chemotherapy is caused by accelerated attrition of the ovarian primordial follicles. As described above, this is age-dependent and relates to the ovarian reserve.

For alkylating agents, a direct dose-dependent cytotoxic effect has been described. Acute toxicity reduces the number of follicles, whereas chronic toxicity affects the quality of follicles resulting in early atresia [32].

Very similar to male patients, alkylating agents are most commonly involved in female gonadal damage. This is well documented after treatment with older chemotherapy regimens such as MOPP or MVPP (Mustargen, vinblastine, procarbazine, and prednisone). In an early study, only 17 of 44 women maintained regular menses when either of these regimens was used [33]. In a similar study, Schilsky and colleagues investigated ovarian function after treatment with MOPP and documented persistent amenorrhea in 11 of 24 women [34]. Similarly, after treatment with alternating COPP/ABVD for advanced-stage HL, therapy-induced ovarian failure was described in 17 of 22 women (77 %) [11]. A further analysis included a total of 84 female patients with HL and NHL treated with at least three cycles of chemotherapy including alkylating agents. Premature ovarian insufficiency (POI) was defined as persistent amenorrhea for at least 2 years after the end of chemotherapy and elevated FSH levels. After a median follow-up of 100 months, 31 (37 %) women with preserved fertility achieved natural pregnancy; in 34 women (40.5 %), premature ovarian insufficiency was reported [35]. A study by Haukvik and colleagues reported POF defined as persistent amenorrhea before the age of 41 in 37 % of women after HL treatment. This occurred more commonly in alkylating-agent-treated patients [36]. In a retrospective GHSG analysis, the menstrual status after HL treatment of 405 female patients younger than 40 years was analyzed. With a median follow-up of 3.2 years, 51.4 % of women who received eight cycles of escalated BEACOPP had continuous amenorrhea. Amenorrhea was significantly less common in women treated with two cycles of ABVD (3.9 %), two cycles of alternating COPP/ABVD (6.9 %), four cycles of alternating COPP/ABVD (37.5 %), or eight cycles of BEACOPP baseline (22.6 %). In a multivariate analysis, amenorrhea was most pronounced in women with advanced-stage HL, women older than 30 years of age at treatment, and women who did not take oral contraceptives during chemotherapy [37]. In a more recent analysis of the GHSG, hormonal levels and fertility questionnaires were analyzed in a total of 562 female survivors after a mean observation time of 46 months. Women were younger than 40 years at HL diagnosis. Normal mean AMH levels (>2 μg/L) were observed in women younger than 30 years after two to four cycles of ABVD early-stage treatment, but AMH levels were compromised in survivors ≥30 years old. After treatment with six to eight cycles of BEACOPP, mean AMH levels were 0 μg/L in both age groups, and highest FSH levels were measured in women older than 30 years. Regular menstrual cycle was reported by more than 90 % of women after early-stage treatment and was mostly completed within 1 year. In contrast, after advanced-stage treatment, age at therapy onset was a decisive factor, and time to resumption of menstrual activity was considerably longer (Table 26.1). The risk of sustained amenorrhea 4 years after chemotherapy was 25 % in 25-year-old women and 50 % in 30-year-old women [27].

After ABVD alone, chemotherapy-induced ovarian failure is less likely, especially when women are younger than 30 years at the time of treatment [17, 38–41]. Older women have a significantly lower likelihood of ovarian recovery than those of younger age [11, 27, 33–35, 37, 42, 43].

Interestingly, the study by Haukvik and colleagues demonstrated a high cumulative percentage

Table 26.1 Regular cycle after therapy depending on age at treatment and chemotherapy regimen in advanced-stage HL Behringer et al. [23]

Age (years)	Chemotherapy regimen	Regular cycle after therapy (%)
<30	8 × BEACOPP escalated	85
≥30		35
<30	6 × BEACOPP escalated	88
≥30		55
<30	8 × BEACOPP-14	70
≥30		44

of POI in the youngest group of women. Compared to women diagnosed at the age of 30 years or older, those younger than 30 years developed POI approximately 5 years later. These findings suggest that younger age at HL treatment delays the development of POI but that the lifetime risk of POI is not decreased [36].

26.3.3 Post-treatment Assessment of Ovarian Reserve with Anti-Müllerian Hormone Levels

In the literature, the definition of gonadal toxicity varies. As described in the prior section, gonadal toxicity is defined by amenorrhea only in some reports, whereas in others also hormonal parameters such as FSH or LH were used. However, all of these parameters only measure the ovarian reserve indirectly and have little sensitivity. Recent studies suggested that AMH is the most sensitive marker of gonadal function. This hormone is produced by the granulosa cells of early developing preantral and antral follicles in the ovary. The serum AMH levels can be used as a marker for the number of growing follicles – the levels decrease when the number of follicles declines. The AMH levels are not influenced by the day of the menstrual cycle. They are therefore a potentially convenient and useful marker [44–46].

However, several recent studies have revealed that AMH is currently of limited use as a routine parameter due to high fluctuations of AMH concentrations in different AMH assays and laboratories. The introduction of an automated and reproducible immunoassay for anti-Müllerian hormone is expected soon. Until then, AMH concentrations should be interpreted with care.

26.3.3.1 Hypogonadism in Women

In the study of the GSHG, hypogonadism was analyzed using the menopause rating scale (MRS). Results demonstrated an age-dependent raise in severe menopausal symptoms for all HL stages and therapies. Severe menopausal symptoms in women >30 years were three- to fourfold higher than in an older (45–60 years) German reference population [27].

26.3.4 Radiation Therapy

Due to the increasing use of combined modality or chemotherapy-only approaches, infradiaphragmatic radiation is rarely used in the treatment of HL. According to a mathematic model described by Wallace and colleagues, the dose of radiation required to destroy approximately 50 % of oocytes has been estimated to be less than 2 Gy [47]. The estimated effective sterilizing radiation dose to the ovary at birth is 20.3 Gy, at the age of 10 years is 18.5 Gy, at the age of 20 is 16.5 Gy, and at the age of 30 is 14.3 Gy [48].

The uterus is more radioresistant than are the ovaries. Nonetheless, partial or complete uterine irradiation, though rarely required, can result in uterine fibrosis with an increased rate of miscarriage. Gonadal and organ damage can be reduced by shielding and other techniques, and pretreatment oophoropexy may also have a role in this process.

26.3.5 Preventative Treatment Strategies in Women

After HL diagnosis, strategies for ovarian protection should be offered to all women who have not completed their family planning. Women should be referred to an experienced center for counseling on protective procedures, after which management approaches should also be discussed with the attending oncologist. Figure 26.1 summarizes the options to preserve fertility in women with HL [49].

26.3.6 Pharmacological Prevention of Gonadal Damage

Gonadotoxic chemotherapy destroys ovarian follicles and leads to decreased estrogen and inhibin secretion. Due to the negative feedback mechanism, the FSH levels increase and induce an increased recruitment of follicles, which are also potentially destroyed by chemotherapy. Pharmacological methods to protect fertility aim at suppressing pituitary gonadotropin secretion

and cyclic ovarian function with the use of GnRH agonists, antagonists, and oral contraceptives.

The following putative protective mechanisms using GnRH analogues have been suggested [50]:

1. Creating a prepubertal, hypogonadotropic milieu: Injected GnRH analogues cause an initial stimulation ("flare up") of the pituitary LH and FSH secretion. As a consequence of the downregulation of the pituitary GnRH receptors, the FSH and LH secretion then declines to low, prepubertal serum levels. This mechanism prevents the FSH levels from increasing and can stop the enhanced recruitment of follicles, thereby rescuing them from accelerated atresia.
2. Decreased utero-ovarian perfusion: Due to the hypoestrogenic milieu, utero-ovarian perfusion is decreased. This may lead to a lower total cumulative exposure of the ovaries to gonadotoxic chemotherapy.
3. A direct effect on GnRH receptors: GnRH-a may directly decrease gonadotoxicity of chemotherapy.
4. Possible role of sphingosine-1-phosphate: Spingosine-1-phosphate (S-1-P) is a lipid mediator of cell growth, survival, invasion, vascular maturation, and angiogenesis. Those processes are involved in cell viability and cancer progression. It has been speculated that GnRH-a may increase intragonadal S-1-P, thus preventing the ovarian follicles from destruction.
5. Possible protection of ovarian stem cells: It is speculated that GnRH-a may protect undifferentiated germ line stem cells that are capable of generating de novo primordial follicles.

Others have challenged the putative protective effect of GnRH-a, as the primordial follicle growth is an FSH-independent process and alkylating agents are not cell-cycle specific.

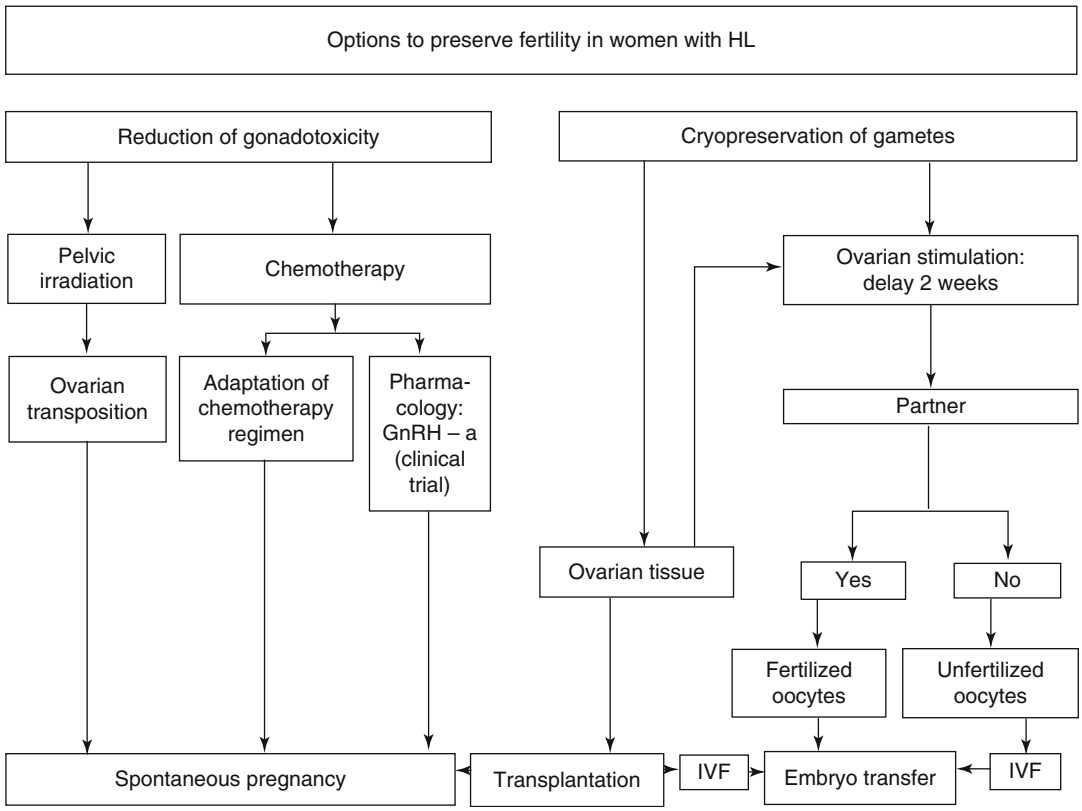

Fig. 26.1 Fertility preservation in women with HL (Modified by Demeestere et al. [47])

Thus, they might damage resting primordial follicles. Thus, GnRH-a might halt the growth of developing follicles, resulting in a resumption of the menstrual cycle in the short term. This might give the false impression that ovarian function is preserved [51].

Recently, two meta-analyses including women with different types of cancer [52] and women with lymphoma [53] have been published.

Del Masto et al. [52] included nine randomized trials in the meta-analysis with 225 events of POI occurring in 765 analyzed patients. The pooled OR estimate indicated a highly significant reduction in the risk of POF (OR = 0.43; 95 % CI 0.22–0.84; $p = 0.013$) in patients receiving GnRH-a. There was neither a statistically significant heterogeneity among studies (I2 = 55.8 %; $p = 0.012$) nor evidence of publication bias. Subgroup analyses showed that the protective effect of GnRH-a against POI was similar in subgroups of patients defined by age and timing of POF assessment, while it was present in breast cancer but unclear in ovarian cancer and lymphoma patients. The authors concluded that GnRH-a significantly reduces the risk of chemotherapy-induced POF in young cancer patients.

Zhang et al. [53] identified three randomized and four case control studies with lymphoma patients. They suggested that GnRH-a may be effective in protecting ovarian function during chemotherapy in lymphoma patients. However, due to the limited number of randomized studies, they also indicated that well-designed prospective studies are needed to improve further understanding of this topic.

Between 2004 and 2007, the GHSG conducted a prospective randomized trial (PROFE) to analyze the protective effect of GnRH-a. This trial was designed for young female patients (18–40 years) with advanced-stage HL receiving eight cycles of escalated BEACOPP. Patients were randomly assigned either to daily oral contraceptives (OC) or the GnRH-analogue (GnRH-a) goserelin, given monthly during eight cycles of polychemotherapy with escalated BEACOPP. The study was closed early after an interim analysis of 23 patients. Twelve patients were enrolled into arm A (OC) and 11 into arm B (GnRH-a). The women's median age was 26 years in arm A and 25 years in arm B. The AMH level after at least 12 months was reduced in all women. Combining both treatment arms, the respective ovarian follicle preservation rate was 0 % (95 % CI 0–12 %); thus, continuation of the study was not justified [54].

Results of a retrospectively performed study of the GHSG demonstrated that the prophylactic use of GnRH-a during therapy was followed by significantly more pregnancies after therapy for early unfavorable HL stages. This finding suggests a protective effect in women receiving less toxic chemotherapy [55].

Clinically relevant side effects of GnRH-a include menopausal symptoms such as hot flushes, headaches, mood changes, and decreased bone density.

26.3.7 Cryopreservation of Oocytes/ Ovarian Tissue

There have been remarkable advances in recent years in the field of cryopreservation of oocytes and ovarian tissue. But which technique (if any) should be recommended to a young woman before chemotherapy? This depends on the treatment to be used, age, availability of a partner, and the clinical condition of the patient and time available. It should be emphasized that results are likely to significantly improve during the reproductive span of patients currently undergoing harvest and storage.

26.3.7.1 Ovarian Stimulation and Cryopreservation of Fertilized and Unfertilized Oocytes

A minimum period of 2 weeks is required for both procedures. This is largely due to the time needed for ovarian stimulation. Modified stimulation regimens requiring 2 weeks have been successfully evaluated [56]. The cryopreservation of fertilized oocytes is a well-established method. If a sufficient number of oocytes can be retrieved and all cryopreserved fertilized oocytes are

transferred, the average cumulative pregnancy rate can be up to 40 %. The success rate of the cryopreservation of unfertilized oocytes has significantly improved due to the introduction of the vitrification freezing technique. It has been shown by specialized centers that the pregnancy rates after vitrification of oocytes are similar to oocytes without cryopreservation [57].

26.3.7.2 Cryopreservation of Ovarian Tissue

Cryopreservation of ovarian tissue is an alternative especially for young patients without a partner. This method requires little or no preparative time but does require a laparoscopy. A combination of this technique with other invasive methods is possible.

The ovarian tissue is retrieved from one ovary and subsequently prepared and preserved using cryoprotective agents. If ovarian function insufficiency develops while relapse-free on follow-up, the cryopreserved tissue can be transplanted orthotopically to the remaining ovary or heterotopically. Currently, 30–40 live births and several ongoing pregnancies have been reported using this approach [58]. Work in mice models led to concern about possible tumor reimplantation from ovaries infiltrated with lymphoma [59]. In practice, however, HL rarely involves the ovaries; the tumor cells are extremely fragile, and so far there are no recorded events of tumor cell reimplantation [60].

26.3.8 Premature Menopause

Early onset of menopause in female patients after treatment for childhood cancer is well described [61, 62] showing higher cumulative incidence of premature menopause by the age of 40 for survivors compared to control siblings (8 vs. 0.8 %) [63]. Alkylating-agent-based combination chemotherapy will very likely lead to premature menopause in female patients. It is important to note that occasionally transient cessation of menses, with or without hot flushes, can occur. Hormone replacement may be indicated to reduce symptoms and prevent osteoporosis. If fertility is desired in younger women and conventional low-dose HRT is used, it is possible to monitor ovarian recovery with FSH levels. If oral contraceptives are used, treatment breaks with re-evaluation of ovarian function may be reasonable.

Conclusions

Remarkable advances have occurred in the management of HL, and today cure can be anticipated for the vast majority of young adults. When alkylating-agent-based combination chemotherapy was first devised in the 1960s, almost any late effect on fertility was acceptable in the context of the hitherto grim prognosis of HL, particularly in advanced stages. Then, regimens such as ABVD proved to be equivalent or superior, inducing less gonadotoxic effects. After the introduction of highly effective alkylating-agent-based therapy such as BEACOPP, impressive tumor control and overall survival rates were achieved but were associated with substantial gonadal toxicity, necessitating the development of adjunctive fertility supporting technology. Current trials evaluate risk-adapted treatment, reserving more effective but more toxic treatment for subgroups of patients with poorer prognosis as judged by positron emission tomography (PET) scanning.

The remarkable advances in the management of HL are paralleled by advances in fertility preservation techniques. It is of particular importance that these are considered and discussed as early as possible after diagnosis in the context of the patient's wishes with regard to treatment and future fertility.

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