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Thomas E. Merchant
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Pediatric Radiation Oncology

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Preface

Cancer is the leading cause of death by disease past infancy among children in the Western world. In the United States in 2014, it is estimated that 15,780 children and adolescents from birth to the age of 19 years will be diagnosed with cancer and 1960 will die of the disease (Ward et al. 2014). In 1975, only barely above 50% of children diagnosed with cancer before age 20 years survived more than 5 years (Ries et al. 1999). Since then results have greatly improved such that in 2004–2010 more than 80% of children diagnosed with cancer before age 20 years survived at least 5 years (Howlader et al. 2014, National Cancer Institute, http://www.cancer.gov). Childhood malignancies include a great variety of different tumor types for most of which multidisciplinary management with a combination of local and systemic treatments is required for optimal outcomes; for many patients, radiation therapy as local treatment is an integral component of the therapeutic strategy.

Pediatric malignancies are a challenge for the radiation oncologist due to their rarity, the great variability of histological subtypes, and the complexity of treatment concepts that undergo constant modification. Radiation therapy technologies also undergo a continuous process of optimization and modern technologies (e.g., intensity-modulated radiotherapy, proton therapy, inclusion of modern imaging in treatment planning, and use of imaging to precisely guide treatment delivery) are rapidly becoming essential in the management of children and teenagers with malignancies. This book addresses the most recent developments in radiation therapy with respect to the different types of childhood malignancies and the use of modern treatment technologies. The chapters also address specific issues in the field of anesthesia, palliative radiation therapy, and quality of life.

The book is therefore designed to provide a comprehensive overview of current and future treatment concepts with emphasis on radiation therapy. Special attention is paid to experiences on past and present trials worldwide

With the increase of the childhood population in low and middle income countries, specific demands will be put on the management of childhood cancer in an environment with limited access to modern technologies. This book therefore also addresses aspects for low and middle income countries.

Ries LAG, Smith MA, Gurney JG, et al (eds) (1999) Cancer Incidence and survival among children and adolescents: United States SEER Program 1975–1995. National Cancer Institute, SEER Program. NIH Pub. No. 99-4649. Bethesda, MD

Howlader N, Noone AM, Krapcho M, et al (eds) (2014) SEER cancer statistics review, 1975–2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site

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1 Introduction

Thomas E. Merchant and Rolf-Dieter Kortmann

Cancer is the leading cause of death by disease past infancy among children in the Western world. In the United States in 2014, it is estimated that 15,780 children and adolescents from birth to the age of 19 years will be diagnosed with cancer and 1960 will die of the disease (Ward et al. 2014). In 1975, fewer than 50% of children diagnosed with cancer before the age of 20 years survived more than 5 years (Ries et al. 1999). Since then results have greatly improved. In 2004–2010 more than 80% of children diagnosed with cancer before age 20 years survived at least 5 years (Howlader et al. 2013, National Cancer Institute, http://www.cancer.gov). Childhood malignancies include a variety of different tumour types. Most require multidisciplinary management with a combination of local and systemic treatments to achieve optimal outcomes; for many patients, radiation therapy as local treatment is an integral component of the therapeutic strategy.

Pediatric malignancies are a challenge for the radiation oncologist due to their rarity, the great variability of histological subtypes, and the complexity of treatment concepts that continue to evolve. Radiation treatment methods, both technology and process, undergo a continuous process of optimization. Poignant example include intensity modulated radiotherapy, proton therapy, inclusion of modern imaging for treatment planning, localization, and verification. All methods and modalities associated with contemporary adult treatment are essential to the management of children and young adults with cancer and allied diseases. This work addresses the most recent developments in radiation therapy with respect to the different types of childhood cancers and conditions that require irradiation. Each chapter addresses specific issues in the field of pediatric radiation oncology by disease, discipline, and topic relevant to the treatment of children and young adults. This work is designed to provide a comprehensive overview of current and future concepts with emphasis on radiation therapy. Experience based on past and present trials are given priority.

With the increase of the childhood population in low and medium income countries specific demands will be put on the management of childhood cancer in an environment with limited access to modern technologies. This work addresses certain challenges associated with low and medium income countries.

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Ewing Sarcoma and Desmoplastic Small Round Cell Tumor

2

Safia K. Ahmed, Siddhartha Laskar, and Nadia N. Laack

2.1 Ewing Sarcoma

2.1.1 Epidemiology and Etiology

Ewing sarcoma is the second most common primary bone tumor, with roughly 250 cases diagnosed in the United States each year. The incidence is approximately 2.8 cases per million in children <15 years of age (Ward et al. 2014). No causative agents have been identified. However, somatic chromosomal translocations involving the EWS gene are the driving force in Ewing sarcoma pathogenesis (see Sect. 2.4).

Males are more commonly affected than females (1.5–2.0:1), and there is a Caucasian predominance which is not fully understood (Postel-Vinay et al. 2012). Cases generally occur in the teenage years, although 30% of cases occur in the first decade of life and another 30% occur in the third decade of life. There is no method of preventing Ewing sarcoma.

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2.1.2 Clinical Manifestations and Diagnosis

2.1.2.1 Patient Presentation and Evaluation

Symptoms depend on the site(s) of disease, but most patients present with localized pain, swelling, and a palpable mass. Musculoskeletal function abnormalities, fractures, neurologic symptoms, and weight loss are also routinely seen. Figure 2.1 illustrates the distribution of primary tumor sites. The lower extremity and pelvis are most commonly involved.

A complete history and physical exam is required when evaluating Ewing sarcoma patients. Studies obtained to evaluate disease extent include routine blood work, urine analysis, plain radiographs of the primary tumor and chest, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the primary tumor, bone marrow biopsy, and CT chest with bone scan and/or fluorodeoxyglucose positron emission tomography (FDG PET) for metastatic disease evaluation.

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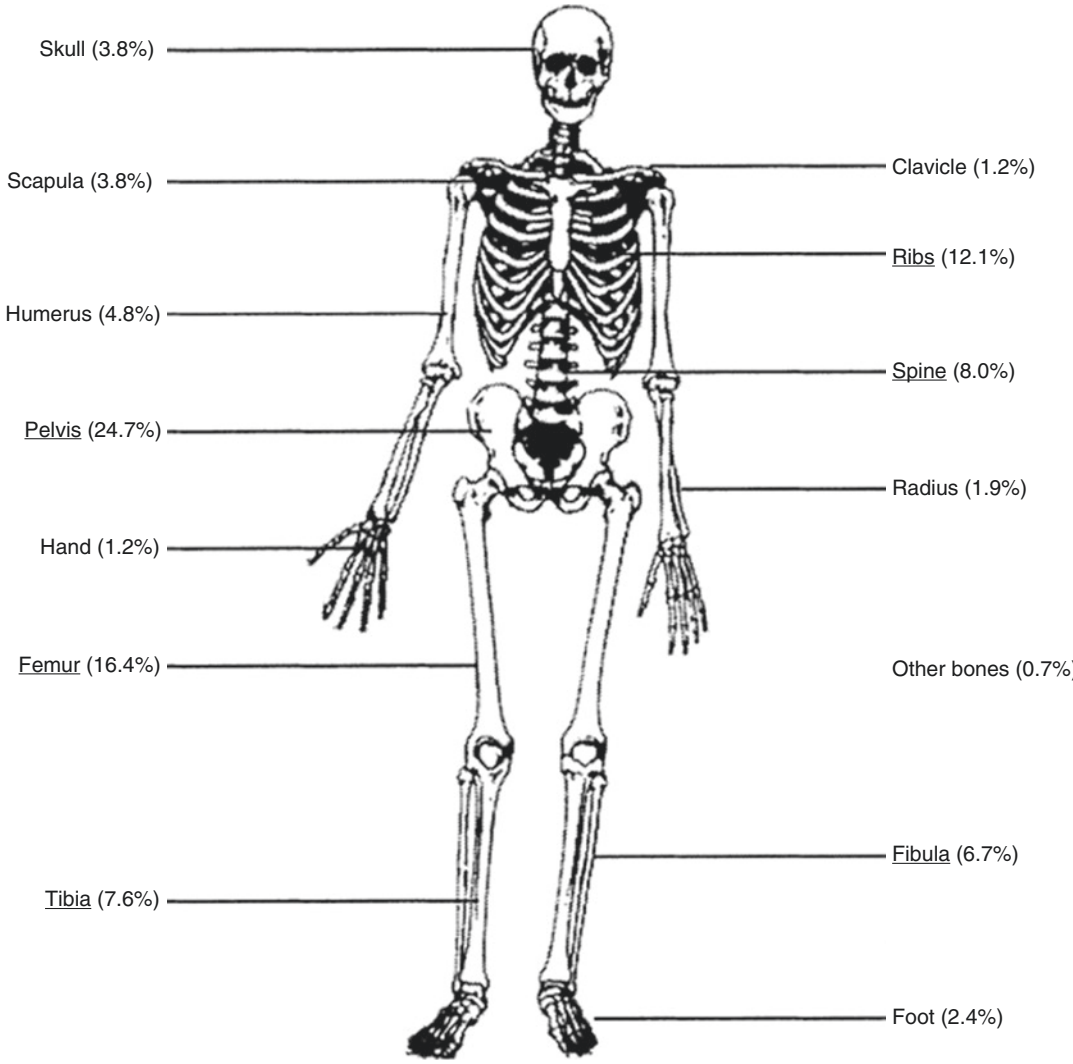

Fig. 2.1 Distribution of primary Ewing sarcoma sites as reported by the European Intergroup Cooperative Ewing's Sarcoma Study Group analysis of 975 patients

2.1.2.2 Imaging

Plain radiographs of the tumor show a lytic, destructive lesion, with or without a soft tissue mass, typically at the diaphysis. Codman's triangle, a consequence of an elevated periosteal reaction, and "onion skin" effect, an outcome of parallel, multilaminar, periosteal reactions, are also detected.

CT of the primary tumor is useful for depicting bone cortex destruction. MRI is essential in elucidating extraskeletal soft-tissue and neurovascular involvement. The tumor has low signal intensity with heterogenous gadolinium enhancement on T1-weighted images and high signal intensity on T2-weighted images (Fig. 2.2). On FDG PET, the tumor displays high FDG uptake. Single institution and small multi-institutional studies suggest FDG PET has improved sensitivity to bone and lymph node metastases compared to bone scan and CT (Hawkins et al. 2005; Raciborska et al. 2016). If CT chest shows subtle abnormalities, an excision may be needed for accurate staging.

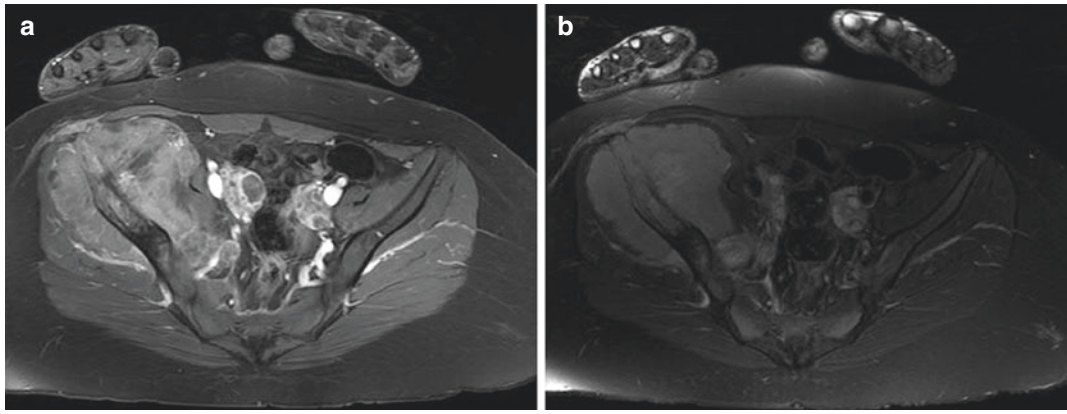

Fig. 2.2 (**a**) Prechemotherapy, post-gadolinium T1 axial MRI of a pelvis Ewing sarcoma. (**b**) Prechemotherapy, T2 axial MRI of a pelvis Ewing sarcoma

2.1.2.3 Diagnosis

Histologic diagnosis is obtained via biopsy, ideally by the surgeon who will perform the resection. It is crucial the biopsy does not increase the extent of surgery, or preclude a limb-sparing procedure or sparing of a skin strip outside the radiation field. The biopsy must also avoid contamination of uninvolved areas and avoid hematoma development.

2.1.2.4 Staging

There is no formal staging system for Ewing sarcoma. Patients are categorized as having localized or metastatic disease. Approximately 25% of patients present with metastatic disease. The most common metastatic sites are lungs (40%) and bones/bone marrow (40%). Lymph node involvement also occurs.

2.1.2.5 Blood and Serum Findings

No specific laboratory test identifies Ewing sarcoma. Abnormalities indicative of inflammation may be seen, including anemia, leukocytosis, elevated erythrocyte sedimentation rate, elevated alkaline phosphatase, and elevated C-reactive protein. Elevated lactate dehydrogenase (LDH) levels can also been seen and have been correlated with large primary tumors and inferior prognosis (Bacci et al. 2006b; Cotterill et al. 2000). LDH levels are not used to guide treatment recommendations.

2.1.2.6 Miscellaneous Evaluations

If the tumor is associated with a pleural or abdominal effusion, cytologic evaluation of the fluid must be obtained. An electrocardiogram and echocardiogram must be obtained prior to starting chemotherapy. Fertility preservation measures should be undertaken if it will not delay initiation of chemotherapy significantly. Nutritional support, physical therapy/occupation therapy, and social work assistance may also be needed in some patients.

2.1.3 Pathology and Molecular Characteristics

Ewing sarcoma is an undifferentiated round blue cell tumor. Presently, it is proposed Ewing cells arise from mesenchymal progenitor or mesenchymal stem cells found in bone marrow (Tirode et al. 2007). By light microscopy, Ewing sarcoma appears as densely packed, small, round, malignant cells with hyperchromatic nuclei and varying amounts of cytoplasm (Link and Donaldson 1991). Tumors with similar histology also arise in soft tissues, including peripheral primitive neuroectodermal tumor (pNET), neuroepithelioma, and Askin tumor. These tumors are collectively referred to as the Ewing sarcoma family of tumors (ESFT).

In general, ESFT are characterized by nonrandom gene rearrangements between the EWS

gene on 22q12 and various members of the ETS gene family (Burchill 2003; Turc-Carel et al. 1988; Zucman et al. 1992). The fusion proteins function as aberrant transcription factors contributing to oncogenic transformation (Bailly et al. 1994). The most frequent gene rearrangement is the (11;22)(q24;q12) translocation resulting in EWS-FLI1 fusion. This rearrangement is found in approximately 85% of Ewing sarcoma cases (Burchill 2003). Other EWS fusions, including t(21;22)(q22:q12) and t(7;22)(p22;q12) resulting in EWS-ERG and EWS-ETV1 fusions, respectively, occur in the remaining 15% of tumors (Burchill 2003). Analysis of outcomes by EWS fusions for 565 patients enrolled on the EuroEWING 99 study did not demonstrate a prognostic benefit to EWS-FLI1 fusions compared to other fusions (Le Deley et al. 2010).

Immunohistochemical studies can also help differentiate Ewing sarcoma from similar soft tissue malignancies. Over 90% of Ewing sarcoma cases demonstrate positivity for the cytoplasmic membrane protein CD99, a product of the MIC2 gene (Ambros et al. 1991). However, CD99 expression is not specific to Ewing sarcoma (Olsen et al. 2006). Vimentin, HBA-71, β_2-microglobulin, cytokeratin and neuron-specific enolase can also be positive.

2.1.4 Prognosis

The most important prognostic factor in Ewing sarcoma is the presence or absence of metastatic disease. The 5-year overall survival (OS) and event-free survival (EFS) rates for patients with metastatic disease on the Children's Oncology Group (COG) INT-0091 study was 34% and 22%, respectively, versus 72% and 69%, respectively, for those with localized disease (Grier et al. 2003).

Primary tumor site, tumor size at presentation, age at diagnosis, and gender are traditional prognostic factors. Data on these variables in more recent studies, however, is conflicting (Table 2.1). Adult (>18 years of age) patients in COG AEWS0031 were associated with inferior EFS (Womer et al. 2012). Conversely, age was not associated with outcomes on the French EW93 study (Gaspar et al. 2012). Gender was not associated with outcomes in the INT-0091 or French EW93 studies (Gaspar et al. 2012; Grier et al. 2003).

There was no association between primary tumor site or size and outcomes in the COG INT-0154 study (Granowetter et al. 2009). On the contrary, AEWS0031 demonstrated inferior OS and EFS for pelvic primaries and the French EW93 study correlated trunk and proximal tumor locations with inferior EFS (Gaspar et al. 2012; Womer et al. 2012). An important facet of the French EW93 study is tumor location lost its prognostic impact once local approach was accounted for (Gaspar et al. 2012). The French EW93 study also demonstrated tumor volume to be a prognostic factor for unresected tumors and histological response to chemotherapy to be prognostic in resected tumors (Gaspar et al. 2012).

FDG PET response to induction chemotherapy may be an effective prognostic tool but needs validation in prospective studies (Hawkins et al. 2005; Raciborska et al. 2016). The prognostic value of histologic response to chemotherapy has not been confirmed in North American regimens. However, single institution reports suggest response correlates with improved survival and local control (Ahmed et al. 2013; Lin et al. 2007; Wunder et al. 1998). Molecular biomarkers, such as p53 mutations and CDKN2A deletions, were thought to correlate with outcomes but did not pan out in prospective evaluation (Lerman et al. 2015).

2.1.5 Current Treatment

Effective systemic and local therapy is essential for cure. Ewing sarcoma is highly radiosensitive; however, fewer than 10% of patients survive with local therapy measures alone. Patients die of metastatic disease within the first few years indicating a need for effective chemotherapy. With modern multimodal treatment regimens of neoadjuvant and adjuvant chemotherapy in combination with surgery and/or radiotherapy, 5-year OS and EFS can exceed 80% and 70%, respectively, in patients with localized disease (Womer et al. 2012).

Table 2.1 Results of selected modern era chemotherapy trials in localized Ewing sarcoma

	Chemotherapy	5 year OS	5 year EFS
Children's Oncology Group			
INT-0091 (Grier et al. 2003)	VACD	61.0%	54.0%
	VACD + IE	72.0% (p = 0.01)	69.0% (p = 0.005)
INT-0154 (Granowetter et al. 2009)	VDC + IE, 48 weeks	80.5%	72.1%
	VDC + IE, 30 weeks	77.0% (p = NS)	70.1% (p = 0.57)
AEWS0031 (Womer et al. 2012)	VDC + IE, q3 weeks	77.0%	65.0%
	VDC + IE, q2 weeks	83.0% (p = 0.056)	73.0% (p = 0.048)
AEWS1031	VDC + IE, q2 weeks	Results pending	
	VDC + IE + VTC, q2 weeks		
Memorial Sloan-Kettering Cancer Center			
P6 (Kolb et al. 2003)	HD-CVD + IE	89.0% (4-year)	82.0% (4-year)
The Cooperative Ewing Sarcoma Study			
CESS-86 (Paulussen et al. 2001)	SR (<100 mL and extremity site): VACD	57.0%, all patients (10-year)	52.0% (10-year)
	HR (≥100 mL and/or central-axis sites): VAID		51.0% (p = 0.92)
European Intergroup Cooperative Ewing's Sarcoma Study			
EICESS-92 (Paulussen et al. 2008)	SR (localized tumors and <100 mL)		
	VAID	84.0%	68.0%
	VACD	82.0% (p = 0.80)	67.0% (p = 0.72)
	HR (metastatic disease or ≥100 mL)		
	VAID	53.0%	44.0%
	EVAID	57.0% (p = 0.23)	52.0% (p = 0.12)
French Society of Pediatric Oncology			
EW-88 (Oberlin et al. 2001)	VD + VD/VA	66.0%	58.0%
EW-93 (Gaspar et al. 2012)	SR (<5% residual cells or <100 mL): VD + VD/VA	69.0%, all patients	70.0%
	IR (5–30% residual cells or ≥100 mL): VD + VD/VA + IE		54.0%
	HR (≥30% residual cells or <50% size response): VD + VD/VA + IE + HD B/M and SCR		48.0%
Euro Ewing Consortium			
EE2012	VDC + IE	Accruing	
	VIDE		

A actinomycin D, *B/M* busulfan/melphalan, *C* cyclophosphamide, *D* doxorubicin, *E* etoposide, *HD* high dose, *HR* high risk, *I* ifosfamide, *IR* intermediate risk, *NS* not significant, *SCR* stem cell rescue, *SR* standard risk, *T* topotecan

2.1.6 Chemotherapy

The evolution of chemotherapy regimens over time demonstrates a pattern of treatment intensification. The first Intergroup Ewing Sarcoma Study (IESS-1) randomized patients to three adjuvant chemotherapy arms after receiving radiation therapy to the primary lesion (Nesbit et al. 1990). The arms were: vincristine, actinomycin D, and cyclophosphamide (VAC); VAC plus doxorubicin (VACA due to trade name adriamycin); or VAC plus bilateral pulmonary radiation therapy. The study showed a significant improvement of all parameters for the VACA arm (Nesbit et al. 1990). This trial established doxorubicin to be a quintessential drug for Ewing sarcoma chemotherapy. IESS-2 demonstrated the importance of doxorubicin dose intensity (Burgert et al. 1990).

INT-0091 investigated the addition of ifosfamide and etoposide to VACA in an alternating fashion administered every 3 weeks for 17 cycles with local control administered at week 12 (Grier et al. 2003). Five-year OS, EFS, and local control were significantly improved in the experimental arm for patients with localized disease only (Grier et al. 2003). INT-0154 demonstrated no difference between standard dose vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE) and dose-intensified VDC/IE (Granowetter et al. 2009).

Most recently, AEWS0031 dosed VDC/IE every 2 weeks versus standard every 3 weeks with filgastrim given in both arms (Womer et al. 2012). An 8% 5-year EFS benefit was observed for interval-compressed chemotherapy (Womer et al. 2012). Furthermore, toxicities were similar between arms (Womer et al. 2012). Interval-compressed chemotherapy is now the standard of care in the United States. The ongoing Euro-Ewing 2012 study will compare interval-compressed VDC/IE with the European standard of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) to help define an international standard induction chemotherapy regimen for Ewing sarcoma.

In Europe, adjuvant chemotherapy is routinely tailored to clinical and tumor characteristics. The French EW93 study stratified consolidation chemotherapy according to risk groups defined by histologic response for resected tumors and tumor size or radiologic response for unresected tumors (Gaspar et al. 2012). High risk tumors (>30% residual cells or <50% radiologic response) received ifosfamide/etoposide prior to high dose busulfan/melphalan with stem cell rescue, and had a 5-year EFS rate of 45% (Gaspar et al. 2012). The results of the European EWING 99 trial randomizing patients with poor pathologic response to either high-dose chemotherapy with busulfan or standard VIDE every 3 weeks are pending.

Given the effectiveness of cyclophosphamide and topotecan in relapsed Ewing sarcoma, COG AEWS1031 added vincristine, topotecan, and cyclophosphamide to the interval compressed VDC/IE backbone. Trial results are pending. This study will also assess initial tumor volume, histologic response to induction chemotherapy, and response measured by FDG PET as prognostic factors for EFS in localized Ewing sarcoma.

2.1.7 Local Therapy

Local treatment consists of surgery, radiation, or surgery in combination with radiation. Local treatment is administered after six cycles of induction chemotherapy. A randomized trial comparing local control modalities does not exist and will likely never transpire. The best approach then in terms of highest local control rate with good functional outcomes is determined on an individual case basis by scrutinizing pertinent patient and tumor characteristics. In the United States, 60–65% of patients undergo surgery, 20–25% receive radiation only, and the remainder are treated with surgery and radiation. European studies report higher rates of patients treated with surgery and radiation and lower rates of surgery alone (Arai et al. 1991; Burgert et al. 1990; Craft et al. 1998; Donaldson et al. 1998). This is a reflection of a risk-adapted approach which is not utilized in the United States due to a presumed lack of effective treatment options for poor responders.

2.1.7.1 Surgery

Retrospective analyses of cooperative group studies suggest local control is improved with surgery. The analysis of 1058 patients treated on the Cooperative Ewing's Sarcoma Studies (CESS) 81, CESS 86, and European Intergroup Ewing's Sarcoma Study 92 (EICESS 92) revealed a 5-year local failure rate of 4.1–7.5% in patients treated with surgery ± radiation versus 26.3% for patients treated with definitive radiation (Schuck et al. 2003). A selection bias for utilizing surgery for more favorable tumors (i.e., tumors in expendable bones) likely exists in these analyses confounding the findings. For instance, in the combined analysis of INT-0091, INT-0154, and AEWS0031, patients treated with definitive

radiation were more likely to have pelvic tumors and patients treated with surgery were more likely to have extremity tumors (Dubois et al. 2015). There was a greater risk of local failure for radiation therapy alone compared to surgery in this cohort, but no difference in survival by modality (Dubois et al. 2015). Despite a lack of OS benefit, surgery is the recommended local control modality for Ewing sarcoma if clear margins can be obtained with minimal morbidity due to the secondary malignancy risk associated with radiation.

Clear surgical margins customarily are at least 1.0 cm in bone, 0.5 cm in soft tissue, and 0.2 cm in fascia. AEWS1031, however, defined a positive margin as either viable tumor or tumor displaying coagulative necrosis at the inked surface. Amputations are rarely indicated due to innovative surgical bone replacement techniques, including endoprostheses, allografts, vascularized autografts, and rotationplasty. Surgical bone replacement complications include infection and abnormal bone healing. Growing patients with endoprosthesis also require regular follow-up for possible alteration/replacement. For tumor-associated pathologic fracture, the bone should first be stabilized surgically. If limb salvage is preferred, radiation is utilized for local control because fracture results in tumor spill.

2.1.7.2 Definitive Radiation

Ewing sarcoma is highly radiosensitive. As such, radiation therapy is curative and recommended for tumors that cannot be resected. This naturally creates a bias for radiating tumors that constitute an unfavorable population. Patients treated with radiation therapy alone usually have large tumors, tumors in unfavorable locations, and/or consist of tumors where gross total resection is not possible. Pelvic and vertebral tumors are classic examples of the aforementioned features.

In the CESS and EICESS trials, 266 of 1058 patients received radiation alone for local treatment. Seventy percent had centrally located tumors (Schuck et al. 2003). The local failure rate was 26.3% for the radiation only group versus 4.1–7.5% for patients who received surgery ± radiotherapy (Schuck et al. 2003). In a single-institution analysis of 512 patients, the local failure rate was 19% with radiation alone, 9% with surgery, and 11% for surgery and radiation (Bacci et al. 2006a). However, radiation alone was associated with inferior EFS and local control in extremity sites only and not in central tumor sites (Bacci et al. 2006a). This indicates obtaining local control in central tumor sites is difficult regardless of approach. The analysis of chestwall tumors in the CESS and EICESS trials demonstrated no statistically significant difference in EFS or local control by local control modality (Schuck et al. 1998). Additionally, there was no difference in local failure rates between surgery or radiation (25%) for pelvic tumors enrolled on INT-0091 (Yock et al. 2006). In fact, the lowest local failure rate was seen in patients who received surgery and radiation (10.5%) (Yock et al. 2006).

Another indication for definitive radiation is when an R2 resection (residual gross disease) is expected. Debulking procedures do not improve local control rates and are associated with unnecessary morbidity. Patients included on the CESS and EICESS trials and analysis of the Bologna experience revealed the same local recurrence rates in patients who underwent intralesional excision followed by radiation versus radiation alone (Bacci et al. 2004; Schuck et al. 1998, 2003).

No clear dose-local control correlation is established. IESS-I showed no association between doses of 30 Gy and 65 Gy and local control (Nesbit et al. 1990). The St. Jude experience documented higher local failure rates in patients treated to doses <40 Gy versus no local failures in patients treated to doses ≥40 Gy (Arai et al. 1991). However, analysis by size revealed a dose threshold for tumors <8 cm (Arai et al. 1991). Similarly, Paulino and colleagues found improved local control rates for doses ≥49 Gy in tumors ≤8 cm and ≥54 Gy for tumors >8 cm in a retrospective analysis of 40 patients (Paulino et al. 2007). A phase II study from St. Jude documented no local failures in patients with tumors ≥8 cm treated to 64.8 Gy (Talleur et al. 2016). Altered fractionation schemes have not improved local control (Dunst et al. 1995).

2.1.7.3 Postoperative Radiation

Postoperative radiation is required in cases of incomplete resection (R1 (microscopic residual disease) or R2 resection), intralesional resections, tumor spill, and/or close margins. In Europe, patients also receive postoperative radiation in cases of poor histologic response.

Outcomes in patients who receive surgery and radiation are comparable to surgery alone despite constituting a heterogenous group with a range of tumor and treatment characteristics. In the CESS and EICESS trials, postoperative radiation was administered if residual tumor-bearing bone remained in situ, intralesional or marginal resections were performed, or if the tumor had poor histologic response to preoperative chemotherapy (Schuck et al. 2003). The risk of local and combined local and systemic relapses was 10.2% (Schuck et al. 2003). Similarly, there was no difference in EFS or local control for patients who received surgery and radiation versus surgery alone in the combined INT-0091, INT-0154, and AEWS0031 analysis (Dubois et al. 2015). A review of patients with good histologic response to chemotherapy on the Euro-EWING 99 R1 trial (comparing two consolidation chemotherapy regimens) found the risk of local recurrence was halved in patients treated with surgery and radiation compared to surgery alone after controlling for confounders (Gaspar et al. 2013).

As mentioned, patients in Europe receive postoperative radiation in cases of poor histologic response to neoadjuvant chemotherapy. The results of the CESS and EICESS showed local control was superior in patients with poor histologic response who received postoperative radiation compared to those who did not (Schuck et al. 2003). However, there was no difference in local failure for postoperative radiation according to histologic response after wide excision (5.6% for good responders versus 5.0% for poor responders) (Schuck et al. 2003).

2.1.7.4 Preoperative Radiation

EICESS 92 incorporated preoperative radiation therapy to sterilize the tumor compartment before surgery and consequently reduce the rate of disease dissemination at the time of surgery (Schuck et al. 2003). However, preoperative radiation was actually utilized when narrow resection margins were expected (Schuck et al. 2003). Analysis of the 246 patients treated with preoperative radiation revealed no difference in EFS, but excellent local control (6% 5-year local and combined local and systemic failure rate) (Schuck et al. 2003). In North America, preoperative radiation is rarely used due to potential increase in infection rate postoperatively and interference with bony union.

2.1.8 Metastatic Disease

Outcomes in patients with metastatic disease remain poor, with overall survival rates of approximately 30% across multiple studies (Grier et al. 2003; Ladenstein et al. 2010; Paulussen et al. 1998; Cangir et al. 1990). Patients with isolated pulmonary metastasis appear to be a more favorable subset of metastatic Ewing sarcoma patients. The 4-year EFS on the EICESS trials was 34% for isolated lung metastases, 28% for bone/bone marrow metastases, and 14% for combined lung and bone metastases (Paulussen et al. 1998).

In the United States, metastatic patients are treated with interval compressed VDC/IE chemotherapy, whole lung irradiation for lung metastases, and definitive surgery and/or radiation for all other metastatic sites. Given the overall poor prognosis of metastatic Ewing sarcoma, radiation is more practical than surgery for treatment of metastatic sites. An exception is resection of a limited number of pulmonary only metastases. Additionally, resection of residual gross pulmonary metastases after completion of all chemotherapy is required before whole lung radiation. If gross disease is not resected, a radiation boost must be incorporated into whole lung irradiation.

An analysis of metastatic patients treated on Euro-EWING 99 demonstrated improved 3-year EFS in patients who received local therapy to the primary tumor and metastases (39%) versus patients who received local therapy to the primary tumor only (17%) or no local therapy at all (14%) (Haeusler et al. 2010). On multivariate analysis, absence of local treatment was a significant risk factor (Haeusler et al. 2010). In terms of

chemotherapy, INT-0091 did not show improved outcomes in metastatic patients who received IE (Grier et al. 2003). Interval compressed chemotherapy is used in metastatic disease despite formal evaluation because of the favorable results in localized patients.

AEWS1221 is the ongoing phase II COG study for metastatic Ewing sarcoma. Patients will be randomized to standard interval-compressed multi-agent chemotherapy with or without ganitumab. It is hypothesized ganitumab, a human monoclonal antibody directed against IGF-1R, increases the sensitivity of Ewing sarcoma cells to the effects of chemotherapy (Benini et al. 2001; Scotlandi et al. 1996). A secondary objective of the study is to evaluate the role of stereotactic body radiotherapy (SBRT) for bone lesions to improve the feasibility of treatment.

Europeans use risk adapted strategies based on the site of metastases. High-dose chemotherapy with autologous stem cell rescue is utilized in bone-metastatic patients. Patients on the Euro-EWING 99 trial received six cycles of VIDE and one cycle of vincristine, actinomycin D, and ifosfamide followed by local treatment (Ladenstein et al. 2010). Patients then received high-dose busulfan-melphalan followed by stem cell rescue (Ladenstein et al. 2010). The 3-year OS was 34% and EFS was 27% (Ladenstein et al. 2010). Given the superior outcomes for pulmonary metastases, an intermediate intensity regimen of standard chemotherapy and whole lung irradiation is utilized. The 4-year EFS with this approach on the EICESS trials was 40% (Paulussen et al. 1998). Results of the Euro-EWING 99 pulmonary metastases arm evaluating standard chemotherapy with whole lung irradiation versus high dose chemotherapy with stem cell rescue are still pending.

2.1.9 Radiation Technique

2.1.9.1 Primary Tumor Radiation Dose

Doses between 55 Gy and 60 Gy are typically given for definitive radiotherapy cases. For pre- and postoperative radiation cases, doses range between 45 Gy and 55 Gy depending on individual risk factors (i.e., resection margins and histologic response). Daily fractionation is 1.8 Gy, and may be reduced to 1.5 Gy when large volumes are treated (e.g., whole abdomen) or when tolerance is poor (e.g., diarrhea). AEWS1031 recommends 45 Gy to pre-chemotherapy target volume, 55.8 Gy to post-chemotherapy residual disease, and 50.4 Gy for microscopic positive margins postoperatively. In patients receiving busulfan-based regimens, caution must be taken with radiation timing and dose because of the radiosensitizing effect of the agent.

2.1.9.2 Primary Tumor Target Volume

Target volume delineation is done with an MRI in treatment position. This allows for smaller margins without increasing the risk of local failure (Granowetter et al. 2009). Current COG recommendations are as follows (Fig. 2.3). The pre-chemotherapy gross-tumor volume (GTV) includes all T1-gadolinium enhancing tumor, all T2 signal abnormality, and all bone abnormalities. Pre-chemotherapy GTV is expanded by 1.0 cm to create pre-chemotherapy clinical target volume (CTV). Pre-chemotherapy GTV and CTV can be modified for pushing, non-infiltrative, borders. Examples include para-spinal tumors pushing into the abdominal cavity or lungs after induction chemotherapy. Volumes in such scenarios can be restricted to fascial planes if there is no evidence of infiltration. Post-chemotherapy GTV includes residual soft-tissue mass after neoadjuvant chemotherapy based on MRI and all pre-chemotherapy bone abnormalities. Post-chemotherapy CTV is a 1.0 cm expansion on post-chemotherapy GTV, modified for anatomic pushing borders and limited to fascial planes if there is no infiltration. Internal target volumes (ITVs) are needed for volumes that demonstrate significant movement with respiration, such as thoracic and abdominal tumors. Depending on tumor location and available daily image-guidance, a 0.5–1.0 cm expansion is done to create planning target volumes (PTVs). Either three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT), or proton therapy may be utilized. IMRT and proton radiotherapy may be beneficial

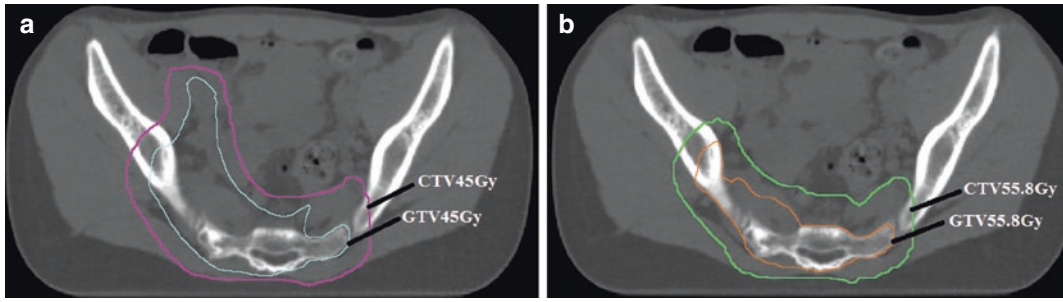

Fig. 2.3 (**a**) Depiction of the GTV45 Gy and CTV45 Gy volumes for a pelvis Ewing sarcoma. (**b**) Depiction of the GTV55.8 Gy and CTV55.8 Gy volumes for a pelvis Ewing sarcoma

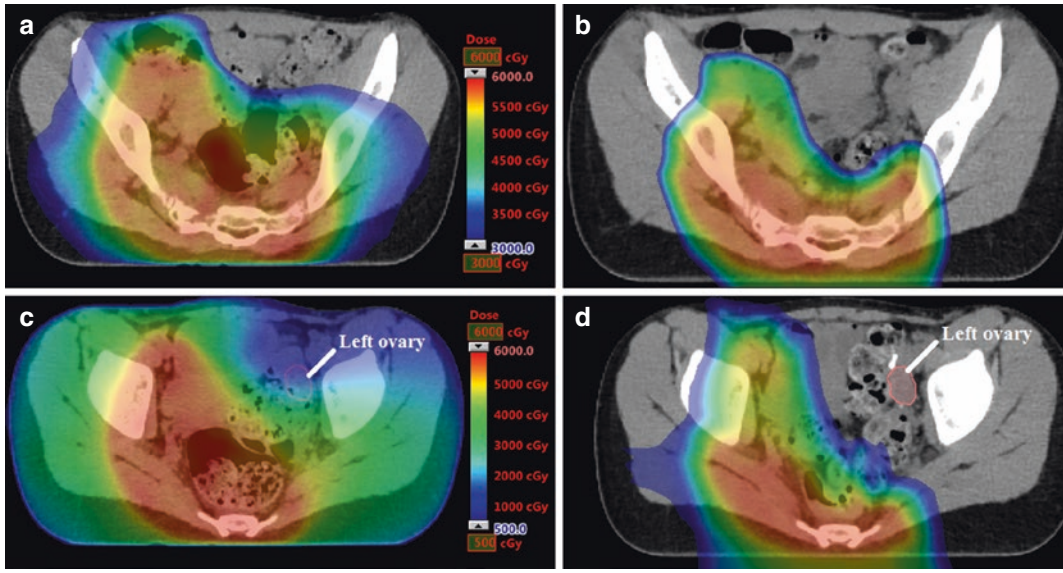

Fig. 2.4 (**a**) Dose distribution resulting from IMRT planning of the pelvis Ewing sarcoma depicted in Fig. 2.3. (**b**) Dose distribution resulting from intensity modulated proton radiotherapy (IMPT) planning of the pelvis Ewing sarcoma depicted in Fig. 2.3. Compared to the IMRT plan, the IMPT plan results in lower integral doses to the surrounding normal tissue. (**c**) IMRT dose distribution at the level of the left ovary. The left ovary was transposed near the left inguinal canal to minimize radiation dose. The right ovary was engrossed with tumor and therefore treated to prescription dose. The mean and maximum doses to the left ovary are 6.01 Gy and 19.73 Gy, respectively. (**d**) IMPT dose distribution at the level of the left ovary. The mean and maximum doses to the left ovary are 0.13 Gy and 1.12 Gy, respectively

in cases where minimization of dose to adjacent critical structures is necessary (Fig. 2.4).

It is important to be cognizant of a few other planning facets. Surgically contaminated areas, scars, and drainage sites must be included in the treatment volumes. Circumferential radiation of extremities should be avoided to reduce the risk of lymphedema. Growth plates for children should either be fully included with a uniform dose up to 30 Gy, or not included at all. Dose gradients through the epiphysis result in asymmetric growth and subsequent functional deficits. Similarly, vertebral bodies should either be fully included or spared. For females receiving pelvic radiation, at least one uninvolved ovary should be spared of radiation dose. The Childhood Cancer Survivor Study found abdominopelvic radiation was a risk factor for developing acute ovarian

failure (AOF) (Green et al. 2009). The percent of survivors with AOF increased with increasing radiation dose to the ovaries (Green et al. 2009). Ovarian transposition and/or proton therapy can be utilized to significantly reduce ovary radiation dose (Fig. 2.4). A meta-analysis found ovarian function was preserved in 65% of gynecologic cancer patients treated with external beam radiation and surgery (with or without brachytherapy) after ovarian transposition (Gubbala et al. 2014).

2.1.9.3 Radiation of Metastases

Whole lung irradiation for lung metastases is done after completion of adjuvant chemotherapy due to risk of pneumonitis with doxorubicin and actinomycin D. AEWS1221 recommends 12 Gy for children ≤6 years and 15 Gy for children >6 years, in 1.5-Gy daily fractions. Opposing beams should include both lungs down to the diaphragmatic recesses. Breath-hold treatment (treatment in deep inspiration) should be used if possible. This reduces the volume of irradiated liver, stomach, and upper kidneys. Cardiac sparing IMRT and four-dimensional treatment planning can reduce cardiac toxicity associated with whole lung irradiation (Kalapurakal et al. 2013).

Definitive radiation (same dose, fractionation, and volumes as the primary tumor) can be administered to all bone metastases simultaneously with irradiation of the primary tumor if there are an acceptable number. Irradiation of more than 50% of bone marrow volume can result in significant myelosuppression and consequently hinder administration of chemotherapy. In patients with multiple bone metastases that preclude irradiation of all sites at the time of local therapy, radiotherapy is administered at the end of chemotherapy. In some circumstances, radiotherapy may be administered to bulky regions, lesions showing slow response to initial therapy (PET residual at the time of local therapy), or lesions with residual PET avidity at the end of therapy. AEWS1221 includes an objective focused on evaluating the role of SBRT in the definitive treatment of bone metastases. All bone metastases <5.0 cm are treated to 35–40 Gy in five daily fractions.

Involved lymph nodes must be included in radiation volumes. Per AEWS1221, the pre-chemotherapy CTV includes regional lymph node chains for clinically or pathologically involved lymph nodes. The post-chemotherapy lymph node GTV is only defined for unresected lymph nodes with a partial response to chemotherapy. The post-chemotherapy CTV is a 1.0 cm expansion on the post-chemotherapy GTV for lymph nodes with a partial response to chemotherapy, or the original involved nodal region for unresected lymph nodes with a complete response to chemotherapy. In the absence of nodal involvement, the draining regional lymph nodes are not electively treated.

2.1.10 Relapsed Disease

The prognosis of patients with relapsed Ewing sarcoma is extremely poor, with a reported 5-year survival rate of less than 15% (Bacci et al. 2003; Leavey et al. 2008; Stahl et al. 2011). The COG analysis of 262 patients and the CESS 81, CESS 86, and EICESS 92 analysis of 714 patients with relapsed Ewing sarcoma found inferior survival rates for those who relapsed within 2 years of initial diagnosis (Leavey et al. 2008, Stahl et al. 2011). Patients with strictly localized relapse appear to have improved outcomes (Bacci et al. 2003; Leavey et al. 2008; Mctiernan et al. 2006; Stahl et al. 2011). Data for outcomes by recurrence site is conflicting. Some analyses correlate a survival advantage for pulmonary recurrence over extra-pulmonary recurrence, while others document no advantage (Bacci et al. 2003, Leavey et al. 2008, Mctiernan et al. 2006, Stahl et al. 2011).

There is no standard second-line treatment. Various agents have been investigated in phase II studies and retrospective reviews, including the Pediatric Oncology Group Phase II study investigating the efficacy of cyclophosphamide and topotecan (Casey et al. 2009; Ferrari et al. 2009; Fox et al. 2012; Hunold et al. 2006; Saylors et al. 2001). rEECur is a randomized phase II/III trial

from the Euro Ewing Consortium investigating the efficacy and toxicity of ifosfamide, irinotecan with temozolomide, topotecan with cyclophosphamide, and gemcitabine with docetaxel to determine optimal second-line treatment. Surgery and/or radiation can be utilized in a more definitive manner if there are a limited number of lesions, and/or palliatively for symptomatic sites.

2.1.11 Follow-Up

Follow-up should occur as appropriate for individual patient care, institutional standards, and expected toxicities of administered therapy. In general, patients undergo a history, physical exam, and basic laboratory evaluation every 3 months for the first year, every 4 months for years 2 and 3, every 6 months for years 4 and 5, and annually afterwards. Plain films are obtained at each visit for the first 2 years, and every 6 months for years 3–5. Surveillance MRI or CT of the primary site should be obtained every 3 months for the first year, every 6 months for years 2–5, and annually thereafter. Chest imaging should be obtained every 3 months for the first 2 years, every 6 months for years 3–5, and annually afterwards. Chest X-ray can alternate with CT chest for surveillance to minimize radiation exposure. However, CT chest must be obtained in cases of previous abnormalities, an abnormal chest X-ray, or symptoms. FDG PET is obtained in cases of other abnormal imaging and/or symptoms. Patients should be followed with echocardiograms based on age at the time of treatment, total dose of anthracycline received, and if chest radiation was administered.

2.1.12 Treatment-Related Late Effects

With an increasing number of long-term survivors, knowledge of treatment-related late effects is essential for determining the best local control modality and to properly educate patients. Ginsberg and colleagues evaluated the health status of 403 long-term survivors participating in the Childhood Cancer Survivor study (Ginsberg et al. 2010). They reported survivors had an increased risk of severe, life-threatening, or disabling chronic health conditions compared with sibling control subjects (Ginsberg et al. 2010). A long-term functional and quality of life outcomes analysis from the Mayo Clinic found older patients, females, and patients with pelvic primary tumors to be at greatest risk for long-term decrements (Stish et al. 2015).

Chemotherapy-related toxicities include cardiomyopathy, neuropathy, bowel toxicity, renal insufficiency, and infertility. Surgical complications depend on the resection site and extent, but can include limb-length discrepancies, weakness, fibrosis, decreased range of motion, pain, lymphedema, pathologic fracture, and prosthesis infection. The most common complication of radiotherapy is abnormal growth and development of irradiated tissue. Radiation can cause premature closure of active epiphyses, emphasizing the importance of uniformly radiating or sparing growth plates within the radiation field in children. Fractures, fibrosis, weakness, cosmetic skin changes, lymphedema, necrosis, pulmonary toxicity, and genitourinary dysfunction are also seen.

The most concerning treatment-related complication is secondary malignancy. Sarcomas are the most common radiation-induced second tumor and leukemias are the most common chemotherapy-induced second tumor. The risk of secondary neoplasia is higher with doses >60 Gy (Kuttesch et al. 1996). The incidence of secondary malignancy is variable in the literature due to varying follow-up periods and calculation methods. The secondary malignancy rate among 674 patients enrolled in the CESS 81 and CESS 86 studies was 4.7% at 15 years (Dunst et al. 1998). The 20 year incidence of second malignant relapse in 543 patients from the Italian sarcoma group was 4.7% (Longhi et al. 2012). Ginsberg and colleagues reported a 9.0% cumulative incidence of secondary malignant neoplasms 25 years after diagnosis (Ginsberg et al. 2010). It is presumed the risk of radiation-induced secondary malignancy is lower in the modern era due to lower radiation doses, more conformal treatment volumes (as opposed to irradiation of the whole bone), and more conformal planning techniques (IMRT, protons).

2.1.13 Conclusions

Outcomes for localized Ewing sarcoma have improved significantly due to advances in multimodal therapy. Future challenges include maintaining/improving upon these outcomes while minimizing treatment-associated toxicity. Risk-adapted treatment based on initial tumor characteristics and pathologic response may assist with this endeavor. Newer radiation techniques, including use of smaller margins and use of IMRT or protons, may also be beneficial. Outcomes for metastatic and relapsed Ewing sarcoma are dismal. This indicates a pressing need for new, effective systemic therapy agents. Continued investigations into the biology of Ewing sarcoma will be beneficial. Finally, increased collaboration among clinical groups is vital for continued advancement in outcomes.

2.2 Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is an extremely rare sarcoma. The true incidence of the cancer is unknown. As such, there is minimal information on clinical presentation, treatment, and outcomes for patients with this disease.

Almost all DSRCT cases occur in young adult Caucasian males (~90%, median age: 19 years) (Hayes-Jordan and Anderson 2011). Patients typically present with an abdominopelvic mass and diffuse peritoneal seeding. Metastatic sites include the liver, lung, spleen, lymph nodes, and bones. Extra-abdominal primaries can occur and include the chest wall, pleura, extremities, genitals, and head and neck region (Biswas et al. 2005). The correct diagnosis of DSRCT can be challenging due to its rare nature. The chromosomal translocation involving the fusion of the Wilms' tumor gene product WT1 and the Ewing sarcoma gene product EWS, t(11;22)(p13q;q12), is unique to DSRCT and confirms diagnosis (Gerald et al. 1998; Ladanyi and Gerald 1994). There is no formal staging system. Workup and pre-treatment evaluations are similar to Ewing sarcoma.

Outcomes for DSRCT are extremely poor, with 5-year OS rates less than 20% (Bent et al. 2016; Kushner et al. 1996; La et al. 2006). Again, due to the rare nature of the disease, there are no randomized trials evaluating therapies. Patients are often treated with induction chemotherapy followed by cytoreductive surgery and consolidative therapy for microscopic residual disease. Treatment for extra-abdominal DSRCT also involves chemotherapy followed by surgery with or without radiation (Biswas et al. 2005).

Induction chemotherapy agents for DSRCT mirror Ewing sarcoma chemotherapy regimens. The routinely used P6 regimen consists of VDC alternating with IE for seven cycles (Kushner et al. 1996). Cytoreductive surgery involves an exploratory laparotomy and complete resection of all visible tumor to a total remaining size of less than 1.0 cm. Studies have demonstrated extensive surgical debulking correlates with improved survival (Schwarz et al. 1998; La et al. 2006). Consolidative therapies include hyperthermic intraperitoneal chemoperfusion (HIPEC) and whole abdominopelvic radiation therapy (WAP-RT).

HIPEC involves heated (40–41 °C), high-dose (100 mg/m^2) cisplatin infused into the peritoneal space for 90 min (Hayes-Jordan et al. 2014). The theory for HIPEC is that heat combined with chemotherapy is cytotoxic to residual microscopic cells. Due to the peritoneal barrier, higher doses of chemotherapy can be used without concern for systemic toxicity. A single-institution retrospective review of patients treated with cytoreductive surgery and HIPEC concluded complete cytoreduction before HIPEC is vital for optimal outcomes (Hayes-Jordan et al. 2014).

The dose and fractionation for WAP-RT is 30 Gy in 1.5 Gy-daily fractions (Goodman et al. 2002; Osborne et al. 2016; Pinnix et al. 2012). If gross residual disease is present, a boost of 6–10 Gy is administered (Fig. 2.5) (Pinnix et al. 2012). The CTV consists of the entire peritoneal and involved retroperitoneal areas, excluding the uninvolved kidneys and liver (Pinnix et al. 2012). An ITV should be created due to diaphragm motion. The PTV is a 0.5–1.0 cm expansion of CTV depending on available daily image guidance. Dose to the liver and kidneys needs to be limited.

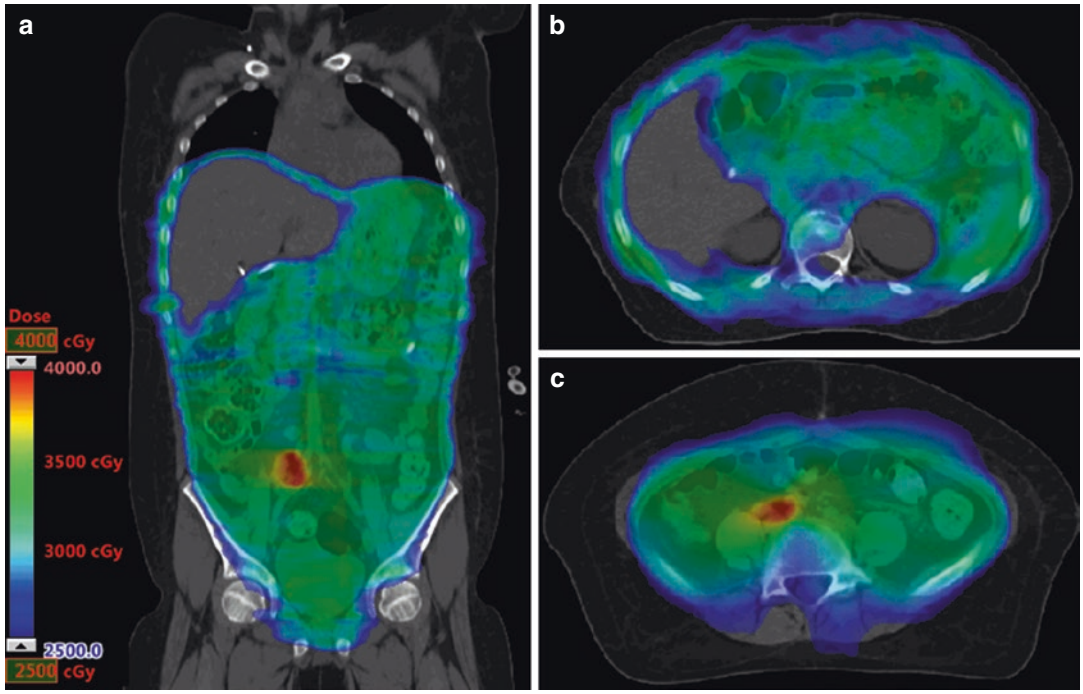

Fig. 2.5 (**a**) Dose distribution resulting from IMRT planning of an intra-abdominal disseminated DSRCT. An area of gross disease was boosted to 3740 cGy. (**b**) IMRT dose distribution at the level of the kidneys and liver. (**c**) IMRT dose distribution at the level of the boost volume

The mean liver dose has been limited to <25 Gy, and to 20 Gy for <33% of each kidney in the literature (Pinnix et al. 2012). Pinnix and colleagues found WAP-RT utilizing IMRT (WAP-IMRT) was well tolerated and resulted in 25% lower dose to the pelvic bone and vertebral bodies compared to conventional radiation plans (Pinnix et al. 2012).

Recently, Osborne and colleagues reported on their experience of 32 patients treated with induction chemotherapy, surgical cytoreduction, HIPEC, and WAP-IMRT. The median OS was 60 months, median disease free survival was 10 months, and median time to intra-abdominal progression was 11.7 months. The liver was the most common site of failure, likely a consequence of the fact that cytoreductive surgery and HIPEC do not address hepatic disease. Eighty-four percent of patients experienced grade 3 or higher toxicities in the cohort. Two patients experienced grade 4 or higher late gastrointestinal toxicities, including small bowel obstruction and gastrointestinal fibrosis.

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Pediatric Rhabdomyosarcoma

3

Stephanie Terezakis and Matthew Ladra

3.1 Introduction

Pediatric rhabdomyosarcoma (RMS) composes just under one half of all pediatric soft tissue sarcomas in the United States (US) (Li et al. 2008). It is a highly malignant neoplasm, originating from mesenchymal cells destined for striated muscle differentiation. It can arise anywhere in the body, including the head and neck (35%), genitourinary tract (24%), extremities (19%), and elsewhere (22%) (Pappo 1995). Pediatric RMS treatment represents a diverse and challenging paradigm, due to the differing prognoses based on site of origin and histology. Chemotherapy comprises the backbone of curative treatment, as RMS tends to disseminate early in its course, with surgery and/or radiotherapy used for local control of the primary site. Since the creation of the Intergroup Rhabdomyosarcoma Study Group (IRSG) in the early 1970s, rates of cure have steadily increased from 15 to 20% in the earliest studies to currently better than 80% for all non-metastatic patients (Crist et al. 1990, 2001; Maurer et al. 1993; Arndt et al. 2009; Raney et al. 2011).

3.2 Epidemiology

There are approximately 250 new cases of pediatric RMS each year within the US (Li et al. 2008). The peak incidence for RMS in children occurs between 3 and 5 years of age, with 70% of cases appearing before the age of 10. RMS affects males more frequently than females (1.4:1) and occurs more commonly in children of European heritage compared to African American or Asian populations (Arndt and Crist 1999). Most RMS cases are sporadic though genetic associations do exist. Children with Li-Fraumeni, Neurofibromatosis type 1, Beckwith–Wiedemann syndrome, Costello syndrome, and Noonan syndrome all experience a higher incidence of RMS (Birch et al. 1990).

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3.3 Histology

RMS histology can be divided into favorable (embryonal, botryoid, and spindle cell) and unfavorable (alveolar) subtypes. The most common histology is embryonal, composing 60–70% of all cases (Parham 2001). The embryonal form is composed of blastemal mesenchymal cells that differentiate into cross striated muscle cells and it is the predominant histology in the genitourinary tract and head and neck (Newton et al. 1995). Botryoid and spindle cell tumors represent roughly 10% of all RMS cases and are both considered variants of the embryonal histology. The botryoid pattern of RMS is defined by its location beneath a mucosal surface and tumors arise from mucosa-lined organs such as the vagina, bladder, biliary tree, nasopharynx and nasal cavity (Asmar et al. 1994). Grossly, botryoid tumors often present as an exophytic "grape-like" mass and are generally non-invasive, with a higher rate of cure. Spindle cell variants most commonly present as paratesticular tumors and have low cellularity consisting exclusively of spindle-shaped cells (Newton et al. 1995).

Alveolar histology comprises the remaining 20% of RMS cases. These tumors have round, often vacuolated, cells with scant cytoplasm most similar to the cells of fetal skeletal muscle. The most common sites for alveolar tumors include the trunk and extremities, perianal and perineal regions, and the head and neck (Pappo et al. 1995). Adolescents more frequently present with alveolar histology, though it is also seen in infants less than 1 year of age, where it carries a very poor prognosis. Alveolar tumors also present with a higher risk of lymph node involvement and are characterized by an early response to chemotherapy though they are at risk for rapid and disseminated progression after treatment (Minn et al. 2010; Rodeberg et al. 2011).

Two translocations involving the transcription factor *FOXO1* on chromosome 13 characterize alveolar genetics. The most common translocation, t(2;13)(p35;q14), involves the fusion of *PAX3* (a transcription regulator) to *FOXO1* and is present in about 60% of children with alveolar RMS. The second, t(1;13)(p36;q14), fuses the *PAX7* transcription regulator to *FOXO1* and is involved in about 20% of cases (Parham et al. 2007). The *PAX 3* translocation is often seen in younger children compared to those harboring the *PAX 7* translocation. The presence of these translocations portends a significantly worse prognosis than fusion negative alveolar tumors. In a review of 434 patients with available pathology from the Children's Oncology Group (COG) D9803 study, event-free survival (EFS) was 54% for tumors with the *PAX3-FOXO1* fusion and 65% for *PAX7-FOXO1,* compared with 90% for fusion negative alveolar patients and 77% for all embryonal patients (Skapek et al. 2013). For those alveolar patients without the *FOXO1* translocation (roughly 20%), the prognosis appears similar to embryonal tumors.

3.4 Classification

Current treatment algorithms for RMS divide patients into low, intermediate, and high-risk groups. The intensity, duration, and extent of multimodality therapy is determined by the risk grouping, which in turn is determined by the primary site, stage, clinical group, and histology.

3.4.1 Primary Site

The site of origin in pediatric RMS is predictive of outcome and is divided into favorable and unfavorable sites. Favorable sites include the orbit, head and neck (scalp, parotid, oropharynx, oral cavity, larynx) genitourinary tract (vagina, uterus, vulva, and paratestes but excluding bladder and prostate) and biliary tract. Unfavorable sites include bladder, prostate, perineal/perianal and retroperitoneum, trunk and extremity, and parameningeal tumors (nasopharynx, nasal cavity, paranasal sinuses, middle ear and mastoid, pterygopalantine fossa, and infratemporal fossa). If the extent of a primary tumor encompasses two sites with differing designations, such as those that involve the parameninges (unfavorable) and orbit (favorable), it is classified as "unfavorable", so as not to risk delivering inadequate treatment. Outcome data from IRS II and III has confirmed that primary site is a strong indicator for survival (Maurer et al. 1993; Crist et al. 1995).

The propensity for differing histologic RMS subtypes to arise in certain locations plays a role in these outcomes, but other factors such as the variation in surgical accessibility, access to lymphatics, and rapidity of diagnosis between different primary sites also likely affect prognosis.

3.4.2 Stage

Staging for pediatric RMS employs the tumor, node, and metastasis (TNM) system but also takes into consideration the primary site (Table 3.1). T1 tumors are confined to the anatomic site of origin and are T1a if they are ≤5 cm and T1b if they are >5 cm. T2 tumors have extension into or fixation to the surrounding tissue and follow the same a/b size designation. Tumors are N0 without nodal involvement and N1 with regional nodal involvement. Stage 1 tumors are favorable sites and can have any T or N designation. Stage 2 tumors are unfavorable sites but must be T1a or T2a and with negative (N0) lymph nodes. Stage 3 tumors are in unfavorable sites and are either T1b/T2b or N1 or both. Stage 4 tumors are any site with hematogenous metastasis.

3.4.3 Clinical Group

Clinical group represents the post-surgical extent of disease at the time of chemotherapy initiation (Table 3.2). Group I designates localized disease that is completely resected. Group II patients have grossly resected disease with microscopic residual and/or nodal disease that is grossly resected. Group III is classified as gross residual disease after an incomplete resection or after biopsy alone, and group IV consists of those with metastatic disease at diagnosis. It should be emphasized that the clinical group designation pertains to the disease status *before* any chemotherapy has been given, and therefore patients who have surgical resection after chemotherapy has begun are still classified based on their initial pre-chemotherapy status. For example, if a child with an extremity tumor that is initially biopsied and classified as group III undergoes a delayed primary resection after 12 weeks of chemotherapy with removal of all gross and microscopic disease, the child remains group III and would be treated with the appropriate intensity of chemotherapy based on the group III status.

Table 3.1 TNM staging for rhabdomyosarcoma

Stage	Sites	Tumor invasiveness	Tumor size	Lymph node status	Metastasis
1	Favorable	T1 or T2	*a* or *b*	Any N	M0
2	Unfavorable	T1 or T2	*A*	N0	M0
3	Unfavorable	T1 or T2	*A*	N1	M0
		T1 or T2	*B*	Any N	M0
4	All	T1 or T2	*a* or *b*	Any N	M1

T1 tumors are confined to the anatomic site of origin. *T2* tumors have extension into or fixation to the surrounding tissue. Tumors are designated "*a*" if ≤5 cm and "*b*" if >5 cm. *N1* clinically involved nodes, *N0* not clinically involved, *NX* clinical status unknown, *M0* no metastasis, *M1* metastasis present

Table 3.2 Clinical groups for rhabdomyosarcoma

Group I	Localized disease that has been completely resected (a) Confined to muscle or organ of origin (b) Infiltration outside the muscle or organ of origin
Group II	Complete resection with: (a) Microscopic residual disease (b) Regional lymphatic spread that has been resected (c) Both
Group III	Gross residual disease: (a) After biopsy only (b) After major resection (greater than 50% resected)
Group IV	Distant metastatic disease present at Diagnosis

3.4.4 Other Prognostic Factors

A multitude of other factors have shown variable prognostic significance in outcome for pediatric RMS. Differences in primary location, age, and histologic frequency all complicate the picture, and while some factors seem universal to RMS, others appear specific to certain sub-populations. Data from IRS I-II data showed that female sex, increasing age, and alveolar histology portended a worse prognosis in some subgroups (Crist et al. 1990). As an example of the difficulty with such classifications, although younger age (<10 years) is typically associated with better outcomes, children with alveolar histology under 1 year of age have significantly worse outcomes than do older children, a finding that is not replicated in infants with embryonal histology (La Quaglia et al. 1994). Lymph node involvement also appears to lead to poorer outcomes, though a review of IRS-IV found that this may only be specific to alveolar histology, and embryonal patients with N1 disease had no worse outcomes than their N0 counterparts (Rodeberg et al. 2011). The frequency of lymph node involvement also varies by site, with a higher incidence seen in bladder/prostate, paratesticular, parameningeal, perineal, retroperitoneal, and extremity tumors and less commonly in tumors of the head and neck, trunk, and uterus/vagina.

Large tumor size has been repeatedly associated with decreasing survival and a recent analysis from D9803 found that local failure in the group III patients was 25% for tumors ≥5 cm and 10% for those <5 cm (Wolden et al. 2015). It is unclear whether the poorer outcomes associated with larger tumors is a result of a more aggressive tumor biology or whether it represents a delay in diagnosis and/or an increased likelihood of access to the lymphatics. A review of RMS patients from Stanford University showed that of all patients presenting with positive lymph nodes, 88% had primary tumors that were considered invasive, extending beyond the primary site (Pedrick et al. 1986). Early response to chemotherapy, which has been linked to improved outcomes in other tumor types, has had a conflicting correlation with survival in pediatric RMS. Two extensive analyses of recent COG trials found no improvement in survival in patients with a complete response (CR) or partial response (PR) after induction chemotherapy, whereas a correlation was seen in multiple German cooperative group soft tissue sarcoma trials (Koscielniak et al. 1992, 1999; Burke et al. 2007; Rosenberg et al. 2014; Dantonello et al. 2009). A recent examination of PET responses in pediatric and adult RMS from Memorial Sloan-Kettering Cancer Center found that decreased PET uptake after induction chemotherapy did appear to predict for local control, indicating that chemotherapeutic response may indeed play a role (Casey et al. 2014b; Dharmarajan et al. 2012). More recently, two smaller studies from the US and Germany found that for embryonal parameningeal tumors, response to chemotherapy was linked to improved local control and EFS, suggesting that response may only be prognostic for specific sites and/or histologies (Dantonello et al. 2014; Ladra et al. 2015).

3.4.5 Risk Group

At present, the COG studies utilize the primary site, stage, and group designations discussed above as well as histology to divide patients into low, intermediate, and high risk groups (Table 3.3). Risk group is highly predictive of

Table 3.3 Current risk groupings for pediatric rhabdomyosarcoma

Risk group	Histology	Site	Stage	Group
Low	Embryonal	Favorable	I	I-III
		Unfavorable	II-III	I-II
Intermediate	Embryonal	Unfavorable	II-III	III
	Alveolar	Any	I-III	I-III
High	Any	Any	Any	IV

outcome and overall survival (OS) ranges from 98% for low risk patients, 78% for intermediate risk patients, and 30% for high risk patients (Arndt et al. 2009; Walterhouse et al. 2014; Oberlin et al. 2008). For the current iteration of COG studies, the risk group designations are as follows:

Low risk: Low-risk RMS is defined as localized embryonal RMS arising in favorable sites (Stage I) with any clinical group (Group I-III) or embryonal RMS arising in unfavorable sites with either completely resected disease (Group I) or microscopic residual disease (Group II).

Intermediate risk: Intermediate-risk RMS is defined as non-metastatic (Group I-III) alveolar RMS arising at any site (Stage I-III) or incompletely excised (Group III) embryonal RMS arising in an unfavorable site (Stage II, III).

High risk: Patients with metastatic RMS (Group IV, Stage IV).

As a greater understanding of the role tumor genetics play in the survival of children with RMS, it is very likely that these risk groupings will continue to change and evolve.

3.5 General Principles of Therapy

All patients typically receive VAC or VAI (vincristine, dactinomycin, and cyclophosphamide or ifosfamide) based chemotherapy. Previous attempts to omit chemotherapy have been almost uniformly unsuccessful, subjecting patients to higher rates of local failure and/or undue surgical morbidity and radiation related toxicity. The decision for surgical resection as primary local control depends on the primary site and extent of disease at presentation. Radiation is given essentially to all patients except those with low risk disease who undergo a complete resection with negative margins. Low risk patients with a gross total resection (GTR) and microscopically positive margins receive 36 Gy, those with positive nodes 41.4 Gy, and those with gross residual disease 50.4 Gy, except in the case of orbital primaries where the dose (at present) is 45 Gy. Intermediate risk patients, those with alveolar histology, or those with gross disease at the start of chemotherapy will receive radiation regardless of surgical margin status (if a delayed primary resection is done). Patients with high-risk (metastatic) disease are treated primarily with chemotherapy, but radiation and surgery can play a role in local control of the primary and metastatic disease depending on location, symptoms, and response to systemic therapy. Because significant variation in the management of pediatric RMS exists between differing primary sites, it is easiest to address the sites separately and we will discuss each of them in more depth in the subsequent section.

3.6 Treatment and Outcomes by RMS Site

3.6.1 Parameningeal Tumors

Radiation therapy plays an integral role in the treatment of parameningeal rhabdomyosarcoma (PM RMS) due to the fact that these tumors are typically infiltrative and seldom surgically resectable. Parameningeal tumors make up about 15% of pediatric RMS and roughly 40% of head and neck sites (Crist et al. 1995, 2001; Merks et al. 2014). Tumors arising in the parameninges are most often embryonal (70%) and tend to invade into the surrounding tissues with more than 30% presenting with intracranial extension (Merks et al. 2014). Lymph node involvement ranges from 15 to 20% (Merks et al. 2014; Rodeberg et al. 2011). Within PM RMS, the most common sites of origin are the nasal cavity and nasopharynx followed by the infratemporal fossa, pterygopalantine fossa, and mastoid areas. Prognosis varies with site, and tumors arising in the infratemporal fossa, pterygopalantine fossa, and paranasal sinuses carry a poorer prognosis (Merks et al. 2014) (Fig. 3.1).

Since parameningeal tumors are classified as an unfavorable RMS site and are nearly always group III, treatment is based on the intermediate risk COG protocols with RT given for local control to a dose of 50.4 Gy. A field reduction after 36 Gy to gross disease can be applied for tumors

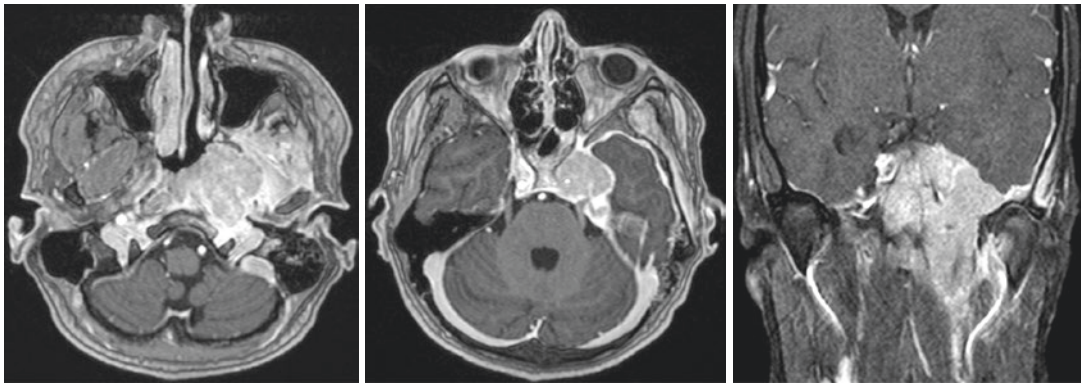

Fig. 3.1 A 16 year old male with embryonal parameningeal rhabdomyosarcoma of the nasopharynx and intracranial extension

with significant tumor response after induction chemotherapy, but the initial volume should include the entire pre-chemotherapy tumor volume as well as areas of concern for microscopic invasion and a clinical target volume (CTV) margin (typically 0.5–1 cm). Gross nodes are treated to full dose (50.4 Gy), regardless of response to chemotherapy, while completely resected nodal disease and the surrounding nodal region receives 41.4 Gy. Prophylactic nodal radiation is typically not used in PM RMS and treatment only includes the involved nodal region(s). The timing of radiation can vary for PM RMS, but in the most recent COG RMS protocol, ARST 0531, it began at week 4. A review of RT timing for PM RMS was recently carried out by Spalding et al., which examined outcomes in relation to RT timing differences from the COG IRS-IV and D9803 RMS studies. In IRS-IV, PM RMS patients received RT at week 6–9 and week 0 for intracranial extension or cranial nerve/cranial base involvement, and in D9803, RT was given at week 12 for all patients except those with intracranial extension (week 0). This study found that local failure for PM RMS was 19% in both trials and that the timing of RT did not appear to affect outcomes for those with CNS extension (Spalding et al. 2013). Based on these findings RT can be given at week 12 to allow for maximal cytoreduction by chemotherapy in all PM RMS patients.

The 5-year failure free survival (FFS) for pediatric PM RMS is approximately 67% but can drop as low as 52% in patients with an unfavorable parameningeal site and/or intracranial extension (Merks et al. 2014; Spalding et al. 2013; Wolden et al. 2005). Local control for PM RMS ranges from 80 to 90%, and again varies with tumor size, histology, and location (Wolden et al. 2005; Arndt et al. 2009; Merks et al. 2014; Ladra et al. 2014a). Still, local failure remains the most common site of failure (68% local, 24% metastatic, and 8% combined) and salvage for these PM tumors after relapse is dismal (Merks et al. 2014). Therefore, great interest lies in improving upfront therapy, and since the best chemotherapeutic drugs are already being given, dose escalation with RT is an attractive option. Increasing tumor size (>5 cm) has been shown to correlate with poorer outcomes in PM RMS and, therefore, dose escalation is being considered in the cooperative group setting. As more information is gathered regarding the biology of PM RMS and more targeted molecular therapies come through the pipeline, the current treatment paradigms will likely continue to change.

3.6.2 Orbit

Tumors arising in the orbit represent 10% of the pediatric RMS cohort and radiation plays a critical role in treatment (Walterhouse et al. 2014; Crist et al. 1990, 2001). Orbital primaries are most often embryonal in histology (80–90%) and

meningeal invasion and/or lymph node involvement are rare, though can be seen in instances where intracranial extension occurs via the superior orbital fissure (Wharam et al. 1987; Walterhouse et al. 2014). Analysis from the early IRS studies found that prognosis varied sharply with histology and the 5-year OS for orbital tumors was 94% with embryonal histology and 74% with alveolar histology (Kodet et al. 1997). The orbit is considered a favorable site and although 60–70% are group III and receive biopsy only, they are treated per the low risk COG protocols if embryonal in histology. As with other sites, orbital tumors with alveolar histology are treated as intermediate risk.

Overall, outcomes for orbital RMS are excellent and 3-year OS from the recently closed COG ARST 0331 was 97% (Walterhouse et al. 2014). Local failure for group III orbital patients was 11.5%. Unlike the parameningeal tumors, tumors of the orbit can often be salvaged (although with great morbidity) after local relapse, as evidenced by the significant difference seen in local failure (LF) and OS rates discussed above. The opportunity for salvage combined with the favorable control rates and concern for late RT-related toxicity led to the omission of RT and use of chemotherapy alone for orbital patients in the European (SIOP) trials (Rousseau et al. 1994). In a large review of these trials and the US counterparts, Oberlin et al. found that although OS was no different with the omission of RT, local control was substantially worse (53% compared with 82% for those receiving RT) (Oberlin et al. 2001). Further, surgical salvage typically consisted of orbital exenteration, which has a profound impact on the quality of life of a child. Therefore, radiation remains a mainstay in the treatment of orbital RMS.

The COG has made great efforts to reduce toxicity in these children though, and has modified the radiation and cyclophosphamide doses with variable success. Local control for orbital tumors in IRS III was 84% with VA chemotherapy and 45–50.4 Gy of radiation (Crist et al. 1995). In an effort to raise control rates, cyclophosphamide was added to systemic treatment and radiation doses were escalated to 50.4 or 59.4 Gy delivered in a hyperfractionated approach, in IRS-IV, leading to an improved local control (LC) rate of 96% (Crist et al. 2001). Subsequently, cyclophosphamide was omitted for orbital tumors in the COG D9602 trial to reduce the male infertility risk and the radiation dose was brought back down to 45 Gy. Unfortunately, local control dropped to 86%, likely highlighting the importance of cyclophosphamide in the treatment of RMS (Raney et al. 2011). The recently closed COG ARST 0331 kept the radiation dose at 45 Gy, but reintroduced cyclophosphamide at a lower dose, leading to a 5-year local control of 89% (Meza 2013). Interestingly, subset analysis of ARST 0331 showed that local control for children with a CR after induction therapy was 100% compared with 81% for those with a PR or stable disease (SD) (Meza 2013). At present, the ideal radiation dose for orbital RMS is still unknown, but dose escalation above 45 Gy should be considered for patients with a poor response to chemotherapy and/or gross residual disease in the orbit.

Radiation volumes for orbit should be planned with careful consideration, due to the extreme sensitivity of the surrounding normal tissue. A 0.5–1 cm CTV is recommended, but this should be tailored to the pre-treatment extent of the tumor as well as the post-treatment change with regard to pushing borders and the re-expansion of the globe after surgery or chemotherapy response. If possible, the muscle of origin should be identified and tracked back to the insertion, as failures can occur in the posterior orbit. The entire orbit should not be covered if the pre-treatment tumor is small or localized. A dose reduction after 36 Gy can be used to help spare sensitive structures such as the lens, retina, and lacrimal gland if surgical resection or response to systemic therapy is present. In very young children, hypoplasia of the orbital bones is a concern as well. Proton therapy has shown to be useful in children with orbital RMS due to the sharp fall off exit dose and multiple studies have demonstrated

equivalent outcomes with reduced dose to the critical structures (Yock et al. 2005; Ladra et al. 2014a, b) (Fig. 3.2).

3.6.3 Other Head and Neck Sites

The remaining head and neck sites (oral cavity, larynx, oropharynx, parotid gland, and scalp) make up approximately 10% of RMS cases and typically come with favorable outcomes (Donaldson et al. 2001; Pappo et al. 2003). Subset analysis from IRS III and IV found that non-parameningeal head and neck patients had a 5-year FFS of 76% and a LF rate of 19% (Pappo et al. 2003). Embryonal histology comprises the majority of cases and certain sites such as the cheek and scalp are often of alveolar histology (Crist et al. 2001). As with the orbit, embryonal patients classified as stage I and II are treated with less intensive chemotherapy on the low risk protocols. Alveolar histology patients receive intermediate risk therapy. Surgical resection is advocated for superficial tumors of the scalp, parotid, and for some oral cavity and oropharynx patients, but invasive or deep-seated tumors are treated with radiation alone for local therapy. Nodal involvement ranges from 10 to 20%, with alveolar patients more commonly presenting with positive nodes (Rodeberg et al. 2011; Donaldson et al. 2001). Radiation doses are in accordance with the low and intermediate risk protocols. As with the parameningeal tumors, regional lymph nodes are not treated prophylactically.

3.6.4 Extremity

Tumors arising in the extremities make up approximately 20% of pediatric RMS. They can occur anywhere in the distal and proximal appendages, with roughly two-thirds appearing in the lower extremities (Neville et al. 2000a). Extremity RMS is considered an unfavorable site and prognosis is poor with a 3-year OS of 70%

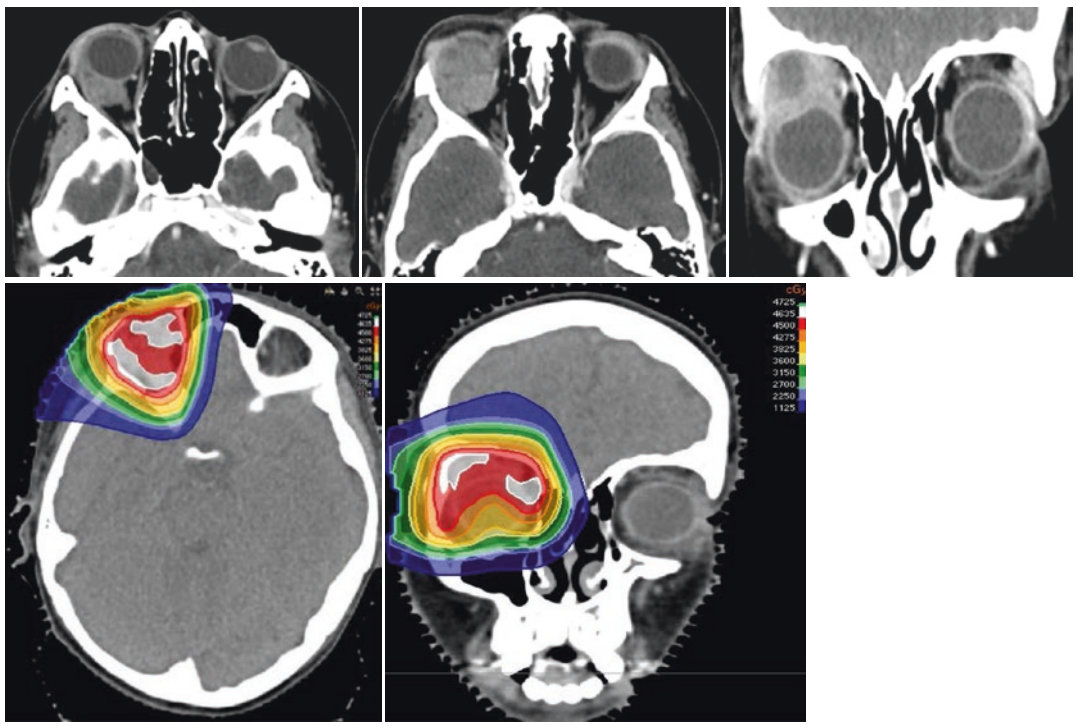

Fig. 3.2 A 9 year old male with embryonal orbital rhabdomyosarcoma treated with proton therapy

and FFS of 55% (Neville et al. 2000a; Arndt et al. 2009). These outcomes are attributable to the high frequency of alveolar histology (60–70%), lymph node involvement (30–40%), and distant metastatic disease (20–30%) seen at presentation (Neville et al. 2000a; Andrassy et al. 1996). Despite this poor prognosis, those with localized disease are extremely curable. Clinical group (which also is an indicator of initial disease extent) was highly predictive of outcome in IRS-IV with a 3-year FFS of 91% for Group I, 72% for Group II, 50% for Group III and, 23% for Group IV (Neville et al. 2000a).

Local control in extremity RMS combines surgical and radiation approaches to maintain form and function. Wide resection generates similar local control to amputation, with an obvious improvement in quality of life (Neville et al. 2000a, b). Amputation still may play a role in certain situations where limited excision and/or radiation therapy would lead to poor functional outcomes. Lymph node staging is recommended for all extremity tumors undergoing surgery, and there is increasing use of sentinel lymph node assessment and biopsy to reduce surgical morbidity as well as radiation treatment volumes. In patients with tumors that are of borderline resectability, delayed primary excision (DPE) can also be employed. After the initial surgical biopsy, resection is delayed until after induction chemotherapy to reduce the risk of amputation or functional deficits and potentially reducing the radiation dose in the case of alveolar tumors. Thirty-one patients on COG D9803 study underwent DPE with a local failure rate of 7% (Rodeberg et al. 2015). Ultimately, 28/31 patients (90%) still required radiation, though all received reduced doses of 36 Gy or 41.4 Gy rather than 50.4 Gy. At present, radiation is still a critical component of treatment in extremity RMS. Attempts to eliminate radiation in these patients have led to poor outcomes, and a pooled analysis of four international cooperative groups showed that local failure occurred more often in patients who did not receive initial irradiation when compared to those who were treated with RT (31% vs. 22%) (Oberlin et al. 2015).

Radiation in extremity RMS is delivered to all patients except those with completely resected embryonal tumors who do not have involved lymph nodes. Dose levels follow the same guidelines as with other RMS sites, giving 36 Gy to completely resected tumors with alveolar subtype, 41.4 Gy to resected nodal regions, and 50.4 Gy to gross disease. Larger CTV margins are used, with the current COG protocols recommending a 1.5 cm expansion. Care should be taken to remove CTV expansion into bone and joint spaces. Circumferential irradiation of the limb should be avoided when possible, and a strip of soft tissue along the extremity should be spared to reduce the risk lymphedema. Regional lymph nodes are not covered prophylactically and treated only when involved.

3.6.5 Trunk

RMS of the trunk is rare and makes up 4–7% of all cases (Crist et al. 1995, 2001; Maurer et al. 1993). The most common sites of origin are the chest wall and paraspinal area, with tumors also seen arising from the abdominal wall and diaphragm. Tumors of the retroperitoneum and perineal areas are given their own classification and tumors arising in the scapula and buttock are considered to be an extension of the extremity. Tumors of the trunk are classified as an unfavorable site. Due to the rarity of these tumors, small subset analyses of truncal RMS have shown significant variation in the rates of histologic subtypes, with some showing an embryonal predominance and others finding alveolar histology more frequently (Raney et al. 1982; Crist et al. 1982; Chui et al. 2005).

In the largest published series of 33 children from St. Jude Children's Research Hospital with truncal RMS, 5-year OS was 49% and EFS was 42%. These outcomes may be attributable to unfavorable biology, but may also stem from the difficulty of resection and delay in diagnosis in the thoracic region. Small tumor size (<5 cm), embryonal histology, and upfront GTR were all associated with significantly improved outcomes in the St. Jude

series (Chui et al. 2005). In contrast, COG reported on the impact of surgical excision for chest wall cases and found no difference in FFS or OS based on the degree of resection, though this may be attributable to amenability of radiation in this site (Hayes-Jordan et al. 2008). Paraspinal location appears to portend better survival and is more easily resectable, whereas RMS of the diaphragm is typically unresectable and often metastatic at presentation (Hayes-Jordan et al. 2008).

Current treatment guidelines advocate surgical resection when feasible, and delayed primary resection can be considered. RT is given to all patients except those with small, completely excised tumors with favorable histology and uninvolved lymph nodes. For radiation delivery, tumors that have displaced a significant amount of lung parenchyma (which has subsequently returned to normal anatomic position following surgery or chemotherapy) should have the (gross tumor volume (GTV) defined as the preoperative (prechemotherapy) tumor volume excluding the intrathoracic tumor that was removed by surgery or decreased in size by chemotherapy. All areas of pleural involvement need to be included in the GTV regardless of whether the radiation is delivered pre- or postoperatively.

3.6.6 Perineal and Perianal

Perineal and perianal tumors make up only 2% of RMS of pediatric RMS and are considered an unfavorable site (Blakely et al. 2003; Casey et al. 2014a; Fuchs et al. 2014). Prognosis is poor, due to the frequent presence of lymph node involvement and alveolar histology. Pooled analysis of 71 perineal and perianal tumors from the IRS I-IV studies found that the 5-year FFS and OS were 45% and 49%, respectively (Blakely et al. 2003). Alveolar histology was seen in 65% of children and 46% had N1 disease. When the extent of initial disease was accounted for, the IRS review found that the only significant predictor for survival was age, with children <10 years having a 5-year OS of 71% compared to 20% for older children (Blakely et al. 2003). No survival difference was seen between perineal and perianal sites. A more recent review of 14 perineal and perianal pediatric RMS cases treated at Memorial Sloan-Kettering Cancer Center between 1998 and 2012 found a 5-year EFS of 33% and OS of 39% (Casey et al. 2014a). In this series 78% had alveolar histology and 64% had N1 disease. The MSK series also found poorer survival in the older children, with a 5-year EFS of 13% for those ≥10 years compared to 75% for those <10 years. A higher incidence of alveolar

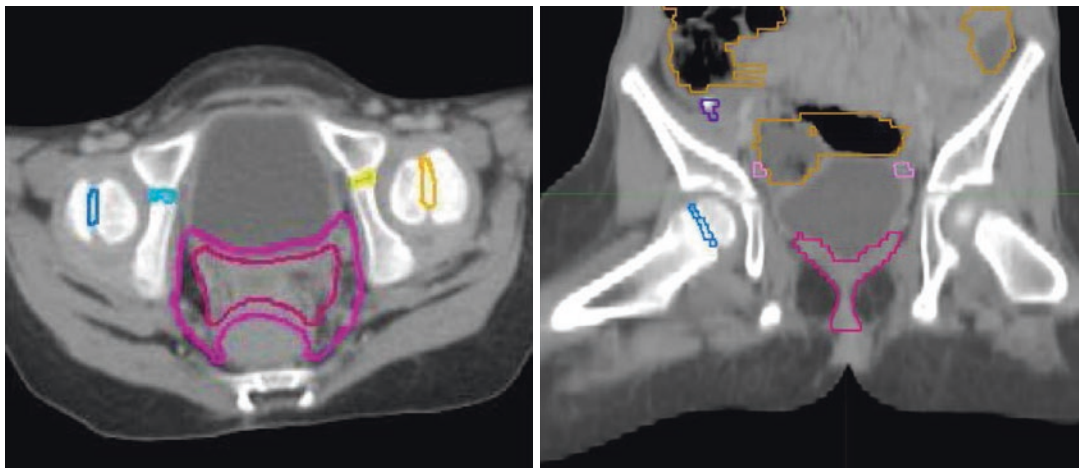

Fig. 3.3 Planning volumes for a perineal rhabdomyosarcoma. The pelvic growth plates (contoured in *blue* and *yellow*) should be avoided when possible to preserve normal growth

histology and N1 disease was found in the older cohort, likely leading to the decreased survival. Distant failure in this series predominated (52% of failures), followed by regional nodal failure (31%) and local failures (17%).

Unlike other RMS sites, the high incidence of regional node recurrence has led some practitioners to suggest prophylactic ilioinguinal lymph node irradiation in children ≥10 years or older (Casey et al. 2014a). For children <10 years, thorough nodal evaluation should be carried out to determine whether prophylactic regional irradiation should be delivered. Treatment volumes for a typical perineal primary site are shown in Fig. 3.3.

3.6.7 Retroperitoneum

Retroperitoneal tumors comprise 11% of RMS with a median age of presentation of approximately 6 years old (Crist et al. 1985). These patients tend to present with embryonal subtypes although alveolar histology can be seen as well. Despite the generally favorable histology, outcomes for this entity have been historically poor. In general, they are large tumors at presentation and expand into the abdominopelvic cavity causing compression of adjacent organs and/or invasion of neighboring critical structures. Lymph node involvement is relatively common with reported rates up to approximately 30% (Lawrence et al. 1997). Given the extensive RT volumes required for treatment, compliance on prior protocols to deliver intended RT was not optimum. For example, the recommended course of RT was not delivered in 39% of patients in IRS I and II due to the difficulties in respecting normal tissue tolerance (Crist et al. 1985). The frequency of protocol violations for this subsite was similar on IRS IV (Raney et al. 2004). As a result, clinical outcomes on prior IRS studies were worse for retroperitoneal sarcomas than for other sites. Five-year survival was approximately 40% and 60% on IRS II and IV, respectively (Blakely et al. 1999). Five-year FFS and OS was 70% and 75%, respectively on IRS IV for retroperitoneal and non-GU pelvic tumors (Raney et al. 2004). Most recently, Wolden et al. reported outcomes of retroperitoneal tumors on D9803 (Wolden et al. 2015). While not statistically significant, there was a trend for increased local failure for retroperitoneal tumors compared to other primary sites. However, patients with tumor size ≥5 cm were significantly more likely to fail than those with tumors <5 cm (25% vs. 10%, p = 0.0004). Nearly all retroperitoneal tumors (98%) had a tumor size of ≥5 cm and there was no difference in LF by site when restricting the analysis to tumors ≥5 cm only, suggesting that the frequency for larger tumors rather than inherent biology was the driver for poorer outcomes in this site (Wolden et al. 2015).

These patients are particularly challenging to attain LC given the proximity of dose-limiting structures. A debulking procedure is strongly considered prior to radiation (Raney et al. 2004). Induction chemotherapy can be utilized to reduce the burden of disease in an effort to facilitate surgical resection and/or reduce radiation volumes. Bowel and organs displaced by the tumor that have returned to normal anatomic position following surgery or chemotherapy should not be included in the delineation of the radiation pretreatment tumor volume, though they can be included in the CTV if concern for microscopic invasion exists. All areas of peritoneal or mesenteric involvement should be included in the GTV regardless of whether the radiation is delivered pre- or postoperatively. If whole abdominopelvic radiotherapy is required for malignant ascites or diffuse peritoneal involvement, 24 Gy at 150 cGy per fraction is recommended with appropriate blocking of the kidneys and liver.

3.6.8 Hepatobiliary Tree

Hepatobiliary RMS makes up less than 1% of all childhood RMS. It most commonly affects young children (median age 3 years) and 2% may have disease present at birth (Aggarwal et al. 2004). It appears to have a male predominance and is nearly always of embryonal botryoid histology,

with alveolar histology appearing quite infrequently (Zampieri et al. 2006). Hepatobiliary RMS considered a favorable site, and can arise in the gallbladder, cystic duct, common bile duct, hepatic ducts, and the ampulla of Vater. Regional lymph node involvement can be as high as 20% and thorough staging with both pre-operative imaging and nodal evaluation is critical.

Due to the rarity of hepatobiliary RMS, data regarding outcomes is scarce. Early in the IRS experience, treatment included aggressive surgery, which led to high rates of post-operative mortality and achieved negative margins in only a minority of cases. In light of the IRS findings, treatment recommendations now advocate for safe maximal debulking to be followed by chemotherapy and radiation, and the outcomes for these patients appear less grim. A review of 25 patients from IRS I-IV found a 5-year OS of 66%, and for those without metastatic disease in whom a GTR was achieved, the 5-year OS was 78% (Spunt et al. 2000).

3.6.9 Pelvic Sites

Pelvic sites are managed with multimodality therapy including chemotherapy and a combination of surgery and/or radiation in an effort to attain local control with organ preservation.

3.6.10 Bladder and Prostate Rhabdomyosarcoma

Bladder and prostate RMS are considered unfavorable sites and together comprise approximately 50% of GU rhabdomyosarcoma (Maurer et al. 1993). These tumors tend to occur in younger children and thus, the local control decision-making process can be particularly challenging. For fine tumor delineation, thin cut CT scan and/or MRI of the abdomen and pelvis provides detail that allows for the initial evaluation of the primary mass and retroperitoneal lymphatics as well as assessment of therapeutic response. PET/CT is also now acquired more routinely for staging of rhabdomyosarcoma and can similarly be used for staging and response (Klem et al. 2007). Endoscopic biopsy via cystoscopy may allow for diagnosis and open biopsy can be obtained if needed (Ferrer et al. 2006). The majority of tumors present with a favorable histology, typically embryonal, and are localized. However, approximately 20–30% of tumors present with regional lymph node metastases, most commonly in the hypogastric and external iliac nodes, although para-aortic involvement can be seen as well (Lawrence et al. 1997).

Cystoprostatectomy was used historically for local treatment, but resulted in high rates of permanent urinary and bowel dysfunction given that 100% of patients require urinary diversion with this procedure. Bladder preservation may be accomplished if conservative surgical approaches are used (Hays et al. 1990, 1995). For example, bladder dome tumors may be excised with partial cystectomy, which maintains bladder function without sacrificing long-term survival (Hays et al. 1990, 1995).

Radiation can be used as an alternative to avoid the need for urinary or bowel diversion. Depending on the extent of the radiotherapy fields, radiation may result in long-term reduction in bladder function. For example, 90 patients were treated on IRS IV and 74 patients received radiation. Of 88 evaluable patients, EFS was 77% but only 40% survived event-free and maintained normal bladder function (Arndt et al. 2004). IMRT or proton therapy will likely improve the preservation of bladder and rectal function and reduce the dose of pelvic bones (Cotter et al. 2011). Ultimately, the goal of multimodality therapy is to achieve cure while still preserving bladder function. Therefore, most treatment approaches today utilize upfront chemotherapy followed by delayed resection with or without radiation to enhance the likelihood of an organ sparing procedure.

At the start of the IRS I study, pelvic exenteration was used for aggressive tumor control. Efforts were made to reduce surgical morbidity by combining chemotherapy and radiation with a more limited surgery. Partial cystectomy resulted

in higher rates of disease control than did definitive chemoradiation, although the chemotherapy utilized was less intense than in future protocols (Hays et al. 1990; Voute et al. 1996). IRS-II went one step further by intensifying chemotherapy to facilitate limited surgery and deferring radiation when possible to avoid late effects. Unfortunately, the results were disappointing. Although 97% of patients were able to preserve their bladders initially, only 22% were alive at 3 years with a retained bladder function (Raney et al. 1990). In IRS III, tailored strategies to attain local control and simultaneous bladder preservation had better success. RT was routinely administered to all patients at week 6 after intensified induction chemotherapy unless complete tumor removal was possible with partial cystectomy only to maintain bladder function. This approach led to a 4-year bladder retention rate of 60% (Heyn et al. 1997).

Further strides were made in IRS IV with 74 of 90 patients with nonmetastatic bladder/prostate RMS receiving RT (Arndt et al. 2004). Second look surgeries were more common than on prior IRS studies with 53 patients undergoing at least one second look surgery. At a mean follow up of 6 years, bladder preservation rates improved to 70% with OS and FFS rates of 82% and 77%, respectively. Functional outcome was disappointing with only 40% of patients maintaining normal bladder function after formal evaluations were collected through patient questionnaires. Urodynamic studies are generally recommended for routine follow-up for these patients to monitor long-term bladder function.

Radiation design for bladder/prostate RMS must take into account distribution of dose to surrounding tissues including bowel, pelvic bones, femoral head growth plates, penile bulb and testes. Three-dimensional approaches including IMRT can provide benefit to reduce dose off of immediately adjacent critical structures. Proton therapy may prove beneficial particularly for sparing of growth plates and gonadal structures (Cotter et al. 2011). Margins should account for possible shifting of normal tissues in the pelvic region including bladder and prostate motion, rectal and bowel shifting.

3.6.11 Paratesticular

Paratesticular RMS accounts for approximately one third of genitourinary rhabdomyosarcomas (Raney et al. 1978, 1987) Patients present most frequently with a painless scrotal mass and are then evaluated by scrotal ultrasound. It is critical to avoid biopsy and violation of the scrotum. Thus, orchiectomy is recommended through an inguinal incision with high ligation of the spermatic cord at the level of the inguinal ring. Histologically, paratesticular RMS present overwhelmingly as embryonal type and frequently spread to the lymphatics. CT scan of the abdomen and pelvis is used to evaluate nodal involvement particularly first echelon spread to the para-aortic nodes (Raney et al. 1987).

The recommendations for lymph node management in these patients have evolved over time. In the United States, unilateral (trans-abdominal) nerve-sparing retroperitoneal lymph node dissection (RPLND) is routinely incorporated in paratesticular RMS staging. While ipsilateral RPLND was required for all patients on IRS III, CT scan of the abdomen and pelvis was explored to evaluate lymph nodes in place of surgery (Wiener et al. 1994). Use of CT scan resulted in an increase in the number of patients with group I disease (81% on IRS IV compared to 68% on IRS III) due to the failure of CT to detect lymph node involvement. Subsequently, the 3-year EFS decreased to 86% on IRS IV when CT was used for staging compared to a 3-year EFS of 92% on IRS III when ipsilateral RPLND was utilized (Wiener et al. 2001). Only patients with positively identified lymph nodes received RT and intensified chemotherapy. Boys aged 10 years or older had a higher risk for RPLN relapse than those younger than 10 years of age.

Improved outcomes with ipsilateral RPLND, likely due to increased identification of group II disease, has led to the current recommendation for ipsilateral RPLND for patients $\geq$10 years old (Wiener et al. 2001). Boys <10 years old are referred for RPLND if they have radiographically positive nodes on computed tomography.

After RPLND, patients with positive lymph nodes should be referred for postoperative radiation delivered to 41.4 Gy to the para-aortic chain. Gross nodal disease should be boosted to 50.4 Gy. Ipsilateral pelvic lymph nodes may be included although it is not clear at this time that treatment of the pelvic nodes is required in cases where initial involvement is not seen. In patients with multiple sites of nodal involvement, comprehensive nodal coverage may be appropriate (Fig. 3.4). Excellent EFS of 93% and OS of 99% were achieved in the most recent low risk COG study ARST0331 with an approach that also included a lower cyclophosphamide dose for patients to enhance fertility preservation (Walterhouse et al. 2014).

Orchiectomy is the recommended surgical approach to remove the primary tumor in these patients. The patient is considered to have group II disease when a trans-scrotal biopsy is performed rather than an inguinal approach. In this case, hemiscrotectomy can be performed or radiation with resection of the violated scrotal tissue (Breneman 1997). For testicular preservation, the remaining testicle can be transposed laterally into the thigh prior to radiation and then re-implanted into the scrotum at the end of therapy.

3.6.12 Vagina and Vulva

RMS of the vagina and vulva comprise 3% of pediatric RMS, the majority of which occur in the vagina (Andrassy et al. 1999). Vaginal and vulvar RMS differ in their presentation, with vaginal RMS presenting in younger children with a mean age of 2 years old and vulvar tumors presenting at a mean age of 8 years old (Hays et al. 1981). Vaginal tumors are nearly always embryonal tumors, most commonly botryoid subtype. Vulvar tumors have a more diverse histologic presentation and may present with alveolar subtype which conversely is very uncommon in vaginal tumors (Hays et al. 1981). MRI can provide more optimum soft tissue delineation than CT scan, although CT scan is still recommended for staging and lymph node evaluation for these patients. Physical exam before the start of chemotherapy is critical for these patients in order to determine the site of origin of the tumor and define the local extent of disease. Despite high quality imaging, physical examination can provide important additive information to define the treatment volume.

Treatment of vaginal and vulvar primaries has also evolved with time in an effort to minimize aggressive surgical resection particularly after their excellent outcomes and chemo responsiveness was

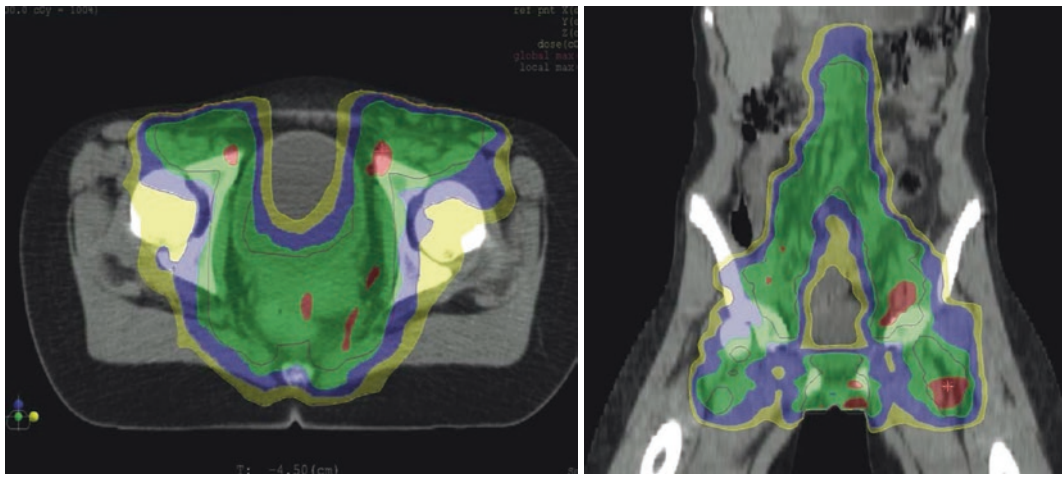

Fig. 3.4 Radiation planning for a paratesticular rhabdomyosarcoma demonstrating comprehensive coverage of the para-aortic and pelvic lymph nodes

recognized in IRS I and II. On IRS II, chemotherapy was started for patients with the goal of delaying surgery. After second look surgery was performed at either week 8 or 16, radiation was administered if surgical resection was not complete. With this approach, 3 year OS was 86% (Raney et al. 1990). Further refinement allowed for avoidance of extensive surgery beyond local excision or biopsy in 87% of patients on IRS IV. Similarly, rates of hysterectomy decreased and use of RT increased for unresectable tumors after chemotherapy induction. On IRS II, 23% of patients received RT compared to 45% of patients on IRS IV (Arndt et al. 2001).

Local control was evaluated in patients with non-resected, localized vaginal RMS enrolled onto the two most recent COG low-risk studies, D9602 and ARST0331 (Walterhouse et al. 2014). Only 4 of the 39 patients with non-resected tumors received radiotherapy. The 5-year cumulative incidence of local recurrence was 26% on D9602 and the 2-year cumulative incidence of local recurrence was 43% on ARST0331. These high LF rates were attributed to the lower doses of cyclophosphamide used on the chemotherapy regimens evaluated on these low risk protocols (Walterhouse et al. 2014). Fortunately, these patients can be salvaged effectively (Arndt et al. 2001).

In the SIOP MMT 84 and 89 protocols, patients were primarily treated with initial chemotherapy. Local control with surgery, external beam radiation, or brachytherapy was used only for patients with either residual disease or relapse. Overall, 44% of patients had no local therapy and also had no evidence of disease at last follow-up. Approximately 50% of patients did require local therapy in order to achieve a complete response (Martelli et al. 1999).

Brachytherapy is the radiation approach of choice in vaginal and vulval primaries, based largely on the experience overseas at the Institut Gustave Roussy. Thirty-nine patients who received vulval or vaginal brachytherapy were evaluated by Magne et al. at a median follow-up of 8.4 years (Magne et al. 2008). In this study, patients were treated to the prechemotherapy volume before 1990 and treated to residual disease only after 1990. Endocavitary brachytherapy was used for vaginal primaries and interstitial brachytherapy was generally used for vulvar RMS with a prescription dose of 60–65 Gy delivered in 1–3 fractions. Overall survival at 5 years was 91%. Toxicity was also minimal in the modern era with decreased rates of late vaginal or urethral sclerosis in the patients treated after 1990, due to improvements in chemotherapy, refinement of surgical indications, and ultimately reduction in radiotherapy treatment volume.

A brachytherapy approach should be strongly considered in these patients for localized tumors. Radical surgery is not generally indicated in these patients except for rare circumstances. If surgery is performed, limited resection is recommended after chemotherapy induction as a second look surgery in an effort to reduce the volume for treatment. If tumors cannot be resected at that point, they are referred for radiation. If microscopic residual remains after surgery, postoperative radiation is also recommended.

3.6.13 Uterus and Cervix

Uterine and cervical RMS are overall less common than vaginal RMS and present most frequently in adolescent girls (Hays et al. 1981). These tumors are histologically embryonal, commonly of botryoid subtype. The treatment approach for uterine and cervical RMS includes pelvic organ preservation if possible. If upfront surgery is performed, RT is administered if microscopic residual disease remains. In patients with group III disease, chemotherapy is administered upfront followed by a second look surgery. RT is given in the scenario where there is gross tumor after hysterectomy or if microscopic disease persists after chemotherapy and/or surgery.

Patients with uterine and cervix RMS have high OS rates akin to vaginal RMS, although they may not respond to chemotherapy as briskly (Arndt et al. 2001). These tumors are rare, with only ten patients having uterine or cervical primaries on IRS I and IRS II combined. For localized tumors, surgery (with either polypectomy and chemotherapy or hysterectomy that removed

all gross tumor) achieved a high rate of success (Hays et al. 1981). The survival of 21 patients with isolated botryoid sarcoma of the uterine cervix was 80% (Brand et al. 1987). However, patients with advanced or metastatic RMS had an unfortunate prognosis with all patients dying of disease within 11 months.

3.7 Metastatic Disease

Roughly 15% of pediatric RMS patients present with metastatic disease (stage IV) (Breneman et al. 2003). The majority of metastatic lesions appear in the lungs, bone, bone marrow, and distant lymph nodes. Metastatic disease tends to appear more frequently in older patients, those of male sex, those with alveolar histology, and very commonly with bulky primary tumors (>5 cm) (Oberlin et al. 2008). Survival is poor for disseminated RMS, and a pooled analysis of US and European patients treated on cooperative group studies found a 3-year OS and EFS of 37 and 27% (Oberlin et al. 2008). Yet prognosis varies within stage IV disease and survival is influenced by a number of factors. In a review of metastatic patients from IRS IV, 3-year OS was significantly influenced by histology (47% for embryonal vs. 34% for all others) and increasing number of metastatic sites. Patients with embryonal histology and two or fewer metastatic sites had an improved 3-year FFS of 40% compared to 5% for those with three or more metastatic sites and alveolar histology (Breneman et al. 2003).

Treatment for metastatic disease relies heavily on aggressive systemic therapy. Attempts to intensify chemotherapy through increasing cyclophosphamide doses, incorporation of novel drugs and targeted therapies, and high dose chemotherapy with stem cell rescue have all failed to significantly improve outcomes for these patients. At present, the optimal regimen is still unknown, but all rely heavily on the standard RMS agents. Radiation is typically delivered to the primary site and all metastatic lesions. Standard RMS doses are used for both the primary and the metastatic sites. For patients with lung metastases, whole lung radiation should be considered with a boost to any gross residual disease. Similarly, patients with diffuse abdominal metastases can be considered for whole abdominal RT.

3.8 Recurrent RMS

Despite significant improvement in front line therapy for non-metastatic pediatric RMS, roughly 30% of patients will experience disease recurrence (Crist et al. 2001; Arndt et al. 2009). The OS after relapse varies widely and can range from 15 to 80%, depending heavily on the extent and site of recurrence (Chisholm et al. 2011). Metastatic failures are seldom controlled. Isolated local recurrences in areas such as the orbit or vagina can be readily salvaged with surgery but local failures in surgically inaccessible areas such as the parameninges portend a dismal outcome. Other factors including a time to relapse of <18 months, prior radiation therapy, large tumor size, and alveolar histology have all been linked to decreased rates of salvage (Chisholm et al. 2011).

Treatment options for recurrent disease also vary based on a number of factors. Second-line chemotherapy is always utilized, even in local recurrences, as the risk of micrometastatic disease is high (Mazzoleni et al. 2005). Local therapy with surgery and/or radiation is dependent on the site and extent of the recurrence as well as prior therapy and the response to second-line chemotherapy. Therefore, treatment decisions in relapsed disease should be made in a multidisciplinary setting.

3.9 Proton Therapy for RMS

In recent years, proton therapy has garnered significant interest in the treatment of pediatric RMS. The elevated sensitivity of children to the late effects of radiation and the propensity of pediatric RMS to arise in close proximity to critical structures had led to widespread adoption of this modality. Currently, the Children's Oncology Group (COG) and International Rhabdomyosarcoma Study Group (IRSG)

protocols allow for the use of proton therapy. Because the relative biologic effectiveness (RBE) of protons is nearly equivalent to that of high-energy X-rays (RBE = 1.1), the interest in protons is based primarily on the physical properties that provide favorable dosimetric distributions (Paganetti et al. 2002). The abrupt dose fall off seen at the distal end of the proton beam often allows for a reduction of dose to adjacent normal tissue and/or an increase in the total dose that can be safely delivered to the target volume (Fig. 3.5). Further, the "integral dose" or total energy deposited in a patient from radiation therapy is decreased with protons, often by two to three times. This reduced exposure is of great importance when considering the secondary malignancy risk in children (Lomax et al. 1999). Previously, clinical outcomes data surrounding the use of proton therapy in pediatric RMS was scarce, and dosimetric studies dominated the literature. As the number of centers with proton capabilities has increased, more and more data have become available to help guide clinicians in their decision-making.

The clinical outcomes for 57 pediatric RMS patients enrolled on a prospective joint proton protocol from Massachusetts General Hospital (MGH) and MD Anderson Cancer Center (MDACC) between 2005 and 2012 were recently published, representing the first prospective trial of proton therapy in pediatric RMS (Ladra et al. 2014a). The 5-year LC, EFS, and OS were 81%, 69%, and 78%, respectively; comparable to published outcomes from the IRS IV-V trials (Crist et al. 2001; Arndt et al. 2009; Pappo et al. 2007; Ladra et al. 2014a). No patient developed acute or late toxicity of grade 4 or 5, and there were three occurrences of grade 3 late toxicity, related to chronic otitis, cataract, and dry eye in head and neck tumors. As part of the MGH/MDACC trial, each patient treated with protons received a comparison IMRT plan, and the results for 54 patients were published. When the proton plans were compared to the theoretical IMRT plans, the mean integral dose for IMRT was 1.8 times higher for head and neck and genitourinary sites, 2.0 times higher for trunk/extremity sites, and

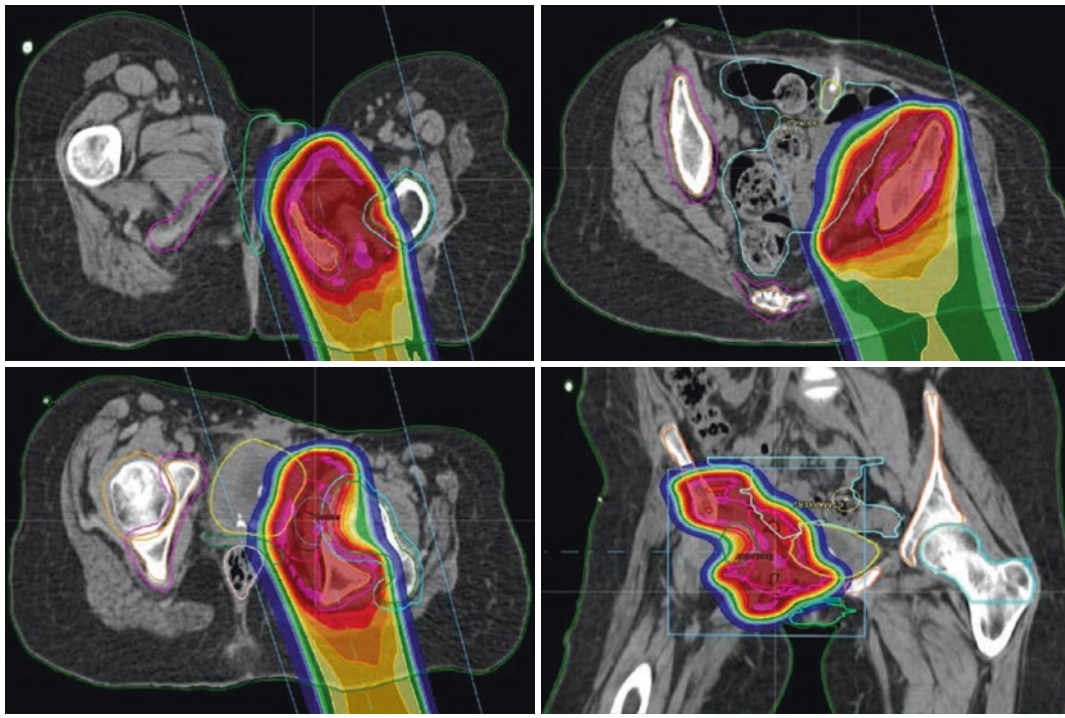

Fig. 3.5 A 14 year-old female with pelvic embryonal rhabdomyosacoma treated with proton therapy. The use of proton therapy in this patient helped to spare dose to the vagina, bladder, contralateral ovary, and bowel

3.5 times higher for orbital sites (Ladra et al. 2014b). The dosimetric study also found that protons had the most significant degree of sparing in organs sensitive to low dose radiation, such as the hypothalamus, lens, and gonads, and greatly reduced the volume of growing bone exposed to radiation in the head and neck and pelvis (Ladra et al. 2014b).

Several smaller site-specific studies addressing proton outcomes for pediatric RMS have been published. A retrospective review by Childs et al. of 17 consecutive children with PM RMS, treated with proton radiotherapy between 1996 and 2005, demonstrated similar outcomes to those seen with standard photon therapy (Childs et al. 2012). In the proton study, the median age was 3.4 years and 59% presented with intracranial disease extension, representing a somewhat unfavorable cohort. The 5-year LC was 84%, FFS was 59%, and OS was 64% (Childs et al. 2012). Patients who had intracranial extension at diagnosis had a 5-year FFS of 50%, whereas those without intracranial disease fared better with a 5-year FFS of 71%. Ten patients (59%) were without tumor recurrence at study completion and available for late toxicity evaluation. Among these patients, late effects of multimodality treatment included mild facial hypoplasia ($n = 7$), lack of permanent tooth eruption ($n = 3$), decreased height velocity ($n = 3$), endocrinopathies ($n = 2$) and chronic sinus congestion ($n = 2$). From the same cohort of proton treated PM RMS patients, a separate dosimetric comparison of proton and IMRT plans was also published (Kozak et al. 2009). With regards to toxicity risk, the proton plans appeared to have some advantage. In this study, only one proton plan had a lens dose higher than 5 Gy, whereas in the photon plans 80% of ipsilateral lenses and 60% of contralateral lenses received above 5 Gy. Contralateral cochlear dose was kept to less than 32 Gy for all proton plans, whereas 50% of photon plans had a contralateral cochlear dose over 32 Gy. Similarly, the mean contralateral parotid gland dose never exceeded 13 Gy for the proton plans but was greater than 26 Gy for 70% of the IMRT plans. Finally, the mean dose to the hypothalamus was 12 Gy for protons vs. 22.4 Gy for IMRT.

The proton experience for seven children with orbital RMS was reported by Yock et al. (2005). With a median age of 7.6 years and a median follow-up of 6.3 years, 6 of the 7 patients were without evidence of disease. The remaining child was salvaged with exenteration and stereotactic radiosurgery after local recurrence. In the single LF, progression of the tumor was seen during chemotherapy and the child was less than 1 year of age at treatment. Late effects of treatment were minimal. All six patients retained good vision in the treated eye and 2 of the 6 patients required drops for lubrication but none demonstrated corneal pathology or dry eye syndrome. All patients did develop mild to moderate orbital bony asymmetry or enophthalmous. None of the patients developed neuroendocrine deficits. Recent publications utilizing IMRT for orbital tumors found neuroendocrine dysfunction ranged from 3 to 10% (Heyn et al. 1986; Wolden et al. 2005; Paulino et al. 2000; Raney et al. 1999).

And finally, Cotter et al. reported the outcomes of 7 children treated with protons for bladder/prostate RMS with a median follow-up of 27 months (Cotter et al. 2011). Patients had a mean age of 30 months and radiation dose range from 36 to 50.4 CGE. Five of seven patients (71.4%) were without evidence of disease with intact bladders at study completion. One patient had a local recurrence in the treatment field, while a second had a local and a distant recurrence. Two of the five patients with intact bladders at the end of treatment reported bladder dysfunction, both of which were attributable to prior surgical procedures. No long-term skeletal or gastrointestinal effects were noted, and all patients were too young to assess sexual function. IMRT plans were created for study purposes and compared to the proton plans used for treatment. Proton radiotherapy showed a statistically significant decrease in mean organ dose to the bladder (median proton dose of 25 Gy vs. median IMRT dose of 33.2 Gy; $p = 0.03$), testes (0.0 CGE vs. 0.6 Gy; $p = 0.016$), femoral heads (1.6 Gy vs. 10.6 Gy; $p = 0.016$), pelvic growth plates (21.7 Gy vs. 32.4 Gy; $p = 0.016$), and pelvic bones (8.8 Gy vs. 13.5 Gy; $p = 0.016$).

There were no significant differences seen in dose to the bowel, prostate, penile bulb, and rectum.

Conclusion

Tremendous progress has been made in the treatment of pediatric RMS though both improvements in multimodality therapy as well as the work of cooperative group studies. While there is still significant room for improvement in outcomes, advances in molecular profiling, targeted therapy, and tumor detection all provide reason for optimism regarding the future of pediatric RMS.

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4 The Non-rhabdomyosarcoma Soft Tissue Sarcomas, Desmoid Tumor and Osteosarcoma

Christopher L. Tinkle and John T. Lucas Jr.

4.1 Non-rhabdomyosarcoma Soft Tissue Sarcoma

4.2 Introduction

Soft-tissue sarcoma (STS) are a group of rare tumors diagnosed in children and adults that require multi-modality specialty care. The etiology of STS in children is largely unknown although they are among the tumor types associated with cancer predisposition syndromes and included in the differential of radiation-induced malignancies. STS include a broad variety of histologic subtypes, diverse presentations, and wide-ranging lethality. Evaluation and management of STS in pediatric patients has evolved based on knowledge derived from clinical trials performed in adults and more recently prospective studies performed exclusively with children. Surgery, irradiation modalities, and conventional chemotherapy have identified roles in the treatment of pediatric patients with current studies focused on toxicity reduction in low-risk patients, optimal sequencing of therapy and new agent testing in intermediate and high-risk patients, and systematic salvage strategies for patients that do not respond to front-line therapy.

4.3 Epidemiology

An estimated 12,310 new cases of STS representing 0.7% of all new cancers were diagnosed in the United States in 2016 (Siegel et al. 2016). Of this, approximately 8.6%, or 1058 new cases, will be diagnosed in patients younger than 20 years of age (SEER 2016). Despite an overall scarce incidence, STS are disproportionally represented in the pediatric patient population, constituting about 7% of all childhood cancers (SEER 1999). While rhabdomyosarcoma, a sarcoma of striated muscle, accounts for approximately 50% of these pediatric cases, the more histologically heterogeneous non-rhabdomyosarcoma (NRSTS) represent the remaining 500–550 children and adolescents diagnosed annually (SEER 1999; Ferrari et al. 2011b). A bimodal incidence distribution of NRSTS within the pediatric age group is seen, with a peak during infancy and rising incidence again throughout adolescence (Hawkins et al. 2013; Spunt et al. 2008).

Further population-based studies through the Surveillance, Epidemiology, and End Results (SEER) have revealed a unique histologic distribution among NRSTS in the pediatric population in comparison to adults (Ferrari et al. 2011b;

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Spunt and Pappo 2006). Important distinctions include distinct histologic subtypes, including infantile fibrosarcoma, and varied distribution, with synovial sarcoma and malignant peripheral nerve sheath tumor (MPNST) observed more frequently and liposarcoma, leiomyosarcoma and angiosarcoma diagnosed less frequently in the pediatric population (Spunt and Pappo 2006). Overall, STS demonstrate a slight male preponderance and relatively increased incidence rate in black children compared to white children (rate ratio 1.33:1) (SEER 1999).

The etiology of NRSTS remains elusive in the vast majority of patients. However, several genetic cancer predisposition syndromes have been associated with increased risk for development of STS. Patients with Neurofibromatosis 1 (NF1), an autosomal dominant syndrome resulting from mutation in the *NF1* gene, are at significantly elevated risk of development of malignant peripheral nerve sheath tumors (MPNST) ranging from 4 to 13% lifetime risk (Decou et al. 1995; Evans et al. 2002; Stark et al. 2001). Li-Fraumeni syndrome, an autosomal dominant syndrome linked to germline *p53* mutation, is associated with increased risk of STS development, particularly NRSTS (Chang et al. 1995; Ognjanovic et al. 2012). Hereditary retinoblastoma, resulting from germline mutations in the *RB* gene, has also been associated with an increased risk of STS development and leiomyosarcoma in particular (Kleinerman et al. 2007). Patients with familial adenomatous polyposis, an autosomal dominant syndrome associated with significant risk of colorectal cancer and linked to APC mutation, are at significant risk of development of desmoid-type fibromatosis with approximately 10% lifetime risk (Groen et al. 2008; Nieuwenhuis et al. 2011). Finally, patients with Werner syndrome, characterized by mutations in the *WRN* gene and spontaneous chromosomal instability with susceptibility to cancer and premature aging, are at elevated risk of various STS (Goto et al. 1996).

Environmental factors associated with STS development include occupation-related chemical exposure, viral infection, chronic lymphedema, and treatment-related factors including ionizing radiation and chemotherapy. Vinyl chloride exposure is causally related to angiosarcoma of the liver (Falk et al. 1981). Epstein-Barr viral infection has been linked to leiomyosarcoma development in patients with acquired immune deficiency syndrome (AIDS) (Mcclain et al. 1995). Stewart-Treves syndrome is a rare cutaneous angiosarcoma that develops in the setting of chronic lymphedema, and has been reported as a complication of hereditary lymphedema and therapy related lymphedema (Durr et al. 2004; Kirova et al. 1999). Findings from the Childhood Cancer Survivorship Study (CCSS) suggest an approximate ninefold increased risk of secondary sarcoma development in childhood cancer survivors relative to the general population, and factors significantly associated with this risk include receipt of radiotherapy, radiotherapy dose and anthracycline exposure (Henderson et al. 2012; Henderson et al. 2007).

4.4 Pathology

The current clinicopathologic classification of STS is based on the World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone, with the fourth edition published most recently in 2013 (Fletcher et al. 2013). Histologic classification is based on evidence of cellular differentiation within a tumor sample and tumors are grouped according to similarity to mature non-neoplastic tissues. While over 50 histologic subtypes of STS have been identified, currently the WHO lists the following distinct STS tumor types: adipocytic, fibroblastic/myofibroblastic, so-called fibrohistiocytic, smooth muscle, pericytic (perivascular), skeletal muscle, vascular tumors, chondro-osseous, nerve sheath, uncertain differentiation, and undifferentiated/unclassified. Each of these tumor types is further grouped based on the concept of biologic potential of local and distant spread: benign – rare, non-destructive local recurrence without distant metastasis; intermediate, locally aggressive – frequent, destructive local recurrence without distant metastasis; intermediate, rarely metastasizing – locally aggressive with low risk (<2%) of distant metastasis; malignant – locally aggressive with significant risk (>20%) of distant metastasis. Table 4.1 highlights select NRSTS histologies and associated cytogenetic and molecular alterations.

As histologic subtype is not always indicative of clinical behavior, the concept of grading

Table 4.1 Histologic subtype and associated cytogenetic and molecular aberrations of select non-rhabdomyosarcoma soft tissue sarcoma

Histologic subtype	Cytogenetic aberration	Molecular aberration
Complex Karotype		
Angiosarcoma	Complex	
Leiomyosarcoma	Complex with frequent 1p deletion	
Malignant peripheral nerve sheath tumor	Complex	
Pleomorphic liposarcoma	Complex	
Pleomorphic sarcoma, NOS (malignant fibrous histiocytoma)	Complex	
Simple Karyotype		
Alveolar soft parts sarcoma	t(X;17)(p11;q25)	*ASPSCR1-TFE3* fusion
Angiomatoid fibrous histiocytoma	t(12;16)(ql3;p11)	FUS-ATF1 fusion
	t(2;22)(q33;q12)	EWSR1-CREB1 fusion
	t(12;22)(q13;q12)	EWSR1-ATF1 fusion
Clear cell sarcoma	t(12;22)(q13;q12)	*EWSR1-ATF1* fusion
	t(12;22)(q32.3;q12)	*EWSR1-CREB1* fusion
Chondrosarcoma, extraskeletal mesenchymal	Del(8)(q13.3q21.1)	*HEY1-NCOA2* fusion
Chondrosarcoma, extraskeletal myxoid	t(9;22)9q22;ql2)	*EWSR1-NR4A3* fusion
	t(9;17)(q22;q11)	*TAF2N-NR4A3* fusion
	t(9;15)(q22;q21)	*TCF12-NR4A3* fusion
	t(3;9)(q11;q22)	*TGF-NR4A3* fusion
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13)	*COL1A1-PDGFB* fusion
Desmoid-type fibromatosis	Trisomies 8 and 20	
	Deletion of 5q	
		APC; CTNNB1 inactivation
Epitheliold sarcoma	22q11-12 alterations	*INI1 (SMARCB1)* inactivation
Fibrosarcoma, infantile	tl2;15)(pl3;q26)	*ETV6-NTRK3* fusion
Fibromyxoid sarcoma, low grade	t(7;16)(q33;p11)	*FUS-CREB3L2* fusion
	t(11;16)9p11;p11)	*FUS-CREB3L1* fusion
Inflammatory myofibroblastic tumor	t(1:2)(q22;p23)	*TPM3-ALK* fusion
	t(2;19)(p23;p13)	*TPM4-ALK* fusion
	t(2;17)(p23;q23)	*CLTC-ALK* fusion
	t(2;2)(p23;q13)	*RANB2-ALK* fusion
Liposarcoma, myxoid/round cell	t(12;16)(ql3;p11)	*FUS-DDIT3* fusion
	t(12;22)(q13;12)	*EW5R1-DDIT3* fusion
Myoepithelioma	t(19;22)(q13;q12)	*EWSR-ZNF44* fusion
	t(1;22)(q23;q12)	*EWSR-PBX1* fusion
	t(6;22)(p21;q12)	*EWSR-POU5F1* fusion
Primitive neuroectodermal tumor	t(11;22)(q24;q12)	*EWSR1-FL1* fusion
	t(21;22)(q12q12)	*EWSR1-ERG* fusion
Solitary fibrous tumor	Inv(12)(q13q13)	NAB2-STAT6 fusion
Synovial sarcoma, monophasic	t(X;18)(p11;q11)	*SYT-SSX1, SS18-SSX2* or *SS1S-SSX4* fusion
Synovial sarcoma, biphasic	t(X;18)(p11;q11)	*SS18-SSX1* fusion
Undifferentiated round cell sarcoma	t(4:19)(q35;q13)	*CIC-DUX4* fusion
	t(10:19)(q26;q13)	*CIC-DUX4* fusion
	X chromosome inversion	*BCOR-CCNB3* fusion

Adapted from Mertens et al. (2009), Romeo and Dei Tos (2011), Rubin and Goldblum (2007), Skubitz and D'adamo (2007), and Spunt et al. (2008)

STS based solely on histologic features has long been incorporated in STS pathologic assessment and has been shown to be one of the best predictors of patient outcome (Coindre et al. 2001; Russell et al. 1977). Several grading systems have emerged, most notably the Pediatric Oncology Group (POG), the National Cancer Institute (NCI) and the French Federation of Cancer Centers (FNCLCC) systems. The POG system, a prospectively validated variation of the NCI system, incorporates a combination of histologic type related to propensity for malignancy, percent of necrosis and mitotic count (Parham et al. 1995) (Table 4.2). The NCI classification scheme defines tumor grade based on certain histologic types, while percent necrosis and minor pathologic factors including mitotic index, degree of cellularity and cellular and nuclear morphology are used to establish grade for the remaining histologic

Table 4.2 Pediatric Oncology Group (POG) tumor grading system for pediatric non-rhabdomyosarcoma soft tissue sarcoma

POG grading system for pediatric nonrhabdomyosarcoma soft tissue sarcomas		
Grade I	Grade II	Grade III
Based on histologic type, well-differentiated cytohistologic features, and/or age of the patient	**Soft tissue sarcomas not included in grade I or III by histologic diagnosis (with <5 mitoses/10 high-power fields or ≥15% necrosis)**	**Similar to grade II lesions and include certain tumors known to be clinically aggressive by virtue of histologic diagnosis and non-grade I tumors (with ≥5 mitoses per 10 high-power fields or >15% necrosis)**
	• 15% or less of the surface area shows necrosis (primary criteria)	• Any other sarcoma not in grade I with >15% necrosis and/or ≥5 mitotic figures per 10 high-power fields (40× objective)
	• The mitotic count is <5 mitotic figures per 10 high-power fields (40× objective) (primary criteria)	• Marked atypia and cellularity are less predictive but may assist in placing tumors in this category
	• Nuclear atypia is not marked (secondary criteria)	
	• The tumor is not markedly cellular (secondary criteria)	
Angiomatoid fibrous histiocytoma		Alveolar soft part sarcoma
Dermatofibrosarcoma protuberans		Extraskeletal osteogenic sarcoma
Liposarcoma–myxoid or well-differentiated		Malignant triton tumor
Myxoid chondrosarcoma		Mesenchymal chondrosarcoma
Well-differentiated malignant peripheral nerve sheath tumor		Pleomorphic or round-cell liposarcoma
Well-differentiated or infantile (aged ≤4 years) fibrosarcoma		
Well-differentiated or infantile (aged ≤4 years) hemangiopericytoma		

Abbreviation: *HPF* high-power field
Adapted from Pappo et al. (1999a) and Parham et al. (1995)

subtypes (Costa et al. 1984). The FNCLCC system is based on a score derived from evaluation of tumor differentiation, mitotic rate and extent of tumor necrosis (Trojani et al. 1984) (Table 4.3). Given tumor differentiation is highly dependent on histologic subtype, each of the major STS subtypes is given a differentiation score based the ability to identify a line of cellular specification. While retrospective studies have highlighted both discordance (Guillou et al. 1997) and concordance (Khoury et al. 2010) between the various tumor grading systems and clinical outcomes, an objective of the recently completed Children's Oncology Group (COG) ARST0332 prospective clinical trial is to directly compare the POG and FNCLCC systems and their impact on outcome.

From a molecular biology perspective, sarcomas have traditionally been grouped into two broad categories, including translocation-associated sarcomas with generally simple genetic alterations and specific driver mutations, and karyotypically complex sarcomas with a large number of DNA structural aberrations and unstable genomes (Taylor et al. 2011) (Fig. 4.1). While this framework is still useful, next-generation sequencing and advanced epigenetic analysis have highlighted the distinct molecular profile of various sarcoma subtypes even within these two categories (Fig. 4.1). With the rapid advancement of technologies used to identify the genetic, epigenetic and proteomic underpinnings of diverse tumors, several large scale efforts to characterize the molecular landscape of sarcomas have emerged to drive this approach further, including the National Cancer Institute's The Cancer Genome Atlas (TCGA) Sarcoma study and COG's Strategic Partnering to Evaluate Cancer Signatures (SPECS) within pediatric sarcomas. There is hope that advances in molecular genetics may result in a shift from relatively uniform therapy of surgery, radiation and conventional chemotherapy to a more personalized approach, like that observed in leukemia and melanoma. While a detailed description of emerging genomic alterations and potential

Table 4.3 Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) tumor grading system for adult soft tissue sarcoma

FNCLCC histologic grading system		
Tumor differentiation		
Score 1	Score 2	Score 3
• Sarcoma closely resembling normal adult mesenchymal tissue (e.g., low grade liposarcoma)	• Sarcomas for which histologic typing is certain (e.g., myxoid liposarcoma)	• Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, osteosarcomas, PNET
Mitotic count		
Score 1	Score 2	Score 3
• 0–9 mitoses per 10 HPF	• 10–19 mitoses per 10 HPF	• ≥ 20 mitoses per 10 HPF
Tumor necrosis		
Score 0	Score 1	Score 2
• No necrosis	• < 50% tumor necrosis	• ≥ 50% tumor necrosis
Histologic grade determined by total score		
Total score	*Histological grade*	
2–3	Grade I	
4–5	Grade II	
6–8	Grade III	

Abbreviations: *FNCLCC* Fédération Nationale des Centres de Lutte Contre Le Cancer, *PNET* primitive neuroectodermal tumor, *HPF* high-power field
Adapted from Guillou et al. (1997) and Trojani et al. (1984)

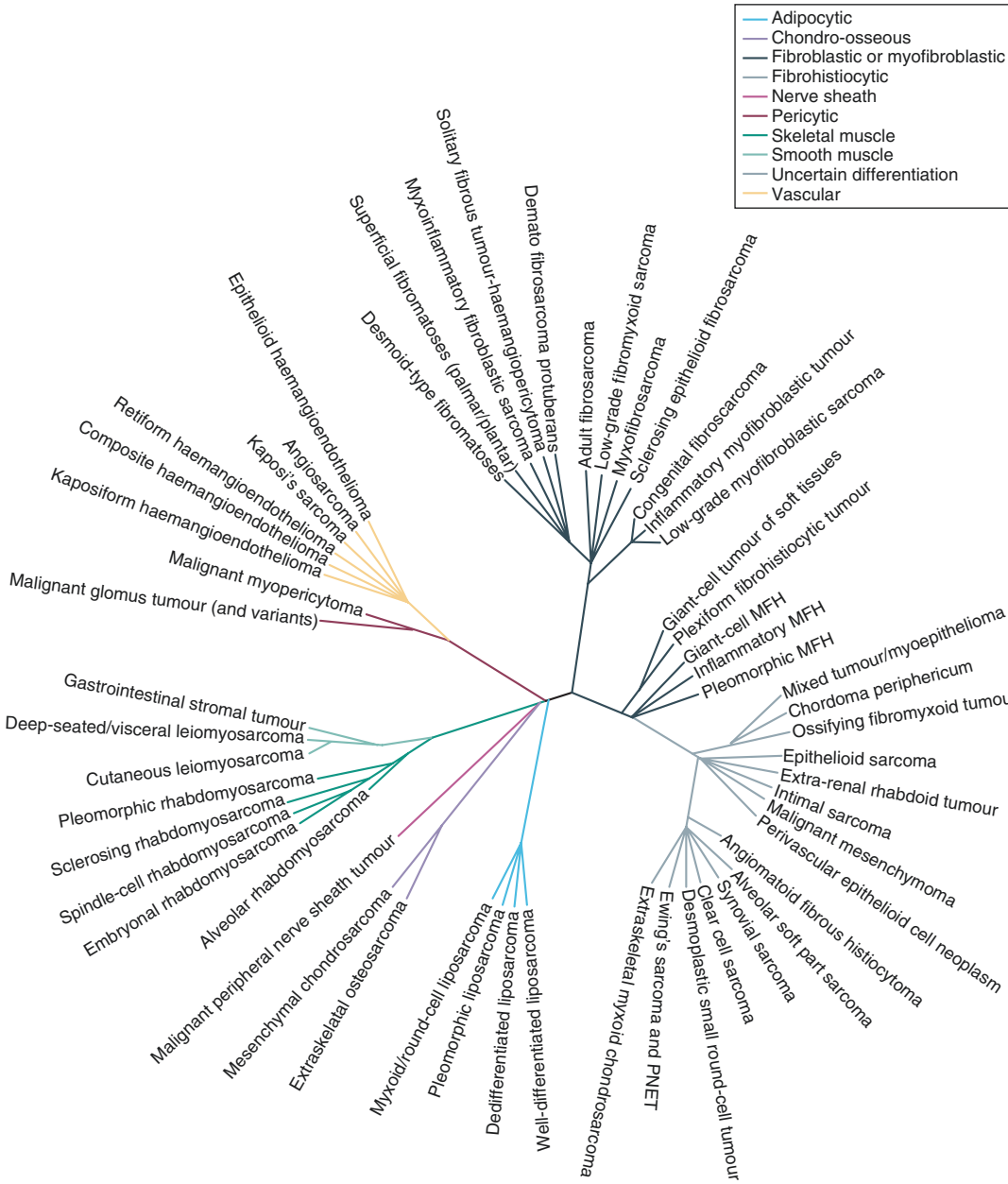

Fig. 4.1 Taxonomy of soft tissue sarcoma. Unrooted phylogeny of ~60 World Health Organization described sarcoma subtypes reflecting relationships among lineage, prognosis, genetic driver alterations and additional parameters. Branch lengths are determined by nearest neighbor joining of a discretized distance matrix based on the variables above. Initial branching reflects differences in lineage, with associated lineages appearing closer in distance. Subsequent branching denotes similarity in prognosis, whether they are translocation-associated, and if so, the genes shared among distinct fusions. Several subtypes currently lack sufficient global molecular profiling data for complete phylogenic classification. Benign sarcoma tumors are excluded. *MFH* represents undifferentiated pleomorphic sarcoma, *PNET* primitive neuroectodermal tumor. Reprinted with permission "Advances in sarcoma genomics and new therapeutic targets", Taylor et al. 2011; Nature Publishing Group. All rights reserved (Taylor et al. 2011)

therapeutic interventions is beyond the scope of this chapter, the reader is directed to several excellent recent reviews (Demicco et al. 2012; Hingorani et al. 2016; Janeway and Maki 2012; Marino-Enriquez 2015; Taylor et al. 2011).

Given the rarity of STS overall and of individual tumor types, as well as the diagnostic complexity involved in assessing the varying subtypes, accurate histopathologic assessment is often difficult. Several studies have suggested wide interobserver variability, with approximately 5–10% of cases initially reported as sarcoma reclassified as non-sarcoma and approximately 15–30% of cases with revision to different STS subtype (Alvegard and Berg 1989; Presant et al. 1986). Further concern resides in tissue procurement methods with limited tumor sampling as well as inherent tumor heterogeneity. To overcome many of these discrepancies and assist with the histologic, immunohistochemical and molecular analysis of STS, specific guidelines for the evaluation and reporting have been developed and are in wide clinical use (Rubin et al. 2006). Additionally, recent data suggests more extensive tissue sampling in the form of incisional biopsy may more accurately establish tumor grade compared to needle biopsy (Khoja et al. 2013; Neuville et al. 2014).

4.5 Clinical Presentation, Evaluation, and Prognosis

Soft tissue tumors generally present as either locally asymptomatic or symptomatic solid masses in the absence of systemic symptoms, including fever, night sweats, and weight loss. When locally symptomatic pain, vascular and neurologic compression as well as bowel dysfunction for tumors within the retroperitoneum are frequently observed. Rarely, paraneoplastic metabolic derangements including hypo- and hyper-glycemia and hypophosphatemic rickets have been associated with several NRSTS subtypes (Rikhof et al. 2009; Weiss and Goldblum 2008). Most palpable soft tissue masses in children are in fact benign, with vascular lesions the most common of the connective tissue neoplasms (Alaggio and Coffin 2015). Given the insidious presentation, the suggestion of benignity and the overall rarity of NRSTS, definitive diagnosis is often delayed with several studies noting significant delay from time to first clinical signs to diagnosis (Brasme et al. 2012; Brouns et al. 2003; Haimi et al. 2004).

The most common site for pediatric NRSTS is the extremities, although these tumors can arise anywhere in the body with the head and neck and trunk also frequently involved (Ferrari et al. 2011b). Distant metastatic spread at the time of diagnosis is relatively infrequent involving approximately 15% of patients, with the lung the most common site of dissemination (Ferrari et al. 2005; Pappo et al. 1999b; Spunt et al. 2008). Other less frequent sites of metastasis include bone, liver, subcutaneous tissue, and brain (Pappo et al. 1999b). Regional lymphatic spread is also rare, with the exception of certain histologies including clear cell sarcoma, epithelioid sarcoma, and perhaps alveolar soft parts sarcoma (Fong et al. 1993; Pratt et al. 1998; Kayton et al. 2006).

Diagnostic evaluation should begin with adequate imaging work-up. Often plain films are obtained early on in order to rule out bone involvement. Cross-sectional imaging in the form of computed tomography (CT) and/or magnetic imaging resonance (MRI) is critical in the delineation of the primary tumor and the pattern of infiltration and locoregional spread, which in turn assist in clinical staging, surgical and radiotherapy planning and therapy response evaluation. With superior soft tissue delineation, MRI is often the image modality of choice to assess the primary site of STS, while CT-based imaging is frequently employed for visceral tumors within the chest, abdomen and pelvis. Evaluation of regional and distant metastasis is histologic subtype and tumor location dependent, with the exception of a chest X-ray or chest CT in all newly diagnosed patients given the predilection for lung metastasis (Fleming et al. 2001). For patients with clinical or radiologic evidence of

regional nodal involvement or those with tumors with elevated risk of regional lymph node metastasis, sentinel lymph node biopsy or lymph node sampling is currently recommended (Alcorn et al. 2013; Spunt et al. 2008). Positron-emission tomography (PET) imaging using [(18)F] fluorodeoxyglucose (FDG) has been increasingly employed in the detection, staging, and treatment monitoring in pediatric NRSTS patients (Chen et al. 2007; Ferner et al. 2008; Magnan et al. 2013; Mody et al. 2010; Tateishi et al. 2007), yet there is a need to further assess the utility of PET imaging for this population. For patients with retroperitoneal or intra-abdominal tumors, dedicated liver imaging is recommended to evaluate for liver metastasis. Brain imaging and bone scintigraphy are generally indicated only in the presence of suggestive symptoms and in patients with widespread metastasis (Espat et al. 2002; Jager et al. 2000), while bone marrow biopsy is not indicated. Among the diverse histologies of NRSTS, low grade myxoid fibrosarcoma and alveolar soft parts sarcoma appear to have distinct imaging features on MRI and CT that may aid in diagnostic work-up (Mccarville et al. 2014; Sargar et al. 2015).

Tissue diagnosis of NRSTS can be obtained through fine needle biopsy, core needle biopsy, incisional biopsy, or excisional biopsy. Fine needle biopsy (FNA), with limited tissue procurement, is generally not recommended given the difficulty in accurate histologic classification and tumor grading of these diverse tumors; yet FNA provides an efficient way to determine if a sarcoma is present. On the other hand excisional biopsies should be restricted to small superficial lesions, 3 cm or less, after an MRI has been obtained to accurately assess tumor infiltration and potential locoregional nodal spread (Smith et al. 1997). Given the number of different pathologic analyses required for NRSTS diagnosis, including conventional histology, immunohistochemistry (IHC), cytogenetics, fluorescence *in situ* hybridization (FISH) and other "molecular" analyses, and electron microscopy, multiple core needle biopsies or incisional biopsy are preferred. These are often performed in the operating room or interventional radiology suite under image guidance using ultrasound, CT, or MRI as appropriate. For deep-seated tumors, incisional biopsy may be preferred to reduce the risk of hematoma formation which could subsequently alter the planned surgical resection and/or radiotherapy (Smith et al. 1997). As a general rule in STS management, the footprint of surgical manipulation prior to definitive resection or radiotherapy is surgically excised or included within the radiation field, respectively. Thus, needle biopsies should be carefully planned and transverse extremity incisions avoided to reduce skin loss and limit normal tissue irradiation. For these reasons, when possible the biopsy should be done by or planned with the surgeon who will perform the definitive resection.

Historically, NRSTS have been clinically staged according to the surgico-pathologic staging system for rhabdomyosarcoma based on the Intergroup Rhabdomyosarcoma Study Group (Maurer et al. 1988). This system is based on the presence of metastatic disease and whether and to what extent the primary tumor is resected. In adults, the predominate staging system used is the Tumor (T; size) Node (N; presence) Metastasis (M; presence), or TNM, system developed by the American Joint Committee on Cancer (AJCC) (2) (Edge et al. 2010). Developed for sarcoma initially in 1969 and first validated in 1977 (Russell et al. 1977), this system incorporates the standard TNM classification as well as tumor depth and tumor grade, which currently is based on the FNCLCC three tiered grading system. While no standardized system currently exists for pediatric NRSTS, the recently completed COG ARST0332 used the sixth edition of the AJCC cancer staging manual.

Prognostic factors associated with survival in pediatric NRSTS have largely been derived from single institution retrospective studies. A series of retrospective analyses from St. Jude Children's Research Hospital (SJCRH) identified three distinct risk groups, including a low risk group with an estimated 89% 5-year survival, an intermediate risk group with a 56% 5-year survival and a high risk group with a 15% 5-year survival (Pappo et al. 1999b; Spunt et al. 1999, 2002). The low risk group consisted of non-metastatic patients with resected, low or high grade, and ≤5 cm tumors, the intermediate group of non-metastatic

patients with resected, high grade and >5 cm tumors, or unresected tumors regardless of grade or size, and the high risk group comprised metastatic patients. An Italian retrospective series generally support these findings, again identifying extent of resection and presence of metastatic disease as adverse risk factors (Ferrari et al. 2005). Further work from this group has refined the concept of tumor size by taking into consideration body surface area as a metric for overall body size in relation tumor size (Ferrari et al. 2009). On the basis of several of these studies and similar reports in adult STS patients (Coindre et al. 1996; Pisters et al. 1996b), the COG derived a risk classification system for pediatric NRSTS which was incorporated into the recently completed large, prospective, multinational study, ARST0332 (Spunt et al. 2014). Importantly, this risk stratification system was validated in a recent review of 941 pediatric and adolescent NRSTS patients within the SEER program between 1988 and 2007 (Waxweiler et al. 2015) (Fig. 4.2).

Histologic subtype impacts prognosis, as outcomes are superior for some pediatric NRSTS (Dillon et al. 1995; Ferrari et al. 2011a). For example, infantile fibrosarcoma, which generally presents in patients younger than 2 years of age and is associated ETV6-NTRK3 translocation, has an excellent prognosis following surgical resection alone, while chemotherapy and a novel targeted tyrosine kinase inhibitor appear to be effective against gross disease (Gadd et al. 2012; Nagasubramanian et al. 2016). On the other hand, NRSTS presenting in older children and adolescents often behave more akin to those in adult patients where current cytotoxic chemotherapy appears less efficacious. Other prognostic factors that have been implicated in adult STS survival include tumor depth of invasion, primary tumor anatomic site, and patient age (Coindre et al. 1996; Kattan et al. 2002; Pisters et al. 1996b), yet these factors have not consistently and independently been identified in the pediatric population.

Factors that influence local tumor control are less clearly defined in the pediatric population. Studies in adults indicate that, in addition to variables that also govern survival including patient age and tumor size, grade and subtype, surgical margin status and recurrent disease are associated with local recurrence risk (Cahlon et al. 2012; Zagars and Ballo 2003). Additionally, extent of resection appears to play a dominant role in determining local recurrence risk in comparison to tumor grade, although within the prospective trial of adult STS of limited size and any histologic

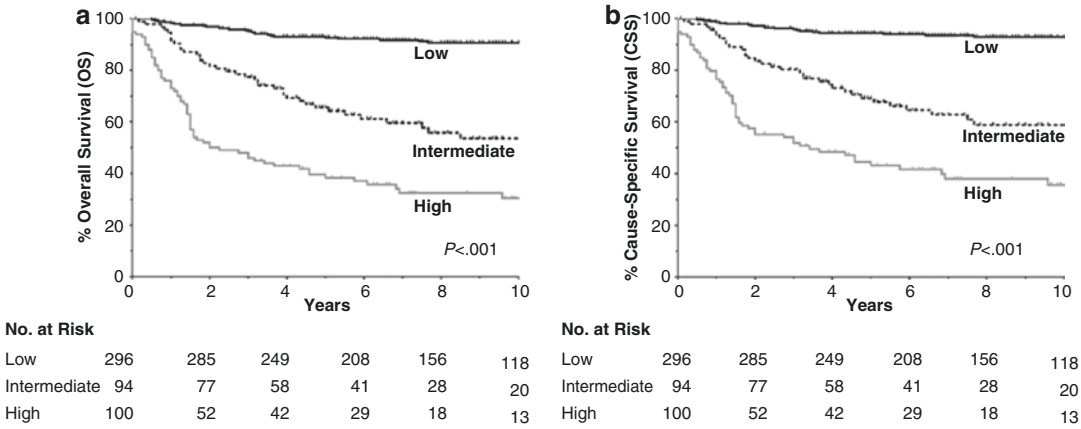

Fig. 4.2 Validation of the Children's Oncology Group (COG) risk stratification of pediatric non-rhabdomyosarcoma soft tissue sarcoma in the Surveillance, Epidemiology and End Results (SEER) program. (**a**) Overall survival. (**b**) Cause-specific survival. *Low risk*: non-metastatic, low or high grade, ≤5 cm, resected; *intermediate risk*: nonmetastatic, high grade, >5 cm, or unresected; *high risk*: metastatic; based on COG ARST0332 protocol. Reprinted with permission "Non-Rhabdomyosarcoma Soft Tissue Sarcomas in Children: A Surveillance, Epidemiology, and End Results Analysis Validating COG Risk Stratifications", Waxweiler et al. 2015; Elsevier publisher. All rights reserved (Waxweiler et al. 2015)

grade following complete resection reported by Pisters et al. (2007), the majority of local recurrences occurred in high-grade tumors. Extent of resection has been clearly implicated in childhood NRSTS as well, with only one-third to one-half of patients without complete resection remaining disease-free (Ferrari et al. 2005, 2011a; Smith et al. 2011b; Spunt et al. 1999, 2002). In a pooled analysis of 304 patients with non-metastatic pediatric NRSTS, omission of surgery or incomplete surgery, as well as tumor subtype, tumor site, tumor size, omission of radiotherapy and limited response to chemotherapy were significantly associated with inferior relapse-free survival on multivariable analysis (Ferrari et al. 2011a). While generally limited to small retrospective series and univariate analysis, additional factors that may influence local control in resected pediatric NRSTS include surgical margin status (Blakely et al. 1999; Smith et al. 2011a), while patient gender and age, and radiotherapy dose have been implicated in patients with unresected disease (Ferrari et al. 2005; Spunt et al. 2002).

4.6 Therapeutic Management

4.6.1 Role of Surgery

Surgical interventions play a key role throughout the management of NRSTS, including tissue biopsy at the time of diagnosis and recurrence, definitive management of disease, combined modality approach (i.e., limb salvage), re-resection of primary tumor, lymph node sampling and dissection, and resection of pulmonary metastatic disease. The role of tissue biopsy has been discussed previously, yet it's worth reiterating the importance of proper biopsy planning to ensure an adequate amount of tissue for diagnosis with minimal disruption of tissue planes in order to limit the extent of tissue excised at the time of definitive surgery. As an example, incisions should be oriented longitudinally on the extremities to allow for wide local excision without significant functional and cosmetic deformities (Andrassy 2002).

Complete surgical resection, when feasible, represents the cornerstone of successful management of NRSTS. These tumors tend to infiltrate in a radial fashion, producing a delicate pseudocapsule of compressed reactive normal tissue closely opposed to microscopic tumor extensions (Gitelis et al. 1989; O'donnell et al. 2014). For this reason the goal of definitive resection is en bloc removal of the tumor and pseudocapsule with adequate margin. A standardized system has been developed to define the surgical staging and margin status of musculoskeletal sarcomas, where an intralesional excision consists of a cut through the tumor with gross or microscopic residual, a marginal resection is through the reactive or inflammatory region adjacent to tumor, a wide excision extends beyond the inflammatory region and a radical excision ranges beyond the anatomic compartment involved by tumor (Enneking et al. 1980). Several studies of both adult and pediatric patients highlight the impact of extent of surgical resection on local control and survival outcomes, and suggest wide local excision with negative margins may provide curative therapy for select tumors (Abbas et al. 1981; Barker et al. 2003; Ben Arush et al. 1999; Hayani et al. 1992; Horowitz et al. 1986; Pisters et al. 2007).

What defines margin adequacy, however, is an area of uncertainty and is often anatomically constrained in the pediatric setting where wide margins are simply unattainable in smaller children. A retrospective adult study of complete surgical resection alone demonstrated a 10-year local control rate of 100% with a surgical margin of >1 cm, yet an impressive 87% in patients with margins <1 cm (Baldini et al. 1999). Yet, in a prospective clinical trial in which adult patients with small extremity and trunk STS of any grade with "no tumor on ink", the cumulative incidence rate of local recurrence at 10 years was 10.6% (Pisters et al. 2007). Several adult practice guidelines have suggested a margin of 1 cm or more may not require adjuvant therapy (Casali and Blay 2010; Kandel et al. 2013). A retrospective report in pediatric NRSTS demonstrated a lower recurrence rate in patients managed with resection alone with margins >1 cm compared to those with closer pathologic margins, and this was true, at least numerically, of patients with low and high grade tumors (Blakely et al. 1999). The recently completed ARST0332 clinical trial defined microscopic surgical margins as "negative" if ≥0.5 cm,

except in cases of resected fascia or periosteum in continuity with the tumor specimen, and should help define the role of resection alone for grossly resected low grade tumors and small, microscopically negative high grade tumors.

In the distant past, amputation served as the primary surgical modality for extremity NRSTS, and in the pediatric setting amputation may still be advocated in very young children where the primary tumor cannot be grossly resected and definitive radiotherapy may result in a non-functional limb with the additional risk of subsequent malignant neoplasms (Spunt et al. 2008). Limb sparing therapy, with the emphasis on preserving the extremity with a satisfactory functional and cosmetic outcome, is generally favored in extremity NRSTS. However, given the difficulty often faced in obtaining clear margins associated with a more radical resection, the majority of limb sparing procedures are performed in conjunction with neoadjuvant or adjuvant radiotherapy. This approach is supported by the landmark randomized study by Rosenberg et al., which demonstrated similar overall survival between amputation and limb-sparing surgery in combination with postoperative radiation in adult patients with high grade extremity STS, albeit with a limited number of patients (Rosenberg et al. 1982). Here again optimal margin width in limb-sparing resection and radiation therapy is controversial. While combination therapy allows for relatively tighter margins within several millimeters, a no tumor on ink approach is generally favored even in the setting of limited surgery and postoperative irradiation (Sadoski et al. 1993).

Non-oncologic resections with concern for microscopic disease are frequently encountered in the adult and pediatric setting. Several reports have revealed a significant proportion of pediatric patients in fact do harbor residual disease following these procedures (Andrassy 2002; Chui et al. 2002), and studies in both populations have suggested improved outcome in patients managed with primary re-excision following unplanned resection (Cecchetto et al. 2001; Giuliano and Eilber 1985; Hays et al. 1989). Further, adult sarcoma management at high volume centers has been shown to be an independent predictor of increased overall survival, highlighting the importance multidisciplinary evaluation and treatment recommendations early in the work-up of soft tissue masses (Gutierrez et al. 2007). Given microscopic residual disease risk following unplanned resection, re-resection is generally recommended and offers the potential to spare adjuvant radiotherapy for select patients who otherwise may be exposed to irradiation.

The incidence of lymph node metastasis in NRSTS as a group is low, ranging from 0% in grade 1 tumors and 12% in grade 3 tumors (Mazeron and Suit 1987; Pappo et al. 1999a). This also varies by histology with rates exceeding 15% documented in epithelioid and clear cell sarcomas in adult studies. Additionally, some studies suggest a significantly elevated rate of regional nodal metastasis in vascular sarcomas, including angiosarcoma and lymphangiosarcoma (Loya et al. 2007; Sherman et al. 2014). While initial studies of synovial sarcoma have suggested high rates of nodal metastasis, more contemporary studies have demonstrated rates less than 5% (Daigeler et al. 2009). Given these findings, lymph node sampling is generally restricted to specific histologic subtypes, while biopsy is employed in patients with clinically suspicious lymph nodes. While this is an evolving field, the utility of sentinel lymph node biopsy in pediatric NRSTS at high risk for lymphatic spread has been reported (Dall'Igna et al. 2014; Kayton et al. 2008; Neville et al. 2000). Optimal management of patients with pathologically confirmed lymph node metastasis is unknown given the relative scarcity of these cases, yet lymph node dissection generally with adjuvant radiotherapy is most commonly employed.

Distant metastatic spread of NRSTS most frequently involves the lungs. While long term survival is clearly limited in this population, several retrospective reports of both adult and pediatric patients have suggested improved outcome and even long-term survival with surgical resection of lung metastasis (Blackmon et al. 2009; Casson et al. 1992; Jablons et al. 1989; Kim et al. 2011). Factors associated with improved outcome based on multivariable analysis include longer disease free interval from primary diagnosis and metastasectomy, single-sided lung metastasis, negative margins of pulmonary resection, and multiple

operations for recurrent pulmonary metastasis (Blackmon et al. 2009; Kim et al. 2011). While patient selection criteria is not well established, generally candidates include patients with control of their primary tumor without obvious extra pulmonary disease and with adequate lung function. Interestingly, the size and number of pulmonary metastasis in some series has not been associated with outcome, and thus resection should not be discounted in patients with advanced pulmonary involvement (Girard et al. 1997; Reza et al. 2014).

4.6.2 Role of Radiotherapy

The principle role of radiotherapy (RT) in the management of NRSTS is to sterilize microscopic extension of the tumor following surgical resection, and thereby minimize excessive morbidity that more radical surgery, would incur in order to ensure complete resection. More recently, radiotherapy, with or without concurrent chemotherapy, has been utilized in the neoadjuvant setting for bulky tumors in order to improve the quality of surgical resection. Less commonly, radiotherapy is employed in the definitive setting for tumors deemed inoperable with the goal of eradication of gross disease. Whole lung irradiation is not indicated in patients with NRSTS with pulmonary metastasis (Scheer et al. 2016), however, adjuvant focal RT may be recommended in cases where microscopic residual disease is suspected or confirmed following metastasectomy. While several encouraging studies of highly conformal, high dose per fraction stereotactic body radiotherapy (SBRT) have been reported in adult STS patients with limited lung metastasis (Dhakal et al. 2012; Navarria et al. 2015), experience with SBRT in metastatic pediatric sarcoma is limited (Brown et al. 2014).

Within this general framework, indications for RT continue to evolve. With the completion of a limited number of prospective clinical trials specific to pediatric NRSTS, recommendations for RT have been derived largely from adult studies (Ferrari et al. 2015; Pappo et al. 2005; Pratt et al. 1998, 1999; Spunt et al. 2014). However, given the effects of RT on growth, development, fertility and the particular vulnerability to subsequent neoplasms within this population, close attention must be paid to the risk of late effects. This is important in light of the findings of the two landmark randomized trials in adult patients in which the omission of adjuvant radiotherapy in patients with STS did not impact overall survival (Pisters et al. 1996a; Yang et al. 1998). Considerations for RT are currently based on the potential for and extent of (e.g., surgical margin status) resection, tumor characteristics including histology, grade, size, and location, disease course (primary vs. locally recurrent), prior receipt of RT, and patient variables.

From 1986 to 1992, the POG conducted a multi-institutional trial of resected pediatric NRSTS (Pratt et al. 1999). This trial was designed to study the role of adjuvant chemotherapy, and attempt was made to standardize postoperative radiotherapy recommendations to include only patients who underwent marginal resections. Of the 81 eligible patients, 9 patients experienced a local failure. In a subsequent report, analysis of local failure by surgical margin status and histologic grade suggested a higher rate of local failure in patients with high grade disease and marginal resection alone (3/4 patients) compared to patients with low grade disease and marginal resection alone (0/2 patients) (Marcus 1996). Addition of RT to marginal resection was equally effective in patients with low or high grade disease (91% local control).

Spunt and colleagues retrospectively evaluated treatment outcomes and prognostic factors of pediatric NRSTS patients treated at SJCRH from the 1960s to 1990s (Blakely et al. 1999; Pappo et al. 1999b; Spunt et al. 1999, 2002). From these reports, the benefit of post-operative radiotherapy in patients with microscopically negative resections appeared to be restricted to patients with high grade tumors with less than 1 cm pathologic margins, while providing no benefit in low grade tumors (Blakely et al. 1999). For patients with positive surgical margins, including patients with low and high grade tumors, adjuvant RT significantly improved local control (Spunt et al. 1999).

Yet, multivariable analysis of factors prognostic of local recurrence revealed positive surgical margins, intra-abdominal tumor site and omission of RT, while tumor size ≥5 cm and high grade tumors were prognostic for distant recurrence (Spunt et al. 1999). Similar findings suggesting large, high grade tumors are at particular risk for distant metastasis were observed in the retrospective analysis of a large group of pediatric patients with NRSTS from the Instituto Nazionale Tumori, Milan, Italy (Ferrari et al. 2005). Additionally, in a pooled American and European analysis of pediatric patients with nonmetastatic, unresected NRSTS, RT was associated with significantly improved overall survival (Ferrari et al. 2011a).

Two seminal reports in adult patients have reached conflicting results in relation to the impact of tumor grade on local recurrence. The NCI randomized trial of surgery alone vs. surgery and post-operative radiotherapy enrolled 91 patients with high grade tumors who all received adjuvant chemotherapy, and 50 patients with low grade tumors who did not receive chemotherapy (Yang et al. 1998). Adjuvant radiotherapy appeared to benefit patients with both high and low grade tumor with 10 year local recurrences in high grade tumors of 0% with RT vs. 22% without RT and 4% with RT and 33% without RT for low grade tumors. Conversely, a randomized trial from Memorial Sloan-Kettering Cancer Center (MSKCC) failed to demonstrate a local control benefit of adjuvant brachytherapy in patients with low grade disease (n = 45), while patients with high grade tumors (n = 119) appeared to benefit from radiation (5 year local control, 91% with brachytherapy vs. 70% with surgery alone) (Pisters et al. 1996a). These results were supported by a separate randomized trial at MSKCC of 45 patients with low grade extremity and trunk NRSTS randomized to adjuvant brachytherapy or observations, in which no significant difference in local control (~75%) was seen (Pisters et al. 1994). Results of the NCI trial have been questioned given the preponderance of tumors that may in fact have been classified as high grade (Roberts and Halperin 2011). Indeed, as discussed earlier, the prospective clinical trial from MDA evaluating omission of adjuvant radiotherapy in adults with T1 extremity and trunk STS resected with microscopically negative margins suggests patients with high grade disease are most at risk for local recurrence, with 11/12 local failures in patients with high grade disease (Pisters et al. 2007).

Several disease-specific studies of NRSTS commonly found pediatric and young adult patients have examined the role of adjuvant RT and impact of margin status. A report from the Italian and German Soft Tissue Sarcoma Cooperative group of 167 patients with MPNST, 38% of which received radiotherapy, suggested a trend for improved crude local control rates with the addition of RT following R0 resection (17% local recurrence with RT vs. 31% without RT) and progressively worse outcomes with or without RT in patients with R1 resection (45% vs. 60%) and gross disease (54% vs. 60%) (Carli et al. 2005). On the other hand, a pooled analysis from four major research groups of pediatric patients with synovial sarcoma revealed significantly improved 5-year local recurrence-free survival (LRFS) with the addition of adjuvant radiotherapy in patients with gross residual disease, yet not in patients with microscopically involved or free margins (Okcu et al. 2003). In support of these findings, results of a pooled analysis of three prospective studies of young patients with non-metastatic synovial sarcoma through the International Society of Pediatric Oncology Malignant Mesenchymal Tumors (SIOP-MMT), demonstrated a low local failure rate of 16% (3/19) in patients with R0 resections who did not receive RT (Orbach et al. 2011). Margin status appears to impact efficacy of RT as well. A retrospective review of pediatric NRSTS patients treated with surgery and RT at the University of Florida from 1973 to 2007 demonstrated the importance of complete microscopic resection (Smith et al. 2011a). Five-year overall local failure was 12% for the 95 pediatric and young adult patients, with a local recurrence rate of 6% for patients with negative margins compared to 27% for patients with close (<1 cm) or positive margins.

Preoperative RT, with or without chemotherapy, is employed most commonly in patients with initially unresectable disease, with the goal of

cytoreduction to permit limb or organ-sparing resection. Given distinct potential advantages, however, preoperative RT is often used even in patients with disease initially deemed resectable. Theoretical advantages of neoadjuvant RT include enhanced RT efficacy in well perfused, non-disturbed tumor, prevention of tumor seeding during surgery and lower risk of subsequent malignant neoplasms and other late effects with the associated smaller irradiated volumes (exclusion of surgically manipulated tissues, incisions, and drain sites) and lower radiation doses used in the neoadjuvant setting. Additionally, much of the irradiated tissue ultimately is resected and may further reduce certain other soft tissue late effects risks. Based on the Canadian randomized phase III study in adult patients with extremity STS comparing preoperative vs. postoperative RT, advantages of preoperative RT may include improved limb functionality with reduced tissue fibrosis, extremity lymphedema, and joint stiffness, although these effects were not statistically significant (Davis et al. 2005). Conversely, wound complications were significantly increased in patients treated with preoperative radiotherapy (Davis et al. 2002; O'sullivan et al. 2002). While differences in these late effects by RT sequence did not meet statistical significance, arguments have been made that these effects are generally permanently limiting while early effects of increased wound complications may be treated curatively. Importantly, RT field size was predictive of greater rates of fibrosis and joint stiffness, with a trend toward greater risk of edema (Davis et al. 2005).

Synthesis of much of the above data has led to the development of the current COG risk-based treatment strategy, which was employed in the first large scale clinical trial for pediatric NRSTS in the US, COG ARST0332 (Fig. 4.3). This trial ran from 2007 to 2012 and enrolled approximately

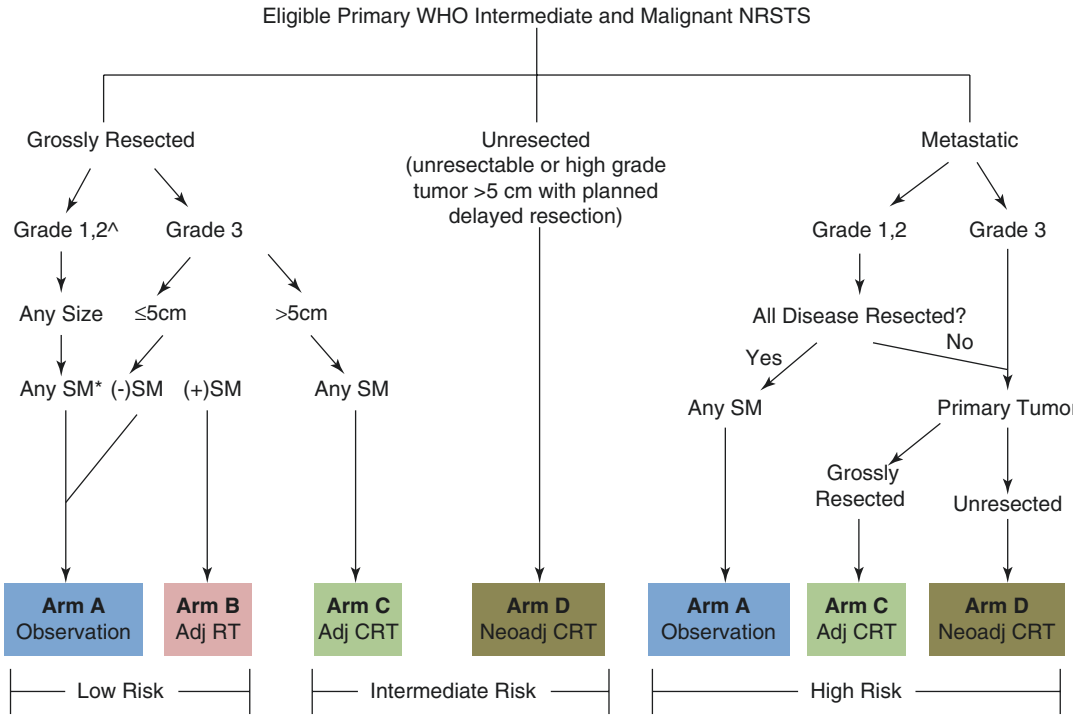

Fig. 4.3 Experimental design schema for Children's Oncology Group ARST0332 clinical protocol, "Risk-based treatment for non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) in patients under 30 years of age." ^Tumor Grade based on the Pediatric Oncology Group (POG) classification system. #Surgical margin status defined as the presence of a cuff of non-malignant tissue measuring at least 5 mm in all directions surrounding the tumor in the operative specimen. When tumor abuts fascia or periosteum and the fascia or periosteum is remove in continuity with the tumor specimen, this margin is also considered negative. *WHO* World Health Organization, *SM* surgical margin, *Adj* adjuvant, *RT* radiation therapy, *CRT* chemoradiation, *Neoadj* neoadjuvant ("Used with permission, © Children's Oncology Group")

600 patients under the age of 30 with primary NRSTS. A major objective of this trial was to restrict the use and minimize the dose of RT with hopes of decreasing long term morbidity. Early results, reported in abstract form, show an estimated 3-year event free survival (EFS) of 91% in Arm A patients, 79% in Arm B, 68% Arm C, and 52% in Arm D, which appear similar to or slightly better than historical controls (Spunt et al. 2014). Contemporaneously, the European Soft Tissue Sarcoma Group (EpSSG) initiated the NRSTS 2005 clinical trial which included a trial for synovial sarcoma, a trial for "adult-type" NRSTS, and treatment guidelines for other rare pediatric STS subtypes (Ferrari et al. 2005). The synovial sarcoma trial, which ran from 2005 to 2012, included 138 patients less than 21 years of age with non-metastatic disease and included risk based multimodality therapy (Ferrari et al. 2015). Low risk (IRS group I, ≤5 cm tumor size) patients were treated with surgery alone, intermediate risk (IRS group I, >5 cm, and all IRS group II) patients were treated with 3–6 course of chemotherapy with or without RT, and high risk (all IRS group III, any N1 tumor, or any axial site tumor—head and neck, trunk, lung-pleura, retroperitoneum) patients were treated with 6 courses of chemotherapy, delayed surgery when feasible and RT following 3 cycles of chemotherapy. Estimated 3-year EFS in low, intermediate and high risk was 92%, 91% and 78%, respectively. While no definitive conclusions can be made regarding the role of RT, only 2/24 low risk patients recurred, both locally and both in second remission at last analysis, and there were no local relapses in the 13 patients with completely resected tumors >5 cm managed with surgery and chemotherapy alone.

Most recently, the COG and NRG have partnered to develop the ongoing ARST1321 protocol (Fig. 4.4), a phase II/III randomized trial of

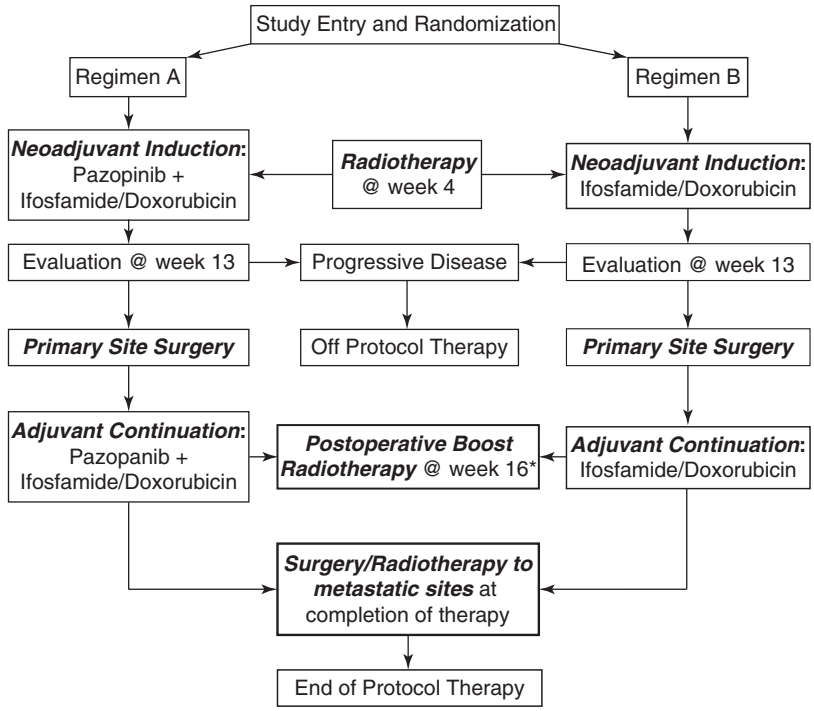

Fig. 4.4 Experimental design schema for Children's Oncology Group/NRG oncology (National Surgical Adjuvant Breast and Bowel Project (NSABP), Radiation Oncology Therapy Oncology Group (RTOG), and Gynecologic Oncology Group (GOG)) efficacy phase of the chemotherapy cohort of the clinical protocol ARST1321, "Pazopanib Neoadjuvant Trial in Non-rhabdomyosarcoma soft tissue sarcoma (PAZNTIS): A phase II/III randomized trial of preoperative chemoradiation or preoperative radiation plus or minus Pazopanib" ("Used with permission, © Children's Oncology Group.") *Postoperative boost radiotherapy is required for gross residual disease and optional for positive margins (tumor on ink)

preoperative chemoradiation or preoperative RT with or without pazopanib, a multitarget tyrosine kinase inhibitor, across both pediatric and adult NRSTS of the extremity and trunk. The study, opened in 2014, will evaluate the use of neoadjuvant RT with MRI-based target delineation and consensus clinical target volume definitions as well as image guided RT (IGRT) to ensure accurate and reproducible RT delivery, replicating metrics studied in RTOG 0630 (discussed below). Additionally, a primary objective of this trial is to evaluate the correlation of pathologic complete response (pCR), defined as >90% tumor necrosis, within the various treatment arms and survival outcomes. Several retrospective studies of primarily adult patients have suggested pCR following neoadjuvant chemoradiation in extremity STS is prognostic of local control and freedom from distant metastasis as well as overall survival (Eilber et al. 2001; Macdermed et al. 2010), although this has not been consistently observed (Mullen et al. 2014).

Radiation dose and volume as a general rule have been lower and smaller, respectively, in the pediatric population given understandable concerns over late effects (Donaldson 1993). In the adult STS setting, patients with high grade completely resected tumors are often treated to a dose of 60 Gy (Mundt et al. 1995), while doses in excess of 64 Gy are recommended for patients with microscopic residual disease (Zagars and Ballo 2003), and doses of 66 Gy to greater than 70 Gy are delivered for gross residual disease (Tepper and Suit 1985). Less is known about optimal dose regimens in pediatric patients, particularly what minimum dose is required for effective local control in patients with microscopic residual disease. While doses as low as 40 Gy have shown some adjuvant local control benefit, a substantial number of local recurrences were observed in a cohort of children with microscopic residual NRSTS (Raney et al. 1979, 1987). On the other hand, given apparent dose response relationship with second malignancy risk with excessive risk observed with doses in excess of 60 Gy in several pediatric cancers (Hawkins 1990; Kuttesch et al. 1996), there is reluctance in using the higher doses employed in adults. Data from the University of Florida and Boston Children's Hospital suggests adequate local control of pediatric NRSTS with adjuvant doses of 54 Gy (Marcus et al. 1997; Marcus 1996). Doses employed in POG 8653 were age and disease extent dependent: R1 patients received 45 Gy if <6 years old and 50 Gy if older, potentially resectable R2 patients received preoperative dose of 55 Gy if <6 years old and 65 Gy if older (Pratt et al. 1999). Based on unpublished data from POG 8653 and data from SJCRH (Spunt et al. 1999) suggesting adequate local control with doses >55 Gy, as well as was historical experience with Ewing sarcoma, ARST0332 used an adjuvant radiotherapy dose of 55.8 Gy. Neoadjuvant doses in pediatric patients is similar to that used in the adult setting, generally between 45 and 50 Gy depending on the use of concurrent chemotherapy (O'sullivan et al. 2002). For patients with residual disease following neoadjuvant (chemo) radiation and surgery, postoperative "boost" RT is recommended. In adults this boost dose generally is 15–20 Gy to achieve doses >64 Gy, while an additional dose of 10.8 Gy (total dose of 55.8 Gy) was given in ARST0332. Durable local control with definitive RT for unresectable NRSTS in adults is thought to require doses in excess of 66 Gy, and even with this outcome is poor with only 30% of patients without local progression with long term follow-up (Kepka et al. 2005; Tepper and Suit 1985). A review of outcomes from the University of Florida of pediatric patients with unresected NRSTS treated with definitive RT showed a 40% 5-year local control rate with a median dose of 55.2 Gy (45–76.8 Gy). A definitive dose of 64.8 Gy was used in ARST0332. RT doses are slightly different from ARST0332 in the ongoing ARST1321: patients enrolled in the non-chemotherapy arm are treated to 50 Gy preoperatively, with potential boosts to 16 Gy and 20 Gy for microscopic and gross residual disease, respectively, and those in the chemotherapy arm are to receive 45 Gy preoperatively with potential boosts of 16.2 Gy and 21.6 Gy for microscopic and gross residual disease, respectively.

Given the longitudinal route of tumor spread along but not across muscle groups in extremity

STS, proximal and distal clinical target volumes (CTV) designed to capture microscopic disease have been substantial while radial margins more constrained. Historically in adult STS patients this has included approximately 4–5 cm longitudinal and 1.5–2 cm radial margins. This has traditionally been followed by a cone down, or a reduction in longitudinal ± radial margins, after the initial 45–50 Gy. Yet with the incorporation of IGRT and improved immobilization, investigations into smaller CTV volumes are ongoing. With the recent publication of RTOG-0630, a phase II trial of neoadjuvant (chemo) RT of adult extremity NRSTS, which demonstrated a significant reduction of late toxicities with IGRT and reduced target volumes in the absence of elevated marginal recurrences, early reports are encouraging (Wang et al. 2015). Margins used beyond the gross tumor volume (GTV) included a 2 cm longitudinal and 1 cm radial for low grade tumors or tumors less than 8 cm, and 3 cm longitudinal and 1.5 cm radial for intermediate or high grade tumors ≥8 cm; a 0.5 mm planning target volume (PTV) encompassed the CTV for all patients. It is important to highlight the advanced target delineation employed on this trial in which pretreatment MRI and planning CT scans were coregistered and gross disease defined based on consensus guidelines, and the daily IGRT using a variety of imaging modalities (Bahig et al. 2013). Reduced target volumes have been explored in the pediatric setting as well, without apparent detriment to local control. A prospective study from SJCRH with limited CTV margins of 2 cm that did not specifically target the initial surgical incision demonstrated an overall 3-year cumulative local failure of 12.5% in a total of 32 pediatric patients with NRSTS (Krasin et al. 2010). When limited to patients with negative surgical margins, no local failures were observed, while cumulative local failure incidence in patients with positive margins was 6.7%. The majority of patients (27) were treated with adjuvant RT, while 5 patients were treated with definitive RT. A similar limited margin approach was incorporated in ARST0332, in which a 1.5 cm CTV was to encompass initially infiltrated tissue in patients with resected disease or the initial tumor volume prior to chemotherapy in patients irradiated preoperatively. The concept of shrinking RT fields was also employed where target volume reduction was to occur after completion of 45 Gy of the initial RT field.

Regardless of margin size, it is important to minimize dose to critical structures. In extremity tumors this generally involves sparing a longitudinal strip of skin and subcutaneous tissue to minimize lymphedema risk, limiting high dose across the full joint space to minimize functional limitations, and limiting dose to weight bearing bone to reduce fracture risk (Wolden 2005; Dickie et al. 2009). Additionally, in the pediatric setting, an appreciation of bone age and growth plate location is critical to RT planning, although it is generally considered more optimal to cover an entire growth plate and shorten a limb rather than spare a portion and angulate the limb if tumor extent demands coverage (Roberts and Halperin 2011). While the role of radiotherapy in the management of adult retroperitoneal STS remains undefined (Cheng et al. 2016), preoperative RT is generally favored for intermediate to high grade tumors out of concern for significant toxicity with adjuvant RT. Attempts at reduced target volumes have been made here as well, with an innovative clinical study utilizing a preoperative CTV limited to the area of tumor-posterior abdominal wall contact thought to be most at risk of residual disease following resection. Within this small cohort, acute toxicity was acceptable and all patients underwent successful resection with encouraging local control on short-term follow-up (Bossi et al. 2007).

RT delivery techniques have advanced from conventional 3D conformal (3DCRT) to now more commonly used intensity modulated RT (IMRT), although tumor specific conformations may facilitate use of 3DCRT more optimally and avoid more extensive low dose exposure often associated with IMRT. However, the ability to maximize conformality to sculpt dose around the tumor/normal tissue interface afforded by IMRT helps minimizes high dose normal tissue exposure while allowing for adequate target coverage. Additionally, while retrospective in nature, there is suggestion in the adult literature that IMRT

may result in significant reduction in local recurrence compared with conventional EBRT for primary NRSTS of the extremities (Folkert et al. 2014a). Further technical advances of external beam RT (EBRT) including helical tomotherapy and volumetric modulated arc therapy (VMAT) may facilitate additional enhanced conformality, however, experience in the NRSTS population is limited (Fogliata et al. 2013; Liu et al. 2016). Particle therapy, with attendant dosimetric advantages and radiobiologic advantages seen specifically with heavy charged particles, represents an alternative to photon-based EBRT. Mature results of proton therapy in pediatric NRSTS are lacking, however, proton therapy was permitted in ARST0332 and results will be examined. Additionally, a single arm, single institution phase II trial of proton therapy for pediatric bone and NRSTS aimed at measuring acute and late toxicities and local control is ongoing through Massachusetts General Hospital (Yock 2007). Studies of neutron and carbon ion therapy that have included adult patients with STS have also been reported, with promising tumor control yet concerns remain regarding late toxicity risks (Jingu et al. 2012; Kamada et al. 2002; Laramore et al. 1989).

While EBRT remains the most common form of RT used to treat NRSTS, intraoperative techniques including interstitial or intracavitary brachytherapy and intraoperative RT (IORT) continue to be utilized. Potential advantages to these techniques include enhanced radiobiologic effectiveness with high dose over a single to few days, enhanced normal tissue sparing and tumor coverage, non-targeting of surgical scar and drain sites and lack of additional irradiated margin, and patient convenience and cost. Intraoperative forms of RT can be utilized as components of the boost phase or as definitive irradiation. Several reports of brachytherapy in pediatric STS, including rhabdomyosarcoma and NRSTS, suggest excellent local control and acceptable toxicity, which is most often related to wound complications (Merchant et al. 2000b; Nag et al. 1997; Viani et al. 2008). IORT, generally involving either linear accelerator generated electrons collimated with defined cones or flexible applicators with high dose rate iridium-192 source, have also been used in the pediatric STS setting with encouraging results (Folkert et al. 2014b; Sole et al. 2014, 2015). Finally, while experience is largely lacking in children, hyperthermia, in combination with chemotherapy or radiotherapy, may represent an additional armamentarium in the treatment of pediatric NRSTS. Retrospective review of the MDA experience of surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in 26 children and young adults with desmoplastic small round cell tumor suggested improved outcomes in completely or microscopically resected patients compared to those with gross residual disease (Hayes-Jordan et al. 2014).

4.6.3 Role of Chemotherapy

The role of chemotherapy in both pediatric and adult NRSTS remains controversial, as it is unclear currently whether chemotherapy provides a survival benefit in children and results are conflicting in adults. Its use stems from the fact that there is a significant risk of distant metastatic disease for localized large, high grade lesions and local recurrence is not insignificant even with adjuvant RT for high grade tumors. Additionally, in the pediatric setting chemotherapy has demonstrated success in related sarcomas including osteosarcoma, rhabdomyosarcoma and Ewing sarcoma. Despite this NRSTS as a whole appear to be relatively chemoinsensitive, with response rates to conventional cytotoxic therapy hovering around 30–40% both in children and adults (Antman et al. 1993; Pappo et al. 2005). Additionally, agents which provide this response rate, namely doxorubicin and ifosfamide, carry considerable toxicity.

At least 18 clinical trials completed over four decades have examined the impact of chemotherapy in the adjuvant setting, with the majority of these conducted in adults. These trials have included single agent vs. observation, comparisons of single agents and comparisons of multiagents, and yet most appear equivocal regarding the benefit of adjuvant systemic therapy. These results have been pooled into several meta-analyses.

Initially published in 1997, the Sarcoma Meta-Analysis Collaboration (SMAC) included 14 randomized clinical trials conducted in the 1970s and 1980s comparing local therapy alone vs. local therapy and chemotherapy (1). While the addition of adjuvant chemotherapy did significantly extend time to local and distant failure and disease free survival was improved, there was no effect on overall survival. Approximately one-half of patients received adjuvant RT and two-thirds of patients had high grade disease. Tumor characteristics, including primary site, histology, size, and grade did not influence survival and various combination chemotherapy added to doxorubicin failed to show additional benefit. Importantly only a single trial in this initial analysis included the addition of ifosfamide. An updated meta-analysis in 2008 helped address this point with the inclusion of five trials where ifosfamide was combined with an anthracycline (Pervaiz et al. 2008). This update confirmed the previous meta-analysis findings of significant reductions in local and distant relapse, yet also showed a small but significant improvement in overall survival with the addition of chemotherapy, with an absolute risk reduction of death of 6%. Of note, overall survival was not improved with doxorubicin alone, while significant improvements were observed when combined with ifosfamide. Caveats to the latter analysis include the fact that patient level data was not used and it did not include two large EORTC randomized trials of adjuvant chemotherapy vs. observation (Bramwell et al. 1994; Woll et al. 2012), which individually were negative and the pooled analysis of which showed no improvement in recurrence free survival in the adolescent and young adult subset of patients (Kasper et al. 2013). Despite the fact that no differences in outcomes were observed by histology within the first meta-analysis, there is limited prospective and retrospective data that suggests that adult patients with synovial sarcoma may derive an overall survival advantage with ifosfamide-containing regimens (Eilber et al. 2007; Ferrari et al. 2004; Rosen et al. 1994).

The impact of chemotherapy in adult patients with locally advanced or metastatic disease is even less clearly defined. Long term survival in patients with metastatic disease is infrequent and generally restricted to completely resected patients, with a debatable influence of chemotherapy (Spunt et al. 2008). That said, there is retrospective data to suggest that a sizable number of patients with locally advanced and metastatic disease may derive significant clinical benefit, defined as an objective response or stable disease lasting ≥6 months, from chemotherapy despite a lack of a clear survival advantage (Karavasilis et al. 2008). The most straightforward indication for chemotherapy in patients with locally advanced disease is some form of cytoreduction and tumor shrinkage to facilitate oncologic resection, with several reports of neoadjuvant chemoradiation in adult patients suggesting improved response rate and outcome in these high risk patients (Kraybill et al. 2010; Mullen et al. 2012; Toma et al. 2003). Long term results of RTOG 9514, a multicenter single arm trial of preoperative mesna, Adriamycin, ifosfamide and dacarbazine (MAID) with interdigitating RT in 66 adult patients with primary or locally recurrent high-grade STS ≥8 cm in diameter, demonstrated estimated 5-year disease-free, distant disease-free and overall survival of 56%, 64% and 71%, respectively, higher than would be expected in this high risk population (Kraybill et al. 2010). However, toxicity was significant with 78% of patients with grade 4 hematologic toxicity and three treatment related fatalities (Kraybill et al. 2006). Most single agents tested in adult high risk STS patients have a response rate less than 30%, including the mainstay agent doxorubicin and several alkylating agents including dacarbazine, cyclophosphamide, temozolomide, and ifosfamide (Spunt et al. 2015). Although conflicting reports exist, several studies do not support dose intensification, either as single agent or in combination with other agents (Le Cesne et al. 2000; Lorigan et al. 2007; Worden et al. 2005). Multiagent regimens have generally demonstrated enhanced response rates compared to single agent regimens, yet are accompanied with increased toxicity and few studies have shown a survival benefit (Judson et al. 2014). Non-randomized studies of regional chemotherapy, in

the form of isolated limb perfusion (Gutman et al. 1997) and isolated limb infusion (Hegazy et al. 2007), and the recently completed EORTC 62961 phase III randomized trial of chemotherapy with or without regional hyperthermia (Issels et al. 2010) have demonstrated encouraging results in high risk patients, however, expertise is limited, and these procedures are not in widespread use in the US.

Studies exploring the role of chemotherapy in pediatric patients with NRSTS are limited, and for ease of review can be broadly divided between those conducted through US and European collaborative groups. Two studies led through the Pediatric Oncology Group in the US were run from the mid-1980s to the early 1990s and enrolled patients younger than age 21 with STS excluding rhabdomyosarcoma, extraosseous Ewing sarcoma or undifferentiated round cell sarcoma. POG 8653 attempted to randomize patients with surgically resected tumors (with RT for patients with microscopic residual) to adjuvant chemotherapy consisting of vincristine, doxorubicin, cyclophosphamide, and dactinomycin (VACA) or observation (Pratt et al. 1999). Of the 81 eligible patients, only 30 accepted randomization and estimated 5-year EFS and overall survival (OS) were significantly worse within this subset of patients who received adjuvant chemotherapy. After stratification by tumor grade, however, this inferior outcome was no longer observed. Despite the imbalance in high grade tumors within the chemotherapy group, these results suggest that adjuvant chemotherapy, in the schedule and dosing delivered, had no discernable impact on survival. POG 8654 enrolled 75 patients with metastatic NRSTS, locally persistent gross residual disease after resection and RT, and chemotherapy-naïve recurrent NRSTS (Pratt et al. 1998). Randomization of the 61 eligible patients was to the chemotherapy regimen used in POG 8653 or VACA plus dacarbazine. The addition of dacarbazine failed to improve either response rate or 4-year EFS. The follow-up study to this was POG 9553, a phase II trial which ran from 1996 to 2000 and included 39 patients with unresected or metastatic NRSTS (Pappo et al. 2005). Patients were treated with neoadjuvant vincristine, doxorubicin, ifosfamide and mesna with granulocyte colony-stimulating factor support followed by RT with or without surgical resection. The combined partial and complete response rate was 41% and the estimated 3-year PFS and OS was 43.6% and 59%, respectively. Patients with unresectable disease fared better than those with metastatic disease and the objective response rate was higher in patients with synovial sarcoma. As previously discussed the recently completed COG ARST0332 built on these prior experiences and employed the combination ifosfamide and doxorubicin systemic regimen in patients with intermediate and high risk disease. Patients were generally treated with a chemoradiation regimen, either in the adjuvant or neoadjuvant setting, consisting of 6 cycles of ifosfamide (9 g/m^2/cycle) and 5 cycles of doxorubicin (75 mg/m^2/cycle) with RT starting at the start of the second cycle. Preliminary results are encouraging, yet we await more mature results from this important study in the very near future. The therapeutic approach used in the ongoing ARST1321 employs a similar systemic therapy regimen and dosing, with or without the addition of pazopanib.

Many of the studies in Europe have included patients with both rhabdomyosarcoma and non-rhabdomyosarcomas. A study led through the German soft tissue sarcoma study, CWS-91, included both tumor groups, yet was restricted to patients with localized disease (Dantonello et al. 2009). Following risk adapted therapy with resection, hyperfractionated RT and chemotherapy, the 5-year EFS and OS was 84% and 90%, respectively, in patients with synovial sarcoma. Three protocols involving pediatric NRSTS treated with systemic therapy have been conducted through SIOP: MMT84, MMT89 and MMT95 (Flamant et al. 1998; Orbach et al. 2011). As discussed earlier, pooled analysis of these prospective studies of young patients with non-metastatic synovial sarcoma has been reported, with an estimated 5-year EFS of 68% and OS of 85% (Orbach et al. 2011). Following surgery or biopsy, all patients received chemotherapy that varied by study protocol and RT was given to patients with incomplete

response to chemotherapy, with or without delayed surgery. This study also suggested the importance of primary tumor site as a prognostic factor for survival, leading to incorporation of tumor site as a variable in the current European synovial sarcoma risk classification system (Ferrari et al. 2015). With the initiation of the European-wide consortium, EpSSG, in 2000 a second international cooperative group has been established. A pilot study through this collaborative group in patients with metastatic STS (most with rhabdomyosarcoma) demonstrated an encouraging response rate of 76% with combination systemic therapy of ifosfamide, vincristine, actinomycin D and doxorubicin (here referred to as IVADo) (Bisogno et al. 2005). As detailed previously, results of the NRSTS 2005 trial of young patients with synovial sarcoma treated with a nearly identical systemic therapy regimen to that used in ARST0332 has demonstrated encouraging early results, with a 3-year EFS of 91.7% for low-risk patients, 91.2% for intermediate risk, and 74.4% for high risk (Ferrari et al. 2015). Additionally, a separate report from this study detailing outcomes of patients with extra-CNS malignant rhabdoid tumor treated per a defined treatment protocol has also recently been published (Brennan et al. 2016).

Like all of oncology, much is expected from the ongoing molecular studies of NRSTS as a whole and individually that are aimed at defining aberrant signaling pathways responsible for the initiation and maintenance of malignancy in order to open up new and more effective therapeutic avenues. While experience is still limited, particularly in the pediatric setting, results of the PALETTE study which demonstrated significant improvement in PFS in adults with metastatic STS treated with pazopanib following failure of conventional chemotherapy (Van Der Graaf et al. 2012), have paved the way for the initiation of the first large scale targeted therapy trial in pediatric NRSTS patients, COG ARST1321. While it is beyond the scope of this chapter, the reader is referred to additional references highlighting the early experience with molecularly targeted therapies in NRSTS (Demetri et al. 2016; Hong et al. 2014; Maki et al. 2009; Mcarthur et al. 2005; Radaelli et al. 2014; Schoffski et al. 2016; Schwartz et al. 2013; Stacchiotti et al. 2009).

4.6.4 Recurrent Disease

The prognosis of recurrent or refractory NRSTS is generally poor, although in the absence of a completed prospective trial in pediatric patients much remains to be defined in this setting. Management is governed by several factors, including site and extent of recurrence, tumor characteristics such as size, grade and invasiveness, prior therapies and individual patient considerations. Studies in adults and children have demonstrated superior outcome in patients with isolated local recurrence compared to those with metastatic recurrence (Spunt et al. 1999; Zagars et al. 2003). Similar to the upfront setting, resection is the primary therapy for patients with local failure. In the absence of prior receipt of radiation, radiotherapy is generally recommended in the recurrent setting, independent of grade or surgical margin status. However, this must be individualized where for example re-resection alone may be sufficient for infantile fibrosarcoma or other "intermediate, rarely-metastasizing" tumors. Data are conflicting regarding the role of adjuvant re-irradiation in those patients treated initially with conservative surgery and radiation, and significant post-salvage toxicity has been reported in patients treated with re-irradiation (Catton et al. 1996; Indelicato et al. 2009; Torres et al. 2007). Alternative radiotherapy techniques geared towards minimization of normal tissue irradiation, including brachytherapy and intraoperative EBRT, have been used in the re-irradiation setting yet are not as well established in the pediatric population (Calvo et al. 2014; Folkert et al. 2014b; Merchant et al. 2000b; Pearlstone et al. 1999). Conversely, for patients with local recurrence where limb-salvage is contraindicated, due to extent of recurrence and/or prior radiation, amputation may represent the optimal therapeutic approach.

Surgical resection of both new and recurrent pulmonary metastasis may provide prolonged disease control for select patients. Resection of new lung metastasis was associated with improved survival in pediatric and young adult NRSTS patients compared to those who did not undergo this surgical intervention (Smith et al. 2011a). Similar findings were observed in a study of pediatric and adolescent patients with synovial sarcoma and lung metastasis, both at diagnosis and after completion of primary therapy, where patients who underwent pulmonary metastatectomy demonstrated improved survival compared to patients who did not, although the 5-year OS in resected patients was still low at 24% (Stanelle et al. 2013). In adults with recurrent pulmonary metastasis, patients with limited adverse risk factors, including high grade tumor, >3 pulmonary nodules, and nodule size >2 cm, pulmonary metastatectomy significantly prolonged disease-free survival compared to patients with more extensive risk factors (Weiser et al. 2000).

Systemic options for recurrent/progressive disease include gemcitabine/docetaxel (Maki et al. 2007), trabectedin (Garcia-Carbonero et al. 2004), and pazopanib (Van Der Graaf et al. 2012). Given the limitations in the therapeutic options and outcome of recurrent NRSTS, patients should be considered for ongoing clinical trials. The COG STS Committee has not conducted NRSTS-specific trials for relapsed disease, and has instead relied on the COG Developmental Therapeutics Committee for single agent phase II studies that have included NRSTS cohorts (Hawkins et al. 2013). Examples of completed and ongoing COG phase II studies applicable to pediatric NRSTS patients include trabectedin (ADVL0221), ixabepilone (ADVL0524), IMC-A12 (ADVL0821), MLN8237(ADVL0921), and IMGN901 (ADVL1522) (Hawkins et al. 2013). The role of adjuvant immunotherapy following conventional chemotherapy has recently been evaluated in patients with recurrent and/or metastatic NRSTS, with encouraging results in a pilot study using dendritic cell vaccinations (Merchant et al. 2016).

4.7 Late Effects of Treatment

Therapy related effects pertinent to survivors of childhood STS, like all childhood cancer survivors, depend critically on patient age at treatment, body site(s) affected, and therapies received. While NRSTS can occur throughout the body, conceptually significant late effects observed in this patient population may be grouped into organ systems including musculoskeletal, neurologic, vascular, cardiac, genitourinary and reproductive. Importantly, survivors of NRSTS are also at risk for psychosocial complications that have been documented in adult survivors of other childhood cancers, including anxiety and posttraumatic stress and mood disorders (Hudson et al. 2003), as well as issues related to physical inactivity and pain including obesity and cardiovascular dysfunction (Fernandez-Pineda et al. 2016). Finally, while many studies have clearly identified treatment related complications and associated exposures, most studies are observational and cross-sectional or retrospective in nature, generally consist of small cohorts of patients with limited follow-up, are derived from older treatment eras, and are rarely exclusive to NRSTS.

The developing musculoskeletal system of children and adolescents is particularly vulnerable to the effects of local control therapies employed in NRSTS management. Muscle atrophy, resulting from decreased development of major muscle groups, is a clinically evident phenomenon seen following surgery and radiation therapy for sarcoma (Raney et al. 1997). Soft tissue fibrosis and resulting joint dysfunction are related to radiation dose and volume (Davis et al. 2005; Krasin et al. 2012; O'sullivan et al. 2002). Skeletal effects range from bone growth restriction, scoliosis and kyphosis, bone fracture, osteopenia/osteoporosis, and osteonecrosis (Gawade et al. 2014; Kaste et al. 2008; Paulino 2004; Wagner et al. 2001). Hypoplasia of the mandible, the bony orbit, and bones of the appendicular skeleton have been well described following radiation therapy for STS (Jaffe et al. 1984; Raney et al. 2000; Raney et al. 1999). Clinically evident bone growth restrictions in children

treated with conventional radiotherapy are generally seen with doses beyond 20 Gy (Donaldson et al. 1998; Mundt et al. 1995; Silber et al. 1990). Surgical resection, often with the intent of cure while avoiding limp amputation, may result with impaired organ function and unsatisfactory cosmetic outcome (Ness et al. 2009). Neuropathy has been associated with high doses of intraoperative radiotherapy in the management of retroperitoneal soft tissue sarcoma (Sindelar et al. 1993). Lymphovascular complications following limb salvage surgery and radiotherapy include lymphedema (Friedmann et al. 2011). Advances in surgical and radiotherapy techniques hold promise to mitigate the incidence and severity of many of these toxicities, as evidenced by the significant reduction in late toxicities in adult patients with extremity sarcoma treated with IGRT and reduced irradiated target volumes on RTOG-0630 (Wang et al. 2015).

Systemic cytotoxic chemotherapy regimens currently employed in NRTS have potential for significant long term morbidity. Alkylating agents, including cyclophosphamide and ifosfamide, can have significant reproductive effects, including acute gonadal failure, infertility and premature menopause (Kenney et al. 2001; Meistrich et al. 1992; Sklar et al. 2006). These agents are also associated with genitourinary complications, including hemorrhagic cystitis which can lead to fibrosis of the bladder and voiding difficulties (Colvin 1999; Mukhtar and Woodhouse 2010). Ifosfamide use in particular can result in permanent nephrotoxicity, which may result in metabolic bone disease (Oberlin et al. 2009; Stohr et al. 2007). Anthracyclines, including doxorubicin, can cause direct cardiomyopathy and eventual clinical heart failure, with even low doses implicated in long term cardiotoxicity (Van Dalen et al. 2006; Van Der Pal et al. 2012).

The receipt of radiation therapy with or without chemotherapy in the majority of patients with NRST demands a discussion of the risk of subsequent malignant neoplasms (SMN). Survivors of soft tissue sarcoma are over-represented among patients who develop a second malignancy compared to their incidence in the general population (Meadows et al. 2009; Neglia et al. 2001). Subsequent neoplasms most frequently observed in survivors of pediatric sarcoma include breast, thyroid, myelodysplastic syndrome and leukemia, and bone and soft tissue sarcomas (Bhatia et al. 2007; Bhatia and Constine 2010). Treatment related risk factor associated with these SMNs include radiation, alkylating agents and anthracyclines (Henderson et al. 2012; Inskip et al. 2016; Thirman and Larson 1996).

4.8 Desmoids and Aggressive Fibromatosis

4.8.1 Overview

Desmoid tumors are composed of locally invasive fibroblasts which exhibit increased proliferative potential. Desmoid tumors were first described in 1847 as a package or bundle from which the name arises. While benign, and without metastatic potential, these tumors can be disfiguring, lead to functional impairment, or in rare cases result in complications which lead to death.

4.8.2 Epidemiology

Desmoid tumors arise in 2–4 people out of a million individuals each year (Bertario et al. 2001; Reitamo et al. 1986; Goldblum and Fletcher 2002). The age of incidence is bimodal with a peak in the early teens and also later in the 4th–5th decade. Classic risk factors for the adult population, such as high estrogen states and prior trauma, have less relevance in the pediatric population (De Cian et al. 1999; Gansar et al. 1987).

4.8.3 Etiology

Desmoids are associated with well-known clinical syndromes such as Familial Adenomatous Polyposis Syndrome, Gardner's syndrome, Tuberous Sclerosis and are typically defined genetically by mutations along the Wnt pathway (Bertario et al. 2001; Gomez Garcia and Knoers

2009; Kumamoto et al. 2015). Gain-of-function mutations in exon 3 of the CTNNB1 are common and cause nuclear localization of β-catenin with constitutive activation of the Wnt pathway (Lazar et al. 2008).

4.8.4 Histology

Desmoid tumors are a spectrum of disease all with similar histology and include desmoid tumors, infantile myofibromatosis, fibromatosis colli, and digital fibromatosis (Kiel and Suit 1984). Hematoxylin and Eosin staining demonstrates bundles of disorganized muscle fibers intermixed with collagen (Fig. 4.5). Consistent with their etiology, β-catenin frequently localizes within the relatively quiescent nucleus in cells with limited to no mitoses (Coffin and Dehner 1986; Greenberg et al. 1981; Nuyttens et al. 2000; Suit and Spiro 2001).

4.8.5 Presentation

These tumors can arise within the appendages and within the trunk or chest. When arising from the limbs, the tumors may feel like a firm, nodular, painless mass which limits movement/mobility (Weyl Ben Arush et al. 1998). The more deep seated trunk or abdominal lesions may present with abdominal fullness, bowel ischemia, bowel obstruction, constipation or as an incidental finding on imaging (Church 1998).

4.8.6 Treatment

The management of localized desmoids in the absence of diffuse fibromatoses is often site/context specific. In regions where functional impairment is unlikely with complete resection, or where reconstruction following the procedure is possible, surgery is preferred and may be curative (Buitendijk et al. 2005; Faulkner et al. 1995; Melis et al. 2008). In other cases where the extent of disease or location precludes complete excision in a young child, chemotherapy to facilitate response or stave off other local therapies (morbid surgery and/or adjuvant or definitive radiotherapy) is preferred. Typical chemotherapy regimens include vinblastine and methotrexate (Skapek et al. 2007), anthracyclines, DTIC/Temodar (Gega et al. 2006) or vinca-alkaloid containing regimens. More recently, attention has turned to hydroxyurea as a potential therapeutic

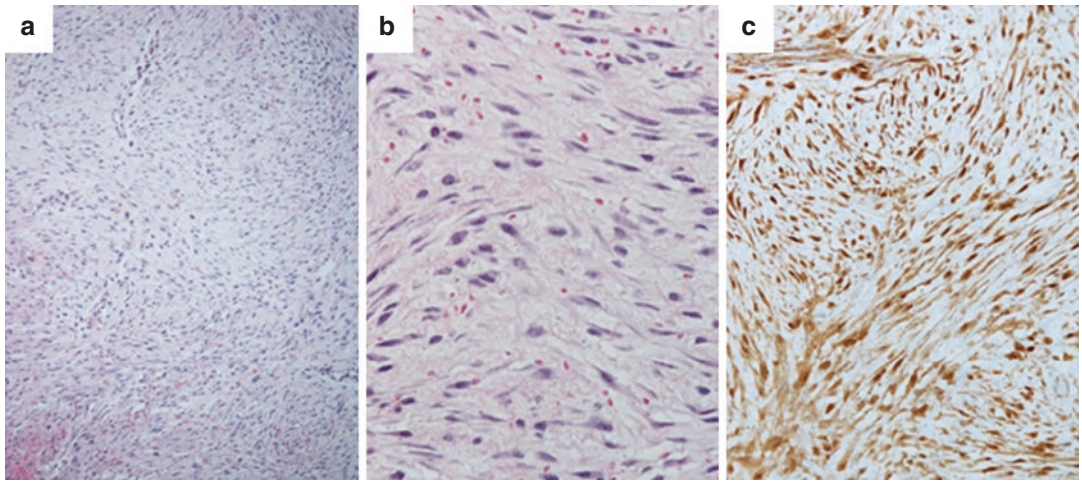

Fig. 4.5 Histopathology of Desmoid tumor. (**a**) Monotonous fascicular proliferation of bland myofibroblasts (Hematoxylin and Eosin, 100×); (**b**) Spindle cells with ill-defined borders, fibrillary cytoplasm and bland nuclei with small nucleoli (Hematoxylin and Eosin, 400×); (**c**) Diffuse nuclear and cytoplasmic positivity for β-catenin (Immunohistochemistry, 200×). Micrographs courtesy of Teresa Santiago

approach given its tolerability as a chronic medication and efficacy in benign connective tissue tumors like meningioma and early reports of acceptable response rates (Bisogno et al. 2013). Hormonal therapy with and without sulindac (Hansmann et al. 2004), assorted and tyrosine kinase inhibitors (Heinrich et al. 2006, 2008; Baker et al. 2004) have shown comparable yet heterogeneous response rates with limited durability. Biologic therapies have also been tried and have shown limited success. Newer therapeutic approaches have focused on more targeted biologically relevant agents such as NCT01265030 which uses an mTOR inhibitor and agents targeting Wnt signaling. Still other trials have resorted to less targeted/so-called "dirty" receptor tyrosine kinase inhibitors like Pazopanib (Italiano 2012). Sequencing and duration of each the systemic options is even less clear, but generally centers on the tolerability of the regimen, hematologic toxicities, stability of the disease on therapy, and risk of continued local progression beyond the progressed extent with each regimen change.

The indication and timing of expected non-surgical local therapy (radiotherapy) is debated but is typically regarded as a last resort (recurrent and definitive cases). Even in the adjuvant setting where positive margins and gross residual disease is present, radiotherapy may be deferred and observation can be considered when the probability of successful re-resection is high or repeat resection and adjuvant radiotherapy at that point is planned (Melis et al. 2008). Patients managed with surgery alone who have positive margins have event free survival (EFS) rates approximating 40–60% (Nuyttens et al. 2000). Residual micro- and macroscopic disease has not been shown to significantly impact relapse free survival in select series (Melis et al. 2008; Soto-Miranda et al. 2013). When the use of radiotherapy is delayed following multiple lines of therapy, local control rates can be poor, with median progression free survival approximating 20 months (Merchant et al. 2000a). Other series which have included both children and young adults have identified a differential effectiveness of radiotherapy based on age which may explain some pediatric series poor results with radiotherapy (Guadagnolo et al. 2008; Rutenberg et al. 2011). While the adult literature has suggested reasonable outcomes with lower doses (Baumert et al. 2007; Keus et al. 2013), subset analyses in the pediatric literature have demonstrated a benefit when >55 Gy is used although it is unclear if this represents an interaction between age and dose (Rutenberg et al. 2011). Treatment volumes are more varied as the pediatric community has not conducted prospective desmoid clinical trials examining the role of radiotherapy, but non-rhabdomyosarcoma soft tissue sarcoma margins are generally considered appropriate. Specifically, a combination of T2 FLAIR and T1 enhancing disease is included with a 2 cm longitudinal and 1 cm radial margin on the edema selectively pulled out of bone and joint spaces (Weiss 2014).

4.9 Osteosarcoma

4.9.1 Overview

Osteosarcoma originates from the bony mesenchyme which yields tumorous osteoid growth emanating from the outer cortex of the bone (Link et al. 1991). It is the most frequent primary bone cancer of children and is managed primarily with surgery and chemotherapy.

4.9.2 Epidemiology

Osteosarcoma has a bimodal distribution but more commonly presents in older children and young adults. Osteosarcoma has an incidence of some 400 cases per year with most cases occurring between the ages of 10–20 years of age. Both males and females are equally affected, however, African Americans are 30% more commonly affected.

4.9.3 Etiology

The most common genetic abnormality is mutation of the Rb gene located on 13q14 (Friend et al. 1986).

Mutations or dysregulation of TP53 is also common (Ladanyi et al. 1993; Overholtzer et al. 2003). The high TP53 mutation prevalence in younger patients is statistically significantly greater than prior reports (Mirabello et al. 2015). Heritable conditions associated with Osteosarcoma include non-spontaneous cases of Retinoblastoma, Li Fraumeni syndrome and Rothmund-Thomson syndrome. Risk factors include prior radiation exposure, Paget's disease in adults, and Li-Fraumeni syndrome (Newton et al. 1991).

4.9.4 Histology

There are many histologic subtypes of osteosarcoma which have differential localization along the bone anatomy. Intramedullary tumors are most commonly the classic high grade variant while small cell, low grade and telangiectatic variants are also occasionally identified. Juxtacortical osteosarcoma can be differentiated from classic osteosarcomas in that they are typically low grade, are common in the popliteal fossa, and uncommonly metastasize and are usually curable with surgery alone. Other histologies include osteoblastic, chondroblastic, and fibroblastic histology. Secondary Osteosarcomas are classified as being associated with Paget's disease of the bone, post-irradiation, or secondary osteosarcomas arising in other skeletal neoplasms.

4.9.5 Presentation

Patients typically present with swelling or pain localized to the knee (appendicular skeleton - most commonly the femur and tibia) and are infrequently metastatic at presentation (Link et al. 1991). Some 80% present with localized disease in the metaphysis of the femur, however, without systemic therapy, many will go on to develop distant metastases most commonly in the lung, bone and bone marrow. Lymph node metastases are infrequent. Clinical exam often reveals that the lesion is firm and fixed with occasional restriction of the adjacent joint.

4.9.6 Diagnosis and Staging

Evaluation usually begins with clinical exam documenting duration, character and location of pain as well as any associated neurologic symptoms. Initial imaging is usually a simple plain film which frequently shows the characteristic appearance of a mixed blastic/lytic region with periosteal thickening, typically referred to as a "sunburst" pattern. This can be differentiated from Ewing sarcoma in that lesions in Osteosarcoma is more commonly localized to the metaphysis, are sclerotic rather than lytic. Additional evaluation should include laboratory evaluation, urinalysis, bone scan, CT of the chest to evaluate for lung metastases, and MRI of the primary region to document any nerve, interosseous, vascular, growth plate or joint involvement. Biopsy of the suspected area should be carried out by the surgeon likely to carry out the oncologic resection and reconstruction to prevent contamination, facilitate resection of the biopsy tract, and limit procedural morbidity. Staging is per the American Joint Committee on Cancer and the Musculoskeletal Tumor Society (Edge et al. 2010; Enneking 1986) (Table 4.4). Laboratory evaluation should include routine labs with the addition of alkaline phosphatase and/or LDH in cases where metastatic disease is suspected. Factors identifiable at diagnosis and staging which portend a poor prognosis include tumors which are >10 cm, extension to two or more adjacent structures, spine/pelvis location, and skip metastases (Link et al. 1986).

4.9.7 Treatment

Neoadjuvant chemotherapy composed of methotrexate, doxorubicin, ifosfamide and cisplatin followed by resection and further adjuvant chemotherapy is the preferred treatment paradigm (Eilber et al. 1987; Link et al. 1986). Adjuvant

chemotherapy improves the relapse free survival at 2 years relative to those who receive surgery alone (Link et al. 1986). Extent of response to neoadjuvant chemotherapy (>90% necrosis) and completeness of resection are key prognostic factors (Bielack et al. 2002; Shukla et al. 2013; Womer et al. 2012). While the percent necrosis is prognostic, it is not predictive of response to subsequent treatment regimens. At the time of local therapy, surgical resection of both the primary and selected metastatic sites should be pursued in order to achieve a minimal residual disease state when possible. Generally, if a complete resection is obtained, the risk of local failure is 3–5%. For patients with localized disease treated with combination surgery and chemotherapy, 5-year survival approximates 65% while for those with metastatic osteosarcoma survival approximates 20%.

Radiotherapy is typically utilized for local therapy in un-resectable cases or scenarios with positive margins, gross residual disease (primary or un-resected lymphatic disease) or palliation. While no primary literature has evaluated the question of whether or not adjuvant radiotherapy for lymphatic disease is warranted, a benefit based on clinical experience is inferred. Typically doses of 55–70 Gy (Delaney et al. 2005) are appropriate pending the amount of residual disease. Patients who forgo resection but receive systemic therapy and local radiotherapy may obtain a 5-year EFS approximating 50–60% (Machak et al. 2003). Heavy particle therapy has been suggested as being potentially beneficial in un-resectable osteosarcoma with local control rates as high as 88% at 5 years for small lesions (Matsunobu et al. 2012). Radionuclide therapy (^{153}Sm-EDTMP) has shown variable success in the treatment of osteosarcoma (Berger et al. 2012; Senthamizhchelvan et al. 2012) and is currently being evaluated in combination with external beam radiotherapy for patients with high risk osteosarcoma (Loeb 2013).

Radiotherapy may have a role in the management of metastatic disease. Specifically, patients with pulmonary metastatic disease only and an un-resectable primary are still likely to benefit from local radiotherapy (Kempf-Bielack et al. 2005) (Fig. 4.6). Management of pulmonary metastatic disease with whole lung or focal radiotherapy is variably used. Treatment whole lung radiotherapy has been employed but is not routinely practiced when used as prophylaxis. Prophylactic whole lung radiation has been studied prospectively but has showed a variable benefit (Burgers et al. 1988).

Table 4.4 Staging of osteosarcomas

AJCC staging (seventh edition)		Musculoskeletal Tumor Society	
T1	Primary tumor <8 cm	Stage 1	Low grade
T2	Primary tumor >8 cm	Stage 2	High grade
T3	Discontinuous tumors in the primary bone site	Stage 3	Distant metastases
N0	No regional lymph node metastases	Notes: A or B is defined according to whether the tumor is intra-compartmental (A) or extra-compartmental (B) Compartmental is defined on the basis of whether or not the tumor extends through the cortex of the bone	
N1	Regional lymph node metastases		
M0	No distant metastases		
M1a	Pulmonary metastases		
M1b	Non-pulmonary metastases		

4.10 Future Directions

Optimal management of children and young adults with NRSTS, desmoid tumor, and osteosarcoma continues to evolve. Given the rarity of these tumors and the extensive array of histologic subtypes, further progress demands large, defined, and timely multi-institutional clinical trials. Initial steps in this regard have been realized for patients with NRSTS and ongoing trials will carry this goal further. We hope to gain further insights into effective therapies and risk stratification which will allow more appropriate selection and application of effective adjuvant therapies. Leading this advancement, major advances in surgical techniques, organ preservation, and new methods in radiation therapy

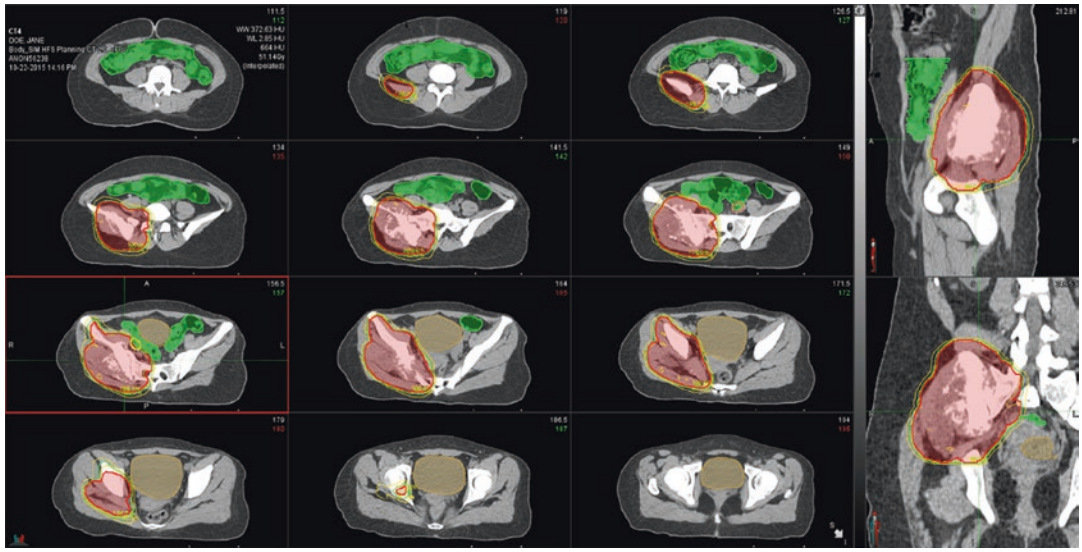

Fig. 4.6 Un-resectable pelvic osteosarcoma in a patient with metastatic disease with an excellent response to initial chemotherapy. The patient received 70 Gy with a two field proton radiotherapy plan

planning, verification, and delivery are critical to maximizing local tumor control and minimizing treatment-related morbidity.

The revolution of molecular oncology will undoubtedly influence the management of soft tissue sarcomas. Leveraging advances in several adult cancers, targeted systemic therapies serve as examples of possible breakthroughs for soft tissue sarcoma. Central to this effort is the ability to obtain tumor tissue and curate pathologic, radiographic, and clinical characteristics across clinical trials to define the incorporation of molecular findings into appropriate risk stratification and treatment schemes. Increasing identification and understanding of underlying germline alterations may also influence disease surveillance and treatment recommendations within this vulnerable population in the years to come.

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Neuroblastoma

5

Joseph Panoff, John Lucas, Luke Pater, and Shefali Gajjar

5.1 Epidemiology and Screening

Approximately 650 cases of neuroblastoma are diagnosed in the United States each year. With an incidence of 10.2 cases per million, it is the most common cancer that arises during the first year of life and the most common extracranial solid malignancy, representing 8–10% of all pediatric malignancies. Neuroblastoma is also responsible for 15% of childhood cancer mortality (Attiyeh et al. 2005; Brodeur 1997; Maris 2010). The median age at diagnosis is 17 months, and the incidence of the disease quickly dissipates with increasing age (Fig. 5.1).

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Attempts have been made to link a variety of factors to increased risk of neuroblastoma. Medications, sex hormones, low birth weight, congenital anomalies, in utero alcohol and tobacco exposures, maternal history of spontaneous abortions, and paternal occupational exposures have all shown weak associations, but often these attempts have been contradicted with no definitive cause proven (Bodeur 1991; Bunin et al. 1990; Johnson and Spitz 1985; Kinney et al. 1980; Kramer et al. 1987; Michalek et al. 1996; Neglia et al. 1988; Schwartzbaum 1992; Spitz and Johnson 1985; Wilkins and Hundley 1990). Familial incidence of neuroblastoma is only 1–2%, with these patients presenting at an earlier age and with bilateral or multifocal disease in approximately 20% of cases.

Japanese, German, and Canadian studies have shown increased detection of neuroblastoma with screening; however, this did not translate into improved outcome. The German study compared 1.4 million children screened at 1 year of age versus a control group of similar size. Most neuroblastomas produce catecholamines, and the catecholamine metabolites vanillylmandelic acid and homovanillic acid can be detected in urine. Therefore, the German group used urinalysis as the mechanism for screening. Consistent with other studies, they detected more cases of neuroblastoma in the screening group; however, the rate of stage-4 disease was similar in the screened and control groups, at 3.7 per million and 3.8 per million, respectively. This translated into

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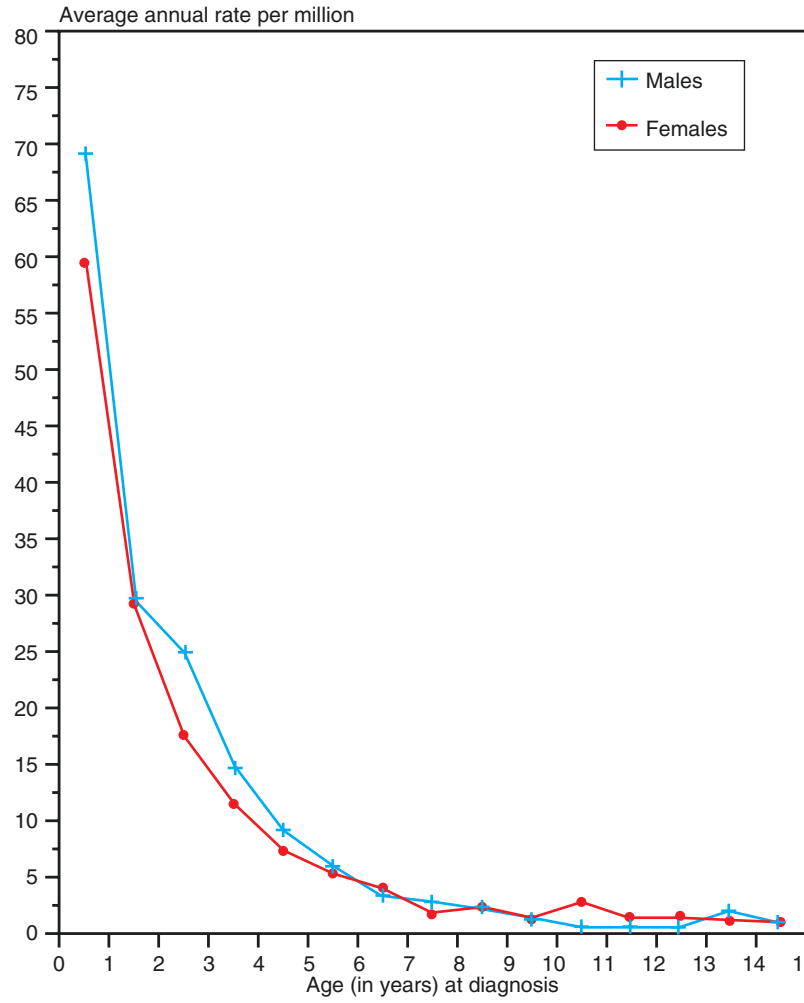

Fig. 5.1 Average annual rate per million people of neuroblastoma according to age and stratified by gender

equivalent mortalities of 1.3 and 1.2 deaths per million, respectively (Schilling et al. 2002; Woods et al. 2002). The results of these studies do not support the screening of infants for neuroblastoma. Many of the anatomically visible lesions in children younger than 18 months spontaneously regress. Therefore, screening this population would result in over diagnosis.

5.2 Biology and Pathology

The cell of origin of neuroblastoma is of sympathetic adrenal lineage and arises from the neural crest, a structure that is present only during embryogenesis. The neural crest gives rise to peripheral neurons, enteric neurons, glia, melanocytes, Schwann cells, and cells of the craniofacial skeleton and adrenal medulla (Anderson and Axel 1986; Anderson et al. 1991; Le Dourin 1999). The cell of origin dictates the relative anatomic incidence of neuroblastoma, and the adrenal gland is the most prevalent primary disease site (Fig. 5.2).

Molecular and genetic studies of neuroblastoma have significantly advanced our understanding of the alterations that cause malignancy, as well as our ability to predict clinical behavior. Alkaline lymphoma phosphatase (*ALK*) and paired-like homeobox (*PHOX2b*) mutations have been discovered in neuroblastoma patients (Mosse et al. 2004, 2008). *ALK* mutations are present in as many as 10% of sporadic neuroblastoma, and an additional 3–4% harbor *ALK* gene amplification. These mutations are more common in the

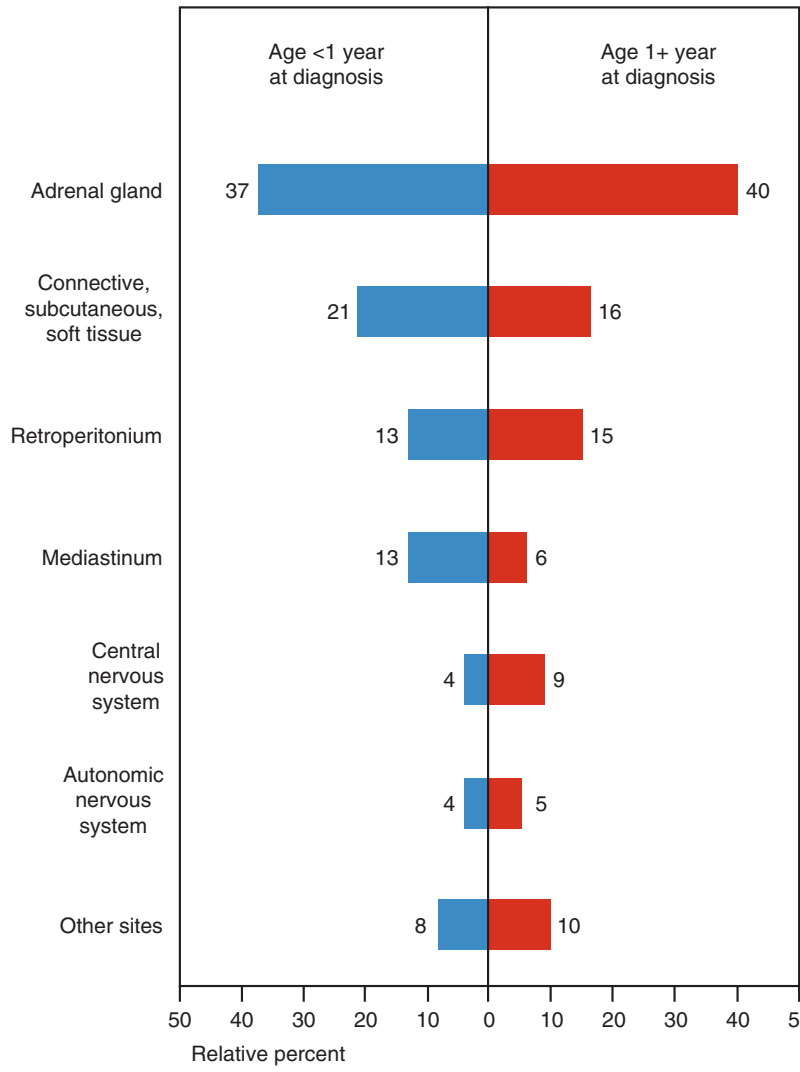

Fig. 5.2 Relative incidence of primary site in neuroblastoma at less than and greater than 1 year of age

high-risk neuroblastoma subgroups and are associated with inferior event-free survival (EFS) and overall survival (OS) (Bresler et al. 2014).

Changes in the *MYCN* gene are the most common genetic alterations in sporadic neuroblastoma, with amplifications occurring in approximately 20% of cases. *MYCN* regulates the proliferation, growth, differentiation, and survival of cells in the developing central nervous system (CNS). Its amplification is also associated with an inferior outcome. Although MYCN's oncologic potential is well known, no active agents that are currently available target the protein; however, upstream targets are being investigated (Chen et al. 2008; Janoueix-Lerosey et al. 2008; Mosse et al. 2008).

High telomerase activity is found in 30% of neuroblastomas at diagnosis and is predictive of poor EFS and OS. Telomerase reverse transcriptase (*TERT*) mutations also have been recently associated with malignancies other than neuroblastoma, most commonly glioma. *TERT* mutations are associated with outcome and may serve as a contributing mechanism for malignant potential and cell survival (Cheung et al. 2012; Eckel-Passow et al. 2015). Chromosomal instability also plays a central role in neuroblastoma. In general, low-risk, intermediate-risk, and stage-4S neuroblastomas have numerical chromosomal gains, whereas high-risk neuroblastomas have intrachromosomal rearrangements (Cheung et al.

2012; Coco et al. 2012; Molenaar et al. 2012). Identified markers of poor prognosis include the loss of 1p (Caron et al. 1996) and/or 11q (Attiyeh et al. 2005) and the gain of 17q (Bown et al. 1999). Chromothripsis, the exact mechanism of which has not been elucidated, is characterized by extensive genomic rearrangements and resultant fluctuating patterns of DNA copy number. Chromothripsis is seen in a small proportion of all cancers and has been identified in 18% of high-risk neuroblastomas (Cheung et al. 2012).

As neural crest cells mature during development, different histologic subtypes of neuroblastoma arise. Ganglioneuromas are the most mature, consisting of ganglion cells and Schwann cells. Ganglioneuroblastomas are intermediaries, histologically and clinically. Neuroblastoma cells are described as small, round blue cells with immunohistochemical positivity for neuron-specific enolase, synaptophysin, and neurofilament. Homer-Wright rosettes are present in approximately 50% of cases. Within the neuroblastoma subtype, Schwannian stroma and differentiation are present in variable amounts (Shimada et al. 1984, 1999).

The currently accepted pathologic classification system for neuroblastoma is the International Pathology Classification (INPC), which was born out of an effort initiated in 1988 and resulted in the formation of the International Neuroblastoma Pathology Committee, which is composed of 6 pathologists, in 1994. The INPC used, with some modifications, the classification scheme first proposed by Shimada et al. (1984). That scheme relied primarily on morphologic changes associated with the maturation sequence. With the addition of age, this histologically derived system is highly prognostic (Table 5.1) (Shimada et al. 1999).

5.3 Clinical Presentation and Evaluation

The clinical presentation of neuroblastoma is extremely variable owing to the wide distribution of anatomic sites, range of ages at diagnosis,

Table 5.1 International Neuroblastoma Pathology Committee (INPC) system (Shimada et al. 1999)

INPC classification system		Original Shimada classification (prognosis)	Prognostic group
Neuroblastoma category	Characteristics		
Favorable	Schwannian stroma–poor	Stroma-poor (favorable)	Favorable
<1.5 years	Poorly differentiated or differentiating and low- or intermediate-MKI tumor		
1.5–5 years	Differentiating and low-MKI tumor		
Unfavorable		Unfavorable	Unfavorable
<1.5 years	Undifferentiated tumor[a]		
1.5–5 years	High-MKI tumor Undifferentiated or poorly differentiated tumor Intermediate- or high-MKI tumor		
>5 years	All tumors		
Ganglioneuroblastoma		Stroma-rich intermixed (favorable)	Favorable
intermixed	Schwannian stroma–rich		
Ganglioneuroma *maturing*	Schwannian stroma–dominant	Well-differentiated (favorable)	Favorable[b]
mature		Ganglioneuroma (favorable)	
Ganglioneuroblastoma *nodular*	Composite schwannian stroma-rich, -dominant, and -poor (schwannian stroma-rich)	Stroma-rich nodular (unfavorable)	Unfavorable[b]

Abbreviation: *MKI* mitosis-karyorrhexis index
[a]Rare subtype, especially in this age group; further investigation and analysis are required
[b]Prognostic grouping for these tumor categories is not related to patient age

and extent of involvement. Head and neck primary sites may result in palpable lesions, Horners syndrome, ocular symptoms, and periorbital ecchymoses. Thoracic involvement can result in airway compromise, pneumonias and dysphagia. Abdominal presentation is most common and can result in bowel or urinary obstruction with associated symptoms. Paraspinal primary sites can produce spinal cord and nerve root compression. Bony metastases are associated with pain and risk of fracture. Constitutional symptoms are common, with anorexia, weight loss, and lethargy often noted. Although rarely, neuroblastoma can be associated with paraneoplastic syndromes related to excessive production of cholamine or vasoactive intestinal peptide. Excess cholamine may manifest as sweating, flushing, and palpitations, and excess vasoactive intestinal peptide may manifest as dehydration, diarrhea, and secondary electrolyte abnormalities. Opsoclonus-myoclonus syndrome has also been observed in neuroblastoma (Chu et al. 2011).

Clinical work-up for neuroblastoma is multifaceted. Primary tumor assessment typically includes computed tomography (CT) and/or magnetic resonance imaging (MRI). MRIs are also useful for assessing spinal canal extension and liver disease status (Brodeur et al. 1993). Surgical resectability, when appropriate, is based largely on this evaluation. Most cases include elevated catecholamine production. This results in detectable metabolites, including vanillylmandelic acid and homovanillic acid (Labrosse et al. 1976). These markers differentiate neuroblastoma from other tumor types during the early stages of workup. Bilateral posterior iliac crest aspirates and biopsies are required for bone marrow evaluation, and relative involvement is important for prognosis. The preferred approach for detecting metastatic disease is ^{123}I-metaiodobenzylguanadine (MIBG) scans (Sharp et al. 2013). Technetium radionuclide bone scan may be used, but this method is less sensitive and less specific. In patients who have MIBG nonavid disease, ^{18}F-fluorodeoxyglucose–labeled positron emission tomography (FDG-PET) is recommended and may be useful for accurate staging (Kushner et al. 2001b). Bone radiography may also detect abnormalities, but it is not a standard of care.

5.4 Staging and Prognostic Factors

Staging of neuroblastoma has evolved over the past few decades. The Evans Staging System, which was published in 1971, formed the foundation for what has been, until recently, a surgically defined staging system (Evans et al. 1971). The most recent risk-group staging system uses the established surgical distinctions, as well as imaging-defined risk factors (IDRFs) (Table 5.2), which are associated with worse survival rates

Table 5.2 Surgical risk factors/image-defined risk factors (IDRFs) (Monclair et al. 2009; Brisse et al. 2011)

Tumor site	Objective IDRFs[a]
Neck	Tumor encasing the vertebral artery Tumor involving other major vessels Tumor encasing the brachial plexus roots Tumor crossing the midline Tumor extending into the thorax Dumbbell tumor[b] Others[c]
Thorax	Tumor encasing the origin and branches of the subclavian vessels Tumor involving other major vessels Lower mediastinal tumor Tumor with abdominal extension Tumor encasing the trachea and/or principal bronchus Dumbbell tumor[b] Others[c]
Abdomen	Tumor infiltrating the porta hepatis Tumor surrounding the origin of coeliac axis Tumor surrounding superior mesenteric artery Tumor encasing the aorta Tumor encasing the vena cava Tumor invading one or both renal pedicles Tumor encasing the iliac vessels Tumor compromising the kidneys or ureters
Pelvis	Tumor crossing the sciatic notch Dumbbell tumor[b] Tumor infiltrating muscle Others[c]

[a]Objective IDRFs are those factors that are unbiased measures. Subjective IDRFs are those factors that are less well-defined, such as tumor size and fragility

[b]Dumbbell tumors refer to tumors with intraspinal tumor extension

[c]Others specifies tumors that infiltrate adjacent organs/structures

and higher rates of surgical complications. The influence of IDRFs on the International Neuroblastoma Risk Group (INRG) Staging System is reflected in Table 5.3. This system takes into account the defined risk factors of age, histologic classification, grade of tumor differentiation, *MYCN* status, 11q-aberration status, and tumor cell ploidy to assign patients to 1 of 4 pretreatment risk groups (Table 5.4), which have substantial outcome variance. In addition, the INRG system serves to standardize risk-group assignment, irrespective of the geographic location of where the diagnosis is made and whether the patient has access to surgical expertise.

As noted above, *MYCN (*Molenaar et al. 2012), 11q aberration (Attiyeh et al. 2005), and DNA ploidy substantially influence clinical outcome. In addition, the histologic categorization, as initially described by Shimada, can further classify tumors with similar presentation and anatomic involvement into different risk categories (Shimada et al. 1984).

IDRFs were first reported in the LNESG1 European study in 2005 and subsequently further expanded (Cecchetto et al. 2005). Most recently, the LNESG1 study demonstrated that in localized neuroblastoma, patients with L1-stage disease have a 5-year EFS of 92% and OS of 98%, and those with L2-stage disease have worse EFS and OS (79% and 89%, respectively) (Monclair et al. 2015). The difference in survival of these two groups was statistically significant, and the difference in stage was based on the presence of IDRFs (Monclair et al. 2015).

Table 5.3 International Neuroblastoma Risk Group (INRG) staging system (Monclair et al. 2009)

INRG stage	Description
L1	Localized tumor not involving vital structures, as defined by the list of IDRFs and confined to 1 body compartment
L2	Locoregional tumor with the presence of 1 or more IDRFs
M	Distant metastatic disease, except stage MS
MS	Metastatic disease in children younger than 18 months with metastases confined to the skin, liver, or bone marrow

Abbreviation: *IDRF* image-defined risk factors

5.5 Very Low-, Low-, and Intermediate-Risk Disease

Very low–risk neuroblastoma, per INRG staging, can be managed with observation due to the tumors' high propensity for spontaneous regression or differentiation into benign ganglioneuroma. Patients with very low–risk disease have an excellent prognosis (EFS and OS of 97.7% and 100%, respectively) (Nuchtern et al. 2012). Some patients with stage-4 s disease, generally those younger than 3 months, may require interventions to relieve symptoms secondary to rapid growth of tumors that often arise within the liver. Symptoms may include cardiorespiratory failure. Chemotherapy and/or radiotherapy may be needed to temporarily limit disease progression and resultant respiratory cardiopulmonary compromise, with radiation preferred for patients with rapid progression or those who have incomplete responses to chemotherapy (Baker et al. 2010). Low-dose radiation (4.5 Gy in 3 fractions) is generally sufficient. Long-term morbidity is limited but can include periportal fibrosis, with normal liver function tests at low doses of radiation and focal nodular hyperplasia at higher doses; thus, long-term surveillance with liver function tests is recommended if radiation doses larger than 20 Gy are delivered (French et al. 2012). Patients with persistently elevated liver function tests should undergo serologic tests for hepatitis and be referred to a gastroenterologist. Patients with stage-4 s disease have an excellent prognosis with an OS of 92%, even with limited intervention (Nickerson et al. 2000).

Low-risk neuroblastoma is treated with surgery alone. Adjuvant radiotherapy or chemotherapy is not typically required, even after incomplete surgical resections, and is reserved for progressive or recurrent disease (Perez et al. 2000). Intermediate-risk neuroblastoma can generally be managed with surgical resection in combination with 4–8 months of multidrug chemotherapy; the sequence of treatments is

Table 5.4 International Neuroblastoma Risk Group (INRG) pretreatment classification scheme (Monclair et al. 2009)

INRG stage	Age (mos)	Histologic category	Grade of tumor differentiation	*MYCN*	11q aberration	Ploidy	Pretreatment risk group
L1/L2		GN maturing, GNB intermixed					A (very low)
L1		Any, except GN maturing GNB intermixed		NA Amplified			B (very low) K (high)
L2	<18 ≥18	Any, except GN maturing, GNB intermixed GNB nodular neuroblastoma	Differentiating Poorly differentiated or undifferentiated	NA NA NA Amplified	No Yes No Yes		D (low) G (intermediate) E (low) H (intermediate) H (intermediate) N (high)
M	<12			NA		Diploid	I (intermediate)
	12 to <18			NA		Diploid	J (intermediate)
	<18 <18			NA Amplified		Hyperdiploid	F (low) O (high)
	≥18						P (high)
MS	<18			NA Amplified	No Yes		C (very low) Q (high) R (high)

Abbreviations: *GN* ganglioneuroma, *GNB* ganglioneuroblastoma, *mos* months, *NA* not amplified

determined by the tumor's resectability at diagnosis. A Children's Oncology Group study (COG A3961) (clinicaltrials.gov identifier: NCT00003093) showed that surgery and multidrug chemotherapy results in a 3-year OS of 96% in patients with intermediate-risk neuroblastoma. Historically, adjuvant radiotherapy was recommended for patients with residual disease; however, modern series have shown that radiotherapy can be reserved for salvage therapy (Matthay et al. 1989).

5.6 High-Risk Disease

The prognosis for patients with high-risk neuroblastoma remains poor. Therefore, these patients are treated with aggressive multimodality therapy, including surgery, cytotoxic myeloablative chemotherapy with stem cell rescue, adjuvant radiotherapy to the primary site and limited MIBG-positive metastatic sites, and maintenance differentiation and immunotherapy with 13-*cis*-retinoic acid (isotretinoin) and anti-GD2 immunoglobulin in combination with granulocyte macrophage colony–stimulating factor (GM-CSF). Induction chemotherapy using platinum-based and alkylating agents facilitates objective response rates of approximately 80%, thereby facilitating cytoreduction and improving resectability. Response to induction therapy, as measured by the Curie score, is prognostic (Matthay et al. 2003). Patients whose scores are greater than 2 after induction chemotherapy exhibit dismal prognoses compared to those with scores of 2 or less (3-year EFS = 15.4% vs. 44.9%) (Yanik et al. 2013). Surgical resection following induction chemotherapy appears to improve EFS, but the impact on OS is poorly defined. Some studies have implied that gross-total resection (100%) or near-total resection (>90%) of the tumor may improve outcome (3-year OS = 20% vs. 58%) (Englum et al. 2015).

The role of high-dose myeloablative chemotherapy has been called into question in light of the advances associated with differentiation and biologic therapies. Three randomized studies were reviewed in a recent Cochrane meta-analysis, which showed that the use of myeloablative chemotherapy improves EFS (HR 0.79, 95% CI, 0.70–0.90) but not OS (HR 0.86, 95% CI, 0.73–1.01) (Yalcin et al. 2013). This result contradicts those from other studies evaluating the benefit of tandem transplantation in high-risk neuroblastoma. The earlier study suggested that tandem autologous transplantation improves survival over that which results from single autologous stem cell infusion (Sung et al. 2013).

Current approaches to improve outcomes with systemic therapy deviate from cytotoxic treatment-intensification therapy towards approaches using the known potential for differentiation and immunological response. Matthay et al. evaluated the effectiveness of 13-*cis* retinoic acid treatment in patients who did not experience disease progression after high-dose chemotherapy, transplantation, and consolidative total body irradiation (TBI) (Matthay et al. 1999). Patients who received 13-*cis* retinoic acid had better 3-year EFS than did those who did not (46% vs. 29%, $p = 0.027$) (Matthay et al. 1999). The updated Children's Cancer Group protocol (CCG 3891) failed to demonstrate a statistically significant benefit of retinoid therapy in patients with minimal residual disease due to the small number of patients in the study, though the results demonstrated a clear trend (Matthay et al. 2009; Park et al. 2009).

Successive advances in radiotherapy, in the context of trials like COG 3891, have improved our understanding of the required dose and minimized acute and late morbidities. Namely, a retrospective analysis of COG 3891 patients with neuroblastoma demonstrated that radiotherapy doses higher than 10 Gy [10 Gy TBI + 10 Gy focal external-beam radiation therapy (EBRT)] is required to improve local control (Haas-Kogan et al. 2003). For this reason, 21.6 Gy is the preferred radiation dose for sites that demonstrate minimal residual MIBG activity. Additional analyses have shown that this approach is well tolerated and results in a low failure rate when delivered based on a conventional or hyperfractionated schedule (Kushner et al. 2001a; Wolden et al. 2000). Higher doses of focal EBRT are preferred to treat MIBG-active, gross residual disease (Bradfield et al. 2004; Simon et al. 2006).

COG investigators built on 3891s improved EFS by supplementing isotretinoin therapy with ch14.18 (an antibody directed against the tumor-associated disialoganglioside GD2), IL-2, and GM-CSF (Yu et al. 2010). Immunotherapy improved 2-year EFS (66% vs. 46%, $p = 0.01$) and OS (86% vs. 75%, $p = 0.02$). Radiotherapy was modified to a focal-only approach without enhancing the rate of treatment failure at distant or new disease sites.

Selecting radiotherapy volumes for high-risk neuroblastoma can be challenging, when one considers the extent of disease present at diagnosis and the potential morbidity caused by extended treatment of a large volume (Cheung and Kushner 2002; Paulino et al. 2002). Treating focal metastatic sites has been controversial, though multiple studies have demonstrated that omission of focal EBRT contributes to treatment failure at MIBG-positive sites present at the time of diagnosis, with or without the use of ^{131}I-MIBG (Fishel Ben Kenan et al. 2015; Polishchuk et al. 2014). Contrary to the above findings, radiation volume coverage of lymph nodes appears to have minimal therapeutic benefit over treating only the primary disease site (Haas-Kogan et al. 2014). Future studies evaluating the role of radiotherapy will need to balance the risk of local morbidity (Cohen et al. 2014; Paulino et al. 2002) with the potential for improved EFS. See Table 5.5 for the important high risk studies.

5.7 Modern Era Therapy and Protocols

Radiation therapy is one piece of the neuroblastoma puzzle. When discussing modern therapy, it is important to have a good understanding of all aspects of therapy, including induction chemotherapy, second-look surgery, consolidative regimens, stem cell transplantation, local and metastatic control with radiotherapy, and all the components of maintenance therapy. Several modern-era protocols are discussed with this multimodality approach in mind. See Fig. 5.3 for the current standard of care treatment algorithm. Please see Table 5.6 for doses and volumes used in all modern protocols.

5.7.1 ABNL 0032

ABNL 0032 was a randomized phase III study that evaluated whether adding immunotherapy to isotretinoin therapy would improve OS in patients with high-risk disease (Yu et al. 2010). Immunotherapy consisted of ch14.18 monoclonal antibody at a dose of 25 mg/m^2 per day, for 4 consecutive days, during 5 consecutive 4-week cycles. During the last 2 weeks of each cycle, patients received 160 mg/m^2 isotretinoin. During Cycles 1, 3, and 5, patients also received 250 μg/m^2 GM-CSF for 14 days, starting 3 days before the antibody therapy. Finally, patients received interleukin 2 (IL-2) via continuous infusion during Cycles 2 and 4. Patients in the control arm received 169 mg/m^2 isotretinoin alone. The trial was stopped early due to efficacy. At a median follow-up of 2.1 years, the 113 patients who had received immunotherapy had superior EFS (66% ± 5% vs. 46% ± 5%, $p = 0.01$) and OS (86% ± 4% vs. 75% ± 5%, $p = 0.02$) compared to the 113 patients randomized to the control arm. This led to the incorporation of the experimental-maintenance regimen into the next phase III study design.

5.7.2 ANBL 0532

The ANBL 0532 trial investigated three new treatments: intensified-consolidation agents, new induction agents, and high-dose local radiotherapy. The study's primary objectives were to improve three measures: (1) the 3-year EFS by using tandem consolidation, (2) the rate of end-induction complete response and very good partial response by using topotecan (TOPO), and (3) local control by increasing the radiation dose for patients with less than gross-total resection of their tumor (clinicaltrials.gov identifier: NCT00567567).

All patients in the high-risk group received 6 cycles of induction chemotherapy that included cyclophosphamide (CPM)/TOPO at Cycles 1 and 2, followed by peripheral blood stem cell harvest. Cisplatin (CDDP)/etoposide (ETOP) was delivered for Cycles 3 and 5, and CPM/doxorubicin

Table 5.5 Key studies in high-risk neuroblastoma

Study name/trial	No. patients/stage of NB	Treatment	Results	Conclusion	First author	Reference
Role of RT after CR to chemo	118 pts. All stages	Surgery, RT ± chemo, depending on age and stage of NB	Pts with stage-4 NB who had a CR or good PR still suffered from local treatment failure with the omission of RT (85% vs. 40%)	Even after CR to chemo, LR rate approached 85%	Rosen EM	JCO Vol 2, No 7, 1984
Dose response of NB after multimodality therapy. Secondary analysis of CCG 3891	539 pts. High-risk NB	Induction chemo Surgery 10 Gy TBI + 10 Gy RT vs. 10 Gy local RT	5-year LR rate was 22% in patients who received 20 Gy RT + TBI vs. 52% in patients who received 10 Gy local RT only	ARR of 30% with dose >20 Gy with minimal increase in morbidity	Haas-Kogan D	IJROBP, Vol. 56, No. 1, pp. 28–39, 2003
RT dose for residual disease NB97 trial	110 pts. Stage 4	Induction chemo myeloablative chemo with stem cell support Intensified local RT (36 Gy) for residual tumor identified by MIBG and MRI	3-year EFS for 13 patients who received RT for residual disease was 85%, which was comparable to that for 74 patients without residual $MIBG^+$ NB (61%)	Higher dose RT appeared to result in local control that was comparable to that in patients without residual disease	Simon T	Strahlenther Onkol 2006;182:389–94
Adjuvant hyper-fractionated RT	99 pts. High-risk NB	Local RT: 21 Gy BID in 1.5-Gy fractions. Primary-site RT covered the extent of tumor at diagnosis with 3-cm marginsa and regional lymph nodes RT to distant sites followed radiologic evidence of response	10 pts. relapsed in or at margins of RT fields at 1–27 months (median, 14 months) Primary-site treatment failure at 36 months: 10.1% (all in patients with incompletely excised tumors)	Hyperfractionated RT to 21 Gy is well tolerated and results in excellent disease control. Patients with residual disease may benefit from dose escalation	Kushner BH	JCO 19:2821–2828. 2001
RT coverage of lymph nodes Secondary analysis of CCG A3973	330 pts. High-risk NB	Induction chemo, myeloablative consolidation, 21.6 Gy RT oral isotretinoin	The absolute difference in the cumulative incidence of LR at 5 years in patients with low vs. high lymph node coverage was no more than 5.1%	Increased lymph node radiation coverage is of minimal benefit	Haas-Kogan D	ASTRO 2014 Poster#247

Study name/trial	No. patients/stage of NB	Treatment	Results	Conclusion	First author	Reference
Immunotherapy with anti-GD2 antibody	226 pts. High-risk NB	Induction therapy SCT 6C isotretinoin vs. immunotherapy (5C ch14.18 + alt GM-CSF and IL-2)	Immunotherapy was superior to standard therapy with regard to rates of EFS (66% ± 5% vs. 46% ± 5% at 2 years, $p = 0.01$) and OS (86% vs. 75% at 2 years, $p = 0.02$)	GD2 immunotherapy improves EFS and OS	Yu AL	NEJM 2010;363:1324–34
Role of ASCT and isotretinoin CCG 3881	539 pts. High-risk NB	Induction chemo Surgery RT BMT or CC ± no progression after 2 cycles chemo randomized to continuation cis-RA TBI: 333 cGy/day × 3 days	BMT was more effective than continuation chemo Isotretinoin improved EFS 5-year OS: 60% (if ABMT and cis-retinoic acid) Higher relapse rate in CC group (51%) vs. ABMT group (33%)	BMT better than continuation chemo Isotretinoin maintenance improves EFS	Matthay K	NEJM 1999 341(16):1165
Role of resection	114 pts. High-risk NB	80% neoadj chemo ASCT GTR (62%) vs. near-GTR (>90%) vs. STR/Bx Only 1 of 3 pts. with major vessel encasement underwent GTR 87% had INSS stage-4 NB	GTR vs. near-GTR/STR/Bx = No diff in OS 5-year OS: GTR [53% (95% CI: 38%–74%)], near-GTR [64% (95% CI, 47%–88%)], STR [35% (95% CI, 18%–68%)], and Bx/no surgery [14% (95% CI, 2%–88%)] GTR vs. near-GTR: SS ($p < 0.008$)	GTR/Near-GTR is beneficial Only 1 of 3 pts. with vascular involvement will have GTR Age > 18 months NB stage, and bone involvement associated with higher HR of death	Englum BR	Pediatr Blood Cancer 2015

Abbreviations: *ARR* absolute risk reduction, *ASCT* autologous stem cell transplantation, *BID* twice daily, *BMT* bone marrow transplantation, *Bx* biopsy, *CC* continuation chemotherapy, *CCG* Children's Cooperative Group, *chemo* chemotherapy, *CR* complete response, *EFS* event-free survival, *GD2* disialoganglioside, *GM-CSF* granulocyte macrophage colony–stimulating factor, *GTR* gross-total resection, *HR* hazard ratio, *IL-2* interleukin 2, *INSS* International Neuroblastoma Staging System, *LR* local relapse, *MIBG* metaiodobenzylguanidine, *MRI* magnetic resonance imaging, *NB* neuroblastoma, *OS* overall survival, *PR* partial response, *pts.* patients, *RA* retinoic acid, *RT* radiotherapy, *SS* statistically significant, *STR* subtotal resection, *TBI* total-body irradiation

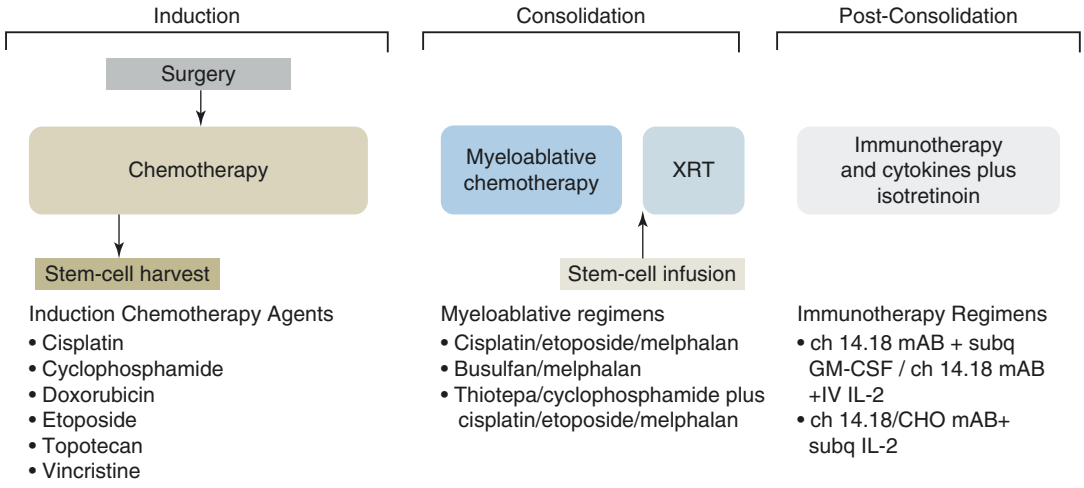

Fig. 5.3 Proportion of patients with involvement of each anatomic site stratified by age

Table 5.6 Volumes of radiation treatment

Radiation treatment volumes based on ANBL1531		
Site	Definition	Radiation dose
GTV1	• Primary volume of tissue containing highest concentration of residual tumor cells • Includes – Disease seen on imaging prior to surgery – Tumor and involved lymph nodes identified during surgery • Does NOT include – Pre-chemotherapy disease extent. – Uninvolved draining lymph nodes • Corrected volumetrically after surgical resection, but NOT at point of attachment • Special considerations – If primary tumor grossly resected at diagnosis, GTV1 is based on initial diagnostic volume – If there is a discrepancy between imaging studies and intraoperative findings, the larger volume will define the GTV – If the tumor displaces normal structures without infiltration and after surgery, normal tissue shifts into prior tumor space, normal tissue should NOT be included in the GTV *CTV1* • Volume of tissue containing subclinical microscopic disease • Defined as GTV1 expanded with 1[a] cm margin. Tailor at tissue interfaces where invasion/infiltration is unlikely *PTV1* • Accounts for set up uncertainty/physiologic motion. • Defined as CTV1 expanded with 0.3–0.8[b,c] cm margin. PTV margin does not have to be uniform in all dimensions, especially if it compromises normal tissue volumes	2160 cGy in 12 fractions

(continued)

Table 5.6 (continued)

Radiation treatment volumes based on ANBL1531		
Site	Definition	Radiation dose
GTV2	• Boost volume including residual tumor AFTER induction chemotherapy, surgery and MIBG therapy measuring >1 cm^3 • Includes disease defined by CT, MR, and MIBG imaging *CTV2* • Volume of tissue containing subclinical microscopic disease surrounding post-surgical residual tumor volume (GTV2) • Defined as GTV2 expanded with 1.0[d] cm margin. Tailor at tissue interfaces where invasion/infiltration is unlikely *PTV2* • Accounts for set up uncertainty/physiologic motion • Defined as CTV1 expanded with 0.3–0.8[e,f] cm margin. PTV margin does not have to be uniform in all dimensions; especially if it compromises normal tissue volumes	Additional boost with 1440 cGy in 8 fractions
Metastatic sites	• Radiation only given to metastatic sites with persistent active disease at time of evaluation prior to BuMel Consolidation seen on imaging • Sites that are negative on imaging prior to BuMel Consolidation will NOT be radiated, even if present at diagnosis • If the patient has >5 persistently positive metastatic sites on imaging prior to BuMel Consolidation, a scan is repeated on Day 28 after SCT. Only remaining positive sites are radiated *PTV metastatic site* • Residual tumor with 2 cm margin • If there is a size discrepancy between scans, the larger volume will be irradiated • For osseous metastases, the margin should not extend more than 2 cm outside the bone or across a joint space	2160 cGy in 12 fractions

Note: Clinical target volume (CTV), gross tumor volume (GTV), planning target volume (PTV). GTV and CTV is the same for protons and photons. PTV for protons is uniquely defined accounting for proton range uncertainty
[a]New expansion that will be incorporated into ANBL1531
[b]Depends on available technology
[c]New expansion that will be incorporated into ANBL1531
[d]New expansion that will be incorporated into ANBL1531
[e]Depends on available technology
[f]New expansion that will be incorporated into ANBL1531

(DOXO)/vincristine (VCR) was given for Cycles 4 and 6. Second-look surgery was performed after Cycle 5. Patients were then randomized to receive carboplatin (CARBO)/ETOP/melphalan (MEL) consolidation or CARBO/ETOP/MEL and thiotepa (TEPA)/CPM tandem consolidation. Maintenance therapy was given per ANBL 0032, once the OS benefit was established. Radiation therapy commenced subsequent to autologous stem cell transplantation (ASCT) (Table 5.6).

This study was closed to accrual in February of 2012 and results will be published shortly.

5.7.3 SIOPEN HR-NBL1

The International Society of Paediatric Oncology Europe Neuroblastoma (SIOPEN) HR-NBL1 trial is investigating busulfan (BU)/MEL as a consolidative preparatory regimen. Of the 1577 patients enrolled, 598 were randomized to either BU/MEL or CARBO/ETOP/MEL. The 3-year OS was significantly higher among patients in the BU/MEL group than in the CARBO/ETOP/MEL group (61% vs. 48%, $p = 0.004$) (Ladenstein and Pötschger 2011). Randomization of the consolidation agents was stopped due to that result. The SIOPEN HR-NBL1 also randomizes patients to two different induction regimens, the European Rapid COJEC regimen or the COG (North American) Modified N7 regimen. All patients then receive second-look surgery and consolidation with BU/MEL, followed by ASCT, radiotherapy, and maintenance therapy.

No data have been published on the use of BU/MEL in the context of induction agents and dose scheduling used in COG studies. COG pilot studies have sought to evaluate the use of BU/MEL as a consolidative preparatory regimen in anticipation of the next phase III trial. Two recent high-risk neuroblastoma phase I protocols used a 5-cycle induction regimen. Both ANBL 09P1 and ANBL 12P1 are both closed to enrollment because accrual goals were met. Off-protocol patients are usually treated with 5–6 cycles of induction chemotherapy.

5.7.4 ANBL 09P1

This trial sought to assess the feasibility of treating patients with high-risk neuroblastoma with an induction block of ^{131}I-MIBG (therapeutic) in addition to the BU/MEL consolidation regimen. The induction regimen gave TOPO/CPM for Cycles 1 and 2, which is similar to the ANBL 0532 study. However, for this trial, CDDP/ETOP was given for Cycles 3 and 5, and CPM/DOXO/VCR is administered for Cycle 4. Patients then progressed to induction therapeutic ^{131}I-MIBG followed by ASCT. Patients then received consolidation with BU/MEL, second autologous stem cell rescue, and radiotherapy using the same parameters as those used in the ANBL 0532 trial. Patients then progressed to maintenance therapy. This trial is closed to enrollment (clinicaltrials.gov identifier: NCT01175356).

5.7.5 ANBL 12P1

Parallel with ANBL 09P1, the ANBL 12P1 trial sought to determine whether the acute toxicity of a BU/MEL consolidation–based regimen was tolerable for high-risk neuroblastoma. The trial is identical to ANBL 09P1, except for two differences: (1) no ^{131}I-MIBG was administered as induction, and (2) only 1 ASCT was performed. Patients received maintenance therapy upon completion of radiation therapy. This trial is closed to enrollment (clinicaltrials.gov identifier: NCT01798004).

5.8 Radiation Therapy

5.8.1 Intensity-Modulated Radiotherapy/Volumetric Arc Therapy

Paulino et al. (2006) evaluated six patients by using three different techniques for each patient. Technique A was a conventional plan, technique B was a step intensity-modulated radiotherapy (IMRT) plan, and technique C was a shoot IMRT plan. The IMRT plans delivered lower mean doses bilaterally to the kidneys of the four children who had midline abdominal tumors but not to the two children who had lateralized tumors. The mean doses of radiation delivered to the spleen, liver, and stomach were higher with IMRT techniques. Fuji et al. (2013) compared proton beam, IMRT, and conformal radiotherapy in five patients with high-risk neuroblastoma. Proton plans delivered a lower mean dose to all organs than did 3-dimensional (3D) plans, but

IMRT delivered lower mean doses to two organs but higher mean doses to four organs.

In the largest review to date to evaluate IMRT for high-risk neuroblastoma, Panandiker et al. (2013) reviewed the medical records of 20 patients, including five with *MYCN* amplification, who received IMRT. None of the patients experienced in-field treatment failure, and none suffered acute toxicity beyond grade 1. In an earlier review, Panandiker and colleagues evaluated 44 patients treated with 3D conformal radiotherapy. In that cohort, 11 patients experienced in-field disease recurrence that was attributed to inadequate radiation dose.

Based on the few studies available, it appears that gross disease requires 36 Gy for local control. Furthermore, IMRT should be used to treat midline tumors due to the difficulty of renal sparing with a 3D conformal radiotherapy approach. However, the treating therapist should be aware that adjacent normal structures will receive higher integral radiation doses. With the widespread evolution to volumetric arc therapy (VMAT) IMRT, future studies need to compare VMAT therapy with traditional step and shoot IMRT to determine if there are significant dose-distribution differences between these techniques, with respect to normal structures.

5.8.2 Proton Therapy

As long-term outcomes steadily improve for high-risk neuroblastoma, long-term sequelae become a focus of concern. Furthermore, although radiotherapy doses are relatively low, large volumes of tissue usually require treatment in very young patients. Proton therapy offers significant advantages in optimizing the treatment of target volumes and sparing normal tissues (Hattangadi et al. 2012). This is due to reduced entrance dose, increased conformality, and elimination of exit dose. Hattangadi et al. (2012) compared IMRT, 3D conformal proton therapy, and intensity-modulated proton therapy plans in nine patients with high-risk neuroblastoma; the median tumor size of the group was 11 cm. The proton therapy plans substantially improved normal-tissue sparing when compared with IMRT, and the dose distribution was better in intensity-modulated proton therapy than it was in 3D conformal proton therapy. In a second study that compared IMRT with proton therapy, the dosimetric plans for 13 patients with high-risk neuroblastoma were compared. Proton therapy improved the median radiation dose delivered to the bowel, total body, and liver. When chest radiation was required, proton therapy improved the median dose to the heart and the mean dose to the lung (Hill-Kayser et al. 2013).

Treatment-planning issues, with regard to proton therapy, are beyond the scope of this chapter. However, two important issues specific to proton therapy planning and solid tumors must be mentioned. First, when treating retroperitoneal tumors, it is important to use a posterior beam. The uncertainty involving bowel filling and air can create significant dose heterogeneity when using an anterior or lateral beam. Second, the beam must be ranged so that the dose gradient does not fall in the middle of the vertebral body (Fig. 5.4). Beams need to properly encompass the vertebral body with a homogenous dose distribution. If the proton beam is not ranged properly, the patient could experience significant growth abnormalities due to the steep dose gradient.

Data on proton therapy for high-risk neuroblastoma are scarce. With increased availability of proton technology, as a result of an increased number of proton centers being established

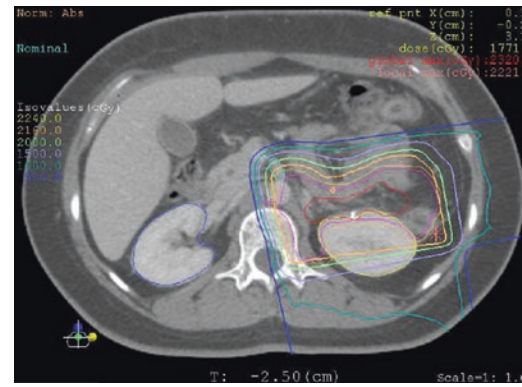

Fig. 5.4 Example of proton therapy plan with significant gradient involving the vertebral body

worldwide, studies with longer follow-up and larger patient cohorts are expected in the near future.

5.8.3 Salvage Radiotherapy

Incremental improvements in salvage chemotherapy regimens have demonstrated objective treatment response rates as high as 63% with TOPO-inhibitor doublets in the setting of first relapse and 47% in that of refractory disease (Ashraf et al. 2013; Kushner et al. 2006b). Because multimodality therapy for neuroblastoma is intensive, myeloablative regimens are not possible in the salvage setting. Therefore, focal radiotherapy may facilitate chemotherapy breaks, pain control, and/or improved response rates. Focal radiotherapy is associated with high and durable response rates (i.e., more than 70% of patients experienced durable responses, and 90% sustained response until their demise) (Paulino 2003). Many patients experience improvements in symptoms beyond pain response, similar to that seen in patients with stage-4s disease. Patients with limited metastatic disease at relapse may benefit from intensified therapy using techniques such as stereotactic body radiation therapy (SBRT). The total doses of SBRT required are generally low, which permits short courses of treatment, minimal morbidity, and sustained quality of life (Taunk et al. 2016). Fractionation and treatment volume are patient- and metastasis location–dependent, and several sites, including the CNS, may warrant large-volume treatment due to the propensity for neurologic compromise and distant CNS failure (i.e., craniospinal) (Kramer et al. 2001). Other sites, such as bone, may be treated with focal EBRT alone (Paulino 2003).

5.9 Maintenance Therapy

For patients with high-risk neuroblastoma who undergo ASCT after induction chemotherapy, surgical resection with or without local irradiation, and myeloablative therapy, the rate of disease relapse is 50%, thus indicating the presence of minimal residual disease requiring maintenance therapy (Matthay et al. 1993). In the 1990s, attempts were made to treat minimal residual disease with isotretinoin because this agent decreases proliferation and induces cellular differentiation in neuroblastoma cell lines (Abemayor 1992; Melino et al. 1997; Reynolds et al. 1991, 1994; Sidell 1982).

Another approach to treating minimal residual disease involves targeting disialoganglioside GD2, a tumor-associated antigen that is uniformly expressed by neuroblastomas (Cheung et al. 1987; Schulz et al. 1984). The chimeric human–murine anti-GD2 monoclonal antibody ch14.18 and the monoclonal antibody 3F8 have shown antibody-dependent, cell-mediated cytotoxicity against neuroblastoma cell lines. Furthermore, the activity of ch14.18 is enhanced in combination with GM-CSF or IL-2 (Albertini et al. 1997; Barker et al. 1991; Cheung et al. 1998; Gillies et al. 1989; Handgretinger et al. 1995; Hank et al. 1990; Kendra et al. 1999; Mueller et al. 1990; Yu et al. 1997, 1998). Based on the results of ANBL 0032, maintenance treatment with immunotherapy, cytokines, and isotretinoin is now considered the standard of care.

5.10 *ALK* Mutations and Targeting

Approximately 14% of patients with high-risk neuroblastoma harbor mutations or gene amplifications involving the *ALK* gene. Crizotinib is a tyrosine kinase inhibitor of the *ALK* and *ROS1* genes. At the time of this writing, a COG phase I clinical trial is evaluating the use of crizotinib in combination with TOPO and CPM for patients with solid tumors or anaplastic large-cell lymphoma (clinicaltrials.gov identifier: NCT01606878). Additionally, two other ALK inhibitors are in early-stage clinical development in the U.S. and Europe (clinicaltrials.gov identifiers: NCT02097810 and NCT01742286). Crizotinib treatment will be incorporated into the next phase III COG high-risk neuroblastoma protocol.

5.11 Complications of Therapy

5.11.1 Acute Toxicities

Acute side effects that arise during chemotherapy and ASCT include decreased white blood cell counts resulting in subsequent infection, mucositis, nausea, vomiting, diarrhea, alopecia, and fatigue, which are managed symptomatically. Acute side effects during radiation treatment depend on the tissues present in the radiation field. Radiation dose to the small bowel may result in nausea and vomiting that is generally well controlled with antiemetic medications. Diarrhea and abdominal pain occur less frequently, and dietary counseling is generally adequate to control those side effects. At times, primary tumors or metastatic sites encompass a substantial portion of the bone marrow, thereby necessitating the regular monitoring of blood cell counts (Halperin et al. 2011).

5.11.2 Long-Term Toxicities

Long-term side effects are of particular concern because patients with neuroblastoma are treated at such a young age. Limited data on the potential toxicities of high-risk neuroblastoma treatment have become available as those paradigms have evolved over time, in terms of the chemotherapeutic and targeted agents used. In addition, radiation doses and targets have changed considerably. Chemotherapy and ASCT have the potential to cause systemic toxicity, whereas radiation-induced toxicity is generally localized to the areas of treatment. Radiation treatment in particular can cause various extents of pulmonary, genitourinary, musculoskeletal, and gastrointestinal toxicity, depending on the dose delivered to the organs at risk. No consensus has been reached on normal-tissue constraints for organs at risk. A retrospective study of 30 patients with high-risk abdominal neuroblastoma included approximately 10% of patients who did not meet the constraints for liver, ipsilateral kidney, or contralateral kidney. Of the 3 patients who did not meet ipsilateral kidney dose-volume histogram constraints, 2 had late kidney hypoplasia but maintained normal kidney function. No late toxicities of the contralateral kidney or late hepatic sequelae were detected. Thus, standardized constraints for organs at risk need to be developed and directly correlated with toxicity (Kandula et al. 2015).

5.11.3 Musculoskeletal Sequelae

Irradiating the epiphyses of tubular bones results in bone shortening, and radiating the diaphysis results in impaired bone modeling and thickening (Halperin et al. 2011). In a retrospective study of 58 children with neuroblastoma, scoliosis developed in approximately 25% of the patients at 15 years after completion of treatment. Factors including laminectomy and radiation treatment were associated with increased risk of scoliosis, and increasing radiation dose, particularly doses that were 20 Gy or more, contributed to the development of scoliosis (Paulino and Fowler 2005). Thus, for all patients, shielding of bone growth centers is imperative to minimize and/or prevent growth abnormalities. Furthermore, when vertebrae are included in the radiation field, it is important to irradiate the entire vertebral bodies to reduce the risk of scoliosis (Halperin et al. 2011).

5.11.4 Audiologic/Neurologic Sequelae

Permanent hearing loss is a common late side effect associated with treating high-risk neuroblastoma because platinum-based chemotherapy (e.g., CDDP), which destroys auditory cells, is a mainstay for the management of the disease. The prevalence of ototoxicity related to CDDP use ranges from 13 to 95% (Bertolini et al. 2004; Blakley and Myers 1993; Brock et al. 1991; Gupta et al. 2006; Ilveskoski et al. 1996; Knight et al. 2005; Kushner et al. 2006a; Laverdiere et al. 2005; Lewis et al. 2009; Li et al. 2004; Montaguti et al. 2002; Skinner et al. 1990; Stohr et al. 2005). In the COG A3973 trial, audiologic testing was completed after the administration of CDDP

alone or CDDP followed by CARBO. Exposure to the combination of drugs significantly increased the risk of severe hearing loss; the prevalence of patients requiring hearing aids was higher among those who had received CDDP than it was among those who did not (58.4% vs. 28.8%; $p < 0.001$) (Landier et al. 2014).

5.11.5 Endocrinologic Sequelae

Acute ovarian failure is a potential complication of treating neuroblastoma. A retrospective review of 63 patients at Memorial Sloan Kettering Cancer Center (New York, NY) showed transient ovarian dysfunction in 50% of the female patients (Laverdiere et al. 2005). The transient nature of this complication may be explained by ovarian resistance to chemotherapy and radiation in the prepubertal state compared to that in the postpubertal state (Sklar 1999). However, even if ovarian function is recovered, premature menopause is still a risk (Byrne et al. 1992). Patients who receive radiation treatment to the neck or radioimmunotherapy are at risk of primary hypothyroidism (Laverdiere et al. 2005). Radiation doses of 20 Gy or higher have been associated with a high incidence of clinically significant hypothyroidism (Acharya et al. 2003; Kaplan et al. 1983; Sklar et al. 2000). The use of ^{131}I-MIBG also causes hypothyroidism in 50–80% of patients, despite attempts to protect patients with high doses of potassium iodine (Picco et al. 1995; van Santen et al. 2002). Growth hormone secretion can also be altered by radiotherapy. Studies have shown that after ASCT, patients with neuroblastoma have poorer growth than do those who undergo ASCT for hematologic disorders (Olshan et al. 1993; Willi et al. 1992). In addition, TBI further impairs growth rates (Hovi et al. 1999).

5.11.6 Gastrointestinal Sequelae

Hepatic veno-occlusive disease (also known as sinusoidal obstructive syndrome) is clinically characterized by rapid weight gain, ascites, hyperbilirubinemia, and painful hepatomegaly. It is thought to be caused by damage to sinusoidal endothelial cells and hepatocytes in zone 3 of the liver acinus, which surrounds the central veins (Coppell et al. 2010). Veno-occlusive disease is more common after allogeneic BMT than after ASCT; historically, the rate of this disease emerging after BMT is as high as 60%, and the syndrome ranges from mild, reversible disease to severe syndrome with multiorgan failure resulting in death (Bearman 1995; Bearman et al. 1993; Carreras et al. 1998; Jones et al. 1987; Mcdonald et al. 1984, 1993; Richardson and Guinan 1999).

5.11.7 Secondary Malignancy

The relative risk of secondary cancer for neuroblastoma survivors has been reported as 6.59 times higher than that of the general population; however, these survivors were treated during an earlier era, and the cohort included all neuroblastoma-risk groups (Neglia et al. 2001). The most common secondary cancers seen in neuroblastoma survivors are myelodysplasia/leukemia, thyroid carcinoma, soft-tissue sarcoma, and osteosarcoma (de Vathaire et al. 1988; Garaventa et al. 2003; Kushner et al. 1998; Laverdiere et al. 2005; Neglia et al. 2001; Rubino et al. 2003; Weiss et al. 2003).

5.12 Current Areas of Treatment Uncertainty

5.12.1 Lymph Nodes

There is very little data on lymph node coverage during radiotherapy for high-risk neuroblastoma. Haas-Kogan et al. 2014 evaluated 339 radiation plans, diagnostic scans, and clinical data from the COG A3973 trial (Hass-Kogan et al. 2014). Three quartiles based on the percentage of lymph node coverage were examined. Regardless of the cutoff selected, no differences were found with regard to cumulative incidence of local recurrence, EFS, or OS. Their conclusion was that the data do not support extending the primary-site radiation field to increase lymph node coverage.

5.12.2 Metastatic Disease

There is a paucity of data on the benefit (or lack thereof) of treating metastatic neuroblastoma sites. Current COG protocols instruct that radiation should be delivered to metastatic sites that demonstrate persistent, active disease, as indicated by persistent soft-tissue mass or MIBG-uptake, at the time of evaluation prior to consolidation. However, if a patient has more than 5 persistent MIBG-positive metastatic sites, then the evaluation scans should be repeated 28 days after ASCT, and only remaining MIBG-positive sites should be treated.

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Wilms Tumor

6

John A. Kalapurakal

6.1 Molecular Biology

Wilms tumor is associated with congenital anomalies in 10–13% of cases (Dome and Coppes 2002). Initial insights into the molecular biology of Wilms tumor were derived from the observation that in patients with *WAGR* syndrome of *W*ilms tumor with *A*niridia, *G*enitourinary malformations, and mental *R*etardation the risk for developing Wilms tumor is more than 30%. Cytogenetic analysis of individuals with this syndrome showed deletions at chromosome 11p13, which was later found to be the locus of a contiguous set of genes including *PAX6,* the gene causing aniridia, and *WT1,* one of the Wilms tumor genes. The *WT1* gene encodes a transcription factor that is crucial to normal kidney and gonadal development (Riccardi et al. 1980). The Denys-Drash syndrome is characterized by pseudohermaphroditism, glomerulopathy, renal failure, and a 95% chance of Wilms tumor development, is caused by point mutations in the zinc-finger DNA-binding region of the *WT1* gene (Little et al. 1993). The Beckwith-Wiedemann syndrome is an overgrowth disorder manifested by large birth weight, macroglossia, organomegaly, hemihypertrophy, abdominal wall defects and predisposition to Wilms tumor and other malignant disorders. Beckwith-Wiedemann syndrome maps to chromosome 11p15, a locus sometimes called "WT2" because it was the second locus shown to be associated with Wilms tumor. Approximately 5% of individuals with this syndrome develop Wilms tumor (Koufos et al. 1989). Further, there is evidence of genetic loci that may be related to more malignant or aggressive Wilms tumors. In NWTS-5, 2021 children were prospectively evaluated for the poor prognostic significance of tumor specific loss of heterozygosity (LOH) for chromosomes 1p or 16q. LOH at either 1p or 16q was only associated with higher risk of relapse for low-stage (stage I/II) patients in comparison to stage III/IV. It was postulated that two-drug chemotherapy was insufficient to overcome the effect of loss of the putative tumor suppressor genes located within these chromosomal regions. Conversely, the more intensive treatment with three drugs did overcome the effect of this loss in stage III/IV patients. The relative risk of relapse and death in low- and high-stage patients was significantly elevated in patients with LOH at both loci (Grundy et al. 2005). In 2007, a previously unknown gene on the X chromosome *WTX* was found to be inactivated in approximately one third of tumors. *WTX* is a Wilms tumor suppressor gene with an important role in normal kidney development (Rivera et al. 2007). Recent

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studies have shown that gain of 1q is a promising biomarker for patients with favorable histology Wilms tumor. In a report from NWTS-4, 27% of patients displayed 1q gain. The 8-year event-free survival (EFS) and overall survival (OS) rates were 76% and 93% (P = 0.002) for patients with 1q gain and 89% and 98% (P = 0.008) for those lacking 1q gain. Gain of 1q did not correlate with tumor stage. After stratification for tumor stage 1q gain was associated with significantly increased risk of relapse (risk ratio 2.72, P = 0.009) (Gratias et al. 2013).

6.2 Pathology and Pathways of Spread

Most Wilms tumors are solitary lesions, although 6% involve both kidneys and 12% show multifocal involvement within a single kidney. The classic triphasic "favorable histology" Wilms tumor consists of varying proportions of three cell types including the blastemal, stromal, and epithelial types recapitulating the various stages of normal renal development (Fig. 6.1a). Not all specimens are triphasic; biphasic and monophasic patterns are frequently encountered. Favorable histologic features characterize 87% of Wilms tumors (Beckwith and Palmer 1978). The histologic feature of greatest clinical significance is anaplasia, defined by the presence of greatly enlarged polyploid nuclei (Fig. 6.1b, c). Anaplasia is present in approximately 8% of Wilms tumors; it is rare in the first 2 years of life and increases in frequency to approximately 13% in children older than age 5 years. The distinction between focal and diffuse anaplasia is prognostically significant (Bonadio et al. 1985; Faria et al. 1996). Further correlations between histologic characteristics and clinical behavior vary according to whether the tumor

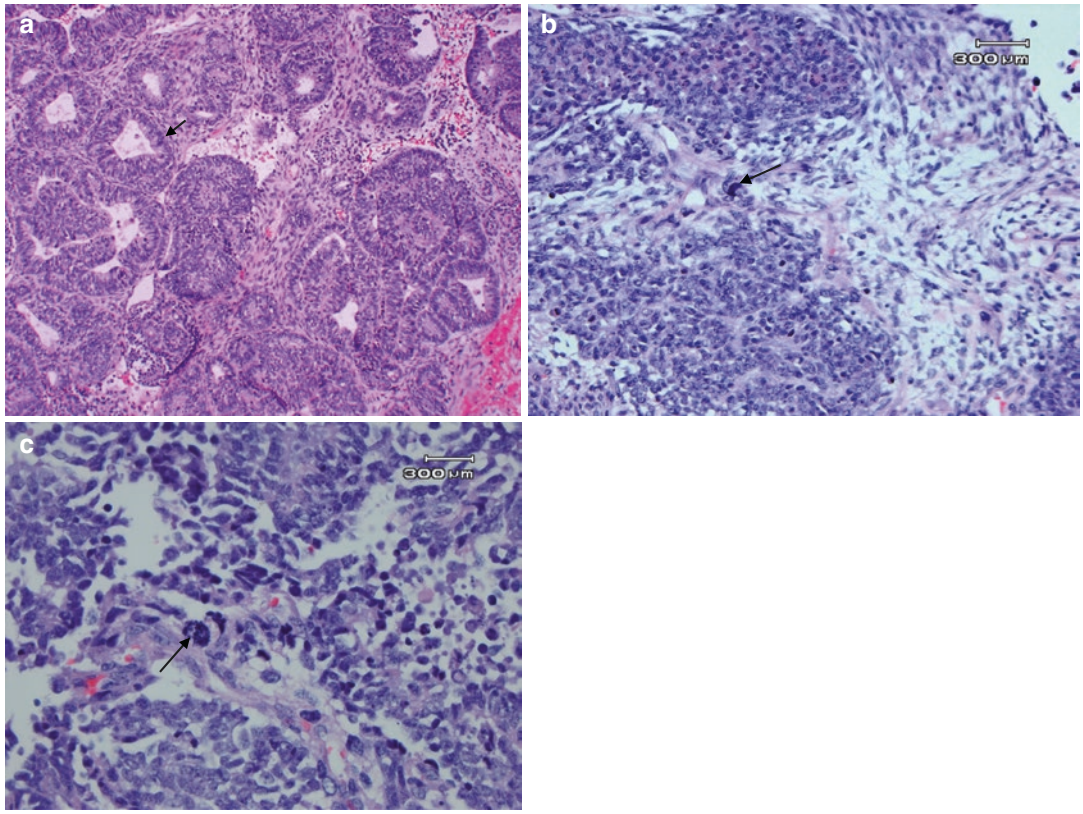


Fig. 6.1 (**a**) Favorable histology Wilms tumor with the classic triphasic pattern consisting of islands or nests of blastemal cells with loose mesenchymal (stromal) tissue in the background. The epithelial component (tubules) (*arrow*) forms the third element of this tumor. (**b**) Diffuse anaplastic Wilms tumor with numerous large cells with large, hyperchromatic nuclei (*arrow*). (**c**) High-power view of diffuse anaplasia

specimen is taken before or after chemotherapy. In patients undergoing immediate nephrectomy, blastemal-rich tumors are typically invasive and present at an advanced stage; however, there is no strong correlation with outcome when correcting for stage (Breslow et al. 1991). In patients undergoing pre-operative chemotherapy, blastemal subtype has a clear correlation with adverse outcome, suggesting that residual blastemal cells that persist after chemotherapy represent a treatment-resistant population (Weirich et al. 2001). The existence of precursor lesions (nephrogenic rests) is rather common. These lesions consist of abnormally persistent intrarenal embryonal nephroblastic tissue with small clusters of blastemal cells, tubules, or stromal cells. Nephrogenic rests can be subclassified by their positions within the kidney and histologic appearance: perilobar nephrogenic rests are limited to the periphery of the renal cortex, and intralobar nephrogenic rests occur randomly throughout the renal lobe. The presence of nephrogenic rests within a kidney resected for Wilms tumor indicates the need for monitoring the contralateral kidney for tumor development, particularly in young infants (Beckwith 1993). Clear cell sarcoma of the kidney (CCSK) once considered a Wilms tumor variant, is now recognized as a separate entity. The tumor cells have poorly stained cytoplasm with cytoplasmic vacuolations. Bone and brain metastases, rare in the other tumor types, are common in CCSK (Beckwith and Palmer 1978; Marsden et al. 1978). Rhabdoid tumor of the kidney (RTK) or malignant rhabdoid tumor is a rare but extremely aggressive neoplasm that predominantly affects infants, in whom hypercalcemia may be present. Rhabdoid cells are characterized by eosinophilic cytoplasm that contains hyaline globular inclusions. Metastases to the lung and intra-abdominal relapses are frequent (Beckwith and Palmer 1978).

6.3 Clinical Manifestations, Patient Evaluations, and Staging

The most common presentation of a child with Wilms tumor is with an asymptomatic abdominal mass, although about 33% of patients present with abdominal pain, anorexia, vomiting, malaise, or a combination of these symptoms. Physical examination reveals hypertension in about 25% of patients. Congenital anomalies (aniridia, genitourinary malformations, hemihypertrophy, or signs of overgrowth) may be seen in 13–28% of children, higher in those with bilateral disease. Up to 30% of patients may have hematuria; fewer than 10% have coagulopathy (Green 1985; Maas et al. 2007; Marsden et al. 1978).

Laboratory evaluation after physical examination should include a complete blood cell count, routine hepatic and renal chemistries, and urinalysis, noting the presence or absence of urinary protein and white or red blood cells. Imaging studies before surgery are designed to evaluate the extent of the renal mass and differentiate primary intrarenal tumors from neuroblastoma (most often arising from the adjacent suprarenal gland or retroperitoneal structures), the presence of a normally functioning, morphologically normal contralateral kidney, the presence of a patent renal vein and inferior vena cava (i.e., free from thrombosis, most often tumor thrombosis when seen), and the presence or absence of metastases in the lungs. Diagnostic imaging studies include abdominal ultrasonography (particularly useful in the detection of tumor thrombosis) and CT or MRI of the abdomen (Fig. 6.2). A chest CT scan should be used to detect lung metastasis. MRI of the abdomen can help to distinguish between

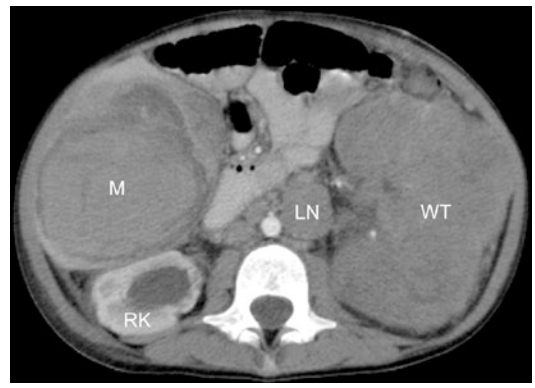


Fig. 6.2 Abdominal CT scan of a 4-year-old girl with a large left-sided Wilms tumor (*WT*) measuring 10.5 × 11 × 17 cm. The right kidney (*RK*) did not show any lesions. There were multiple enlarged para-aortic lymph nodes (*LN*) and liver metastases (*M*)

nephrogenic rests and Wilms tumor (Green 2002; Gylys-Morin et al. 1993). Postoperatively, when the histology is established, a bone scan and brain MRI should be obtained for all patients with CCSK and RTK.

Wilms tumors are staged on the basis of anatomic tumor extent; therapy is currently based on stage and histology. After analysis of the prognostic significance of several clinical and pathologic factors in NWTS-1 and NWTS-2, an NWTS staging system has been in use from NWTS-3 onward. Patients with lymph node involvement, previously included with stage II disease, were classified as having stage III disease, and those with local tumor spill were moved from stage III to stage II disease (Farewell et al. 1981). Refinements to the inclusion criteria for stages I and II disease were introduced in the NWTS-5 study. Criteria for stage I was refined to accommodate an important subset of Wilms tumor currently managed by nephrectomy alone. Before NWTS-5, the distinction between stages I and II in the renal sinus was established by the hilar plane, which was an imaginary plane connecting the most medial aspects of the upper and lower poles of the kidney. This criterion was difficult to apply because of tumor distortion, and thus the hilar plane criterion has been replaced with renal sinus vascular or lymphatic invasion. The latter definition includes not only the involvement of vessels within the hilar soft tissue but also vessels located in the radial extensions of the renal sinus into the renal parenchyma (Weeks et al. 1987). The current COG staging guidelines for Wilms tumor are shown in Table 6.1. These guidelines are essentially similar to those for NWTS-5 except for the fact that children with tumor spillage are upstaged from stage II to stage III because of

Table 6.1 COG staging of Wilms tumor

Stage	Description
I	Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or sampled before removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection
II	The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond kidney, as is evidenced by any one of the following criteria
	• There is regional extension of the tumor (i.e., penetration of the renal capsule or extensive invasion of the soft tissue of the renal sinus)
	• Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor
III	Residual nonhematogenous tumor present after surgery and confined to abdomen. Any one of the following may occur
	• Lymph nodes within the abdomen or pelvis are involved by tumor.
	• The tumor has penetrated through the peritoneal surface
	• Tumor implants are found on the peritoneal surface
	• Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination)
	• The tumor is not completely resectable because of local infiltration into vital structures
	• Tumor spillage occurred either before or during surgery
	• The tumor was sampled (whether Tru-Cut, open, or fine needle aspiration) before removal
	• Tumor is removed in more than one piece (e.g., tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen)
IV	Hematogenous metastases (e.g., lung, liver, bone, brain), or lymph node metastases outside the abdominopelvic region are present (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present)
V	Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease

the higher risk for relapse in these patients when treated with two-drug chemotherapy without RT (Kalapurakal et al. 2010).

6.4 Surgery

Primary surgical resection of Wilms tumor remains the standard initial therapy undertaken in North America. A transabdominal transperitoneal approach is recommended to provide adequate exposure for complete locoregional staging (Shamberger et al. 1999). This procedure includes biopsy of hilar and regional nodes (even if normal appearing), which remains a crucial factors in staging. Although suspicious lymph nodes are excised irrespective of location, a formal lymph node dissection is neither beneficial nor recommended.

Most Wilms tumors that appear to involve contiguous structures only compress or adhere to these adjacent organs without invasion. Therefore, radical en bloc resection in these tumors, which is associated with increased surgical complications, can be avoided. However, wedge resection of infiltrated structures such as the diaphragm, liver, or psoas muscle can be undertaken if all disease can be completely removed with little operative morbidity. This procedure is advantageous because the tumor can be downstaged to stage II and subsequent therapy reduced. Tumor extension into the renal vein and proximate inferior vena cava can, in most cases, be removed en bloc with the kidney. However, primary resection of extension into the inferior vena cava to the hepatic level or into the atrium is associated with higher operative morbidity. In these circumstances, preoperative chemotherapy decreases the size and extent of the tumor thrombus, facilitating subsequent excision. Some tumors are initially judged to be unresectable or to pose too great a surgical risk because of massive size. In these cases, preoperative chemotherapy results in reduction of the tumor mass and renders it resectable.

Tumor spillage remains an important concept in the surgery of Wilms tumor. Surgeons must be aware of any tumor-capsule violation with contamination of the peritoneal cavity during resection. The accurate assessment of a local spill from diffuse contamination is difficult; peritoneal contamination definitely increases the risk for local and abdominal recurrence, and both localized and diffuse peritoneal spill (or preoperative tumor rupture) are now considered stage III disease (Shamberger et al. 1999).

6.5 Radiation Therapy (RT)

RT continues to play an important role in the management of Wilms tumor. Successive NWTS trials have refined the indications for RT. In NWTS-1 and NWTS-2, an age-adjusted dose schedule was used for flank irradiation, ranging from 18 to 24 Gy for children younger than 18 months to 35–40 Gy for children older than 40 months. The abdominal relapse rate was 3–5% for group II and III tumors, and there was no dose-response relationship observed across these dose ranges (D'Angio et al. 1978; Thomas et al. 1984). NWTS-3 proved that RT could be avoided in children with stage II tumors if vincristine and dactinomycin were both given. This study also showed that children with stage III favorable histology tumors who received 10.8 Gy with vincristine, dactinomycin, and doxorubicin had tumor control similar to that of those who received 20 Gy with vincristine and dactinomycin. This was an important finding because it eliminated the need for an age-adjusted dose schedule and significantly reduced the recommended radiation dose (Thomas et al. 1991).

NWTS-1, NWTS-2, and NWTS-3 showed that delay in initiating RT beyond 10 days was correlated with poor outcome primarily in cases with unfavorable histology (D'Angio et al. 1978; Thomas et al. 1984, 1991). A study of the impact of RT delay on patients with favorable histology in NWTS-3 and NWTS-4 showed that a delay of more than 10 days did not significantly influence flank or abdominal tumor recurrence rates. It is currently recommended for children requiring RT that it be initiated without undue delay and within 14 days of nephrectomy (Kalapurakal et al. 2003).

The NWTS evaluated the frequency with which tumor spill of favorable histology produced intra-abdominal recurrence in NWTS-3 and NWTS-4. Flank irradiation but not doxorubicin reduced abdominal relapse rates. The odds ratio for the risk of recurrence was 0.35 for 10 Gy and 0.08 for 20 Gy when compared with those with no radiation therapy. Tumor spillage resulted in higher relapse and significantly lower survival among patients with stage II disease in NWTS-4 (i.e., those without RT). The 8-year relapse-free survival with and without spillage were 79% and 87% (P = 0.07), and OS rates were 90% and 95% (P = 0.04), respectively (Kalapurakal et al. 2010).

In children with lung metastases detected on chest radiographs, whole-lung irradiation (WLI) results in high cure rates. In NWTS-3, the 4-year relapse-free survival and OS were 72% and 78%, respectively, in children with favorable histology tumors (D'Angio et al. 1989). These results are superior to the survival rates reported by the United Kingdom Children's Cancer Study Group (UKCCSG) in which all patients did not receive WLI (Pritchard et al. 1995). In children with pulmonary metastases visible on CT but not chest radiographs, the role of WLI is unclear. In such patients treated on NWTS-3 and NWTS-4, the 4-year EFS with WLI was 89% compared with 80% with chemotherapy alone, a difference that was not statistically significant (Meisel et al. 1999). The current COG protocol recommends WLI based on the response of pulmonary metastatic lesions to one course of chemotherapy with vincristine, dactinomycin, and doxorubicin at week 6 after chemotherapy (Table 6.2). The current RT recommendations of the Children's Oncology Group (COG) Renal Tumors Committee are shown in (Table 6.3). There are several differences in the COG recommendations compared to NWTS-5: (1) patients with local tumor spillage are upstaged to stage III and will receive flank RT; (2) patients with stage I focal and diffuse anaplastic tumors will receive flank RT; (3) the radiation dose for children with stage III diffuse anaplasia and stage I to III RTK will be increased to 19.8 Gy; and (4), in an effort to study if irradiation could be omitted in stage I CCSK, patients who have undergone nodal sampling and central pathology review will not receive flank RT.

Table 6.2 COG Wilms tumor protocol schema

Tumor risk classification	Multimodality treatment
Very low-risk favorable histology Wilms tumor: <2 years, stage I FH, tumor weight < 550 g	Nephrectomy without adjuvant therapy, only if central pathology review and lymph node sampling has been performed
Low-risk favorable histology Wilms tumor: ≥2 years, stage I FH, tumor weight ≥ 550 g, stage II FH without LOH of 1p and 16q	Nephrectomy, no RT, regimen EE4A
Stage I and II FH with LOH of 1p and 16q	Nephrectomy, regimen DD4A
Stage III FH without LOH of 1p and 16q	Nephrectomy, RT, regimen DD4A
Stage III and IV FH with LOH of 1p and 16q, stage IV FH slow/incomplete responders	Nephrectomy, RT, regimen M, whole-lung irradiation
Stage IV FH: complete resolution of lung metastases at week 6 with regimen DD4A (rapid early responders)	Nephrectomy, RT, regimen DD4A. No whole-lung irradiation
Stage I–III focal anaplasia	Nephrectomy, RT, regimen DD4A
Stage I diffuse anaplasia	
Stage IV focal anaplasia	
Stage II–IV diffuse anaplasia	
Stage IV CCSK	
Stage I–IV RTK	Nephrectomy, RT, regimen UH1
Stage I–III CCSK	Nephrectomy, RT, regimen I (RT omitted for stage I)

CCSK clear cell sarcoma of kidney; *FH* favorable histology; *LOH* loss of heterozygosity; *RTK* rhabdoid tumor of kidney
Regimens: *DD4A* vincristine/dactinomycin/doxorubicin; *EE4A* vincristine/dactinomycin; *I* vincristine/doxorubicin/cyclophosphamide, cyclophosphamide/etoposide; *M* vincristine/dactinomycin/doxorubicin, cyclophosphamide/etoposide; *UH1* cyclophosphamide/carboplatin/etoposide, vincristine/doxorubicin/cyclophosphamide

6.6 Intensity Modulated Radiation Therapy (IMRT) for Wilms Tumor

Like in other pediatric tumors, radiation therapy techniques used in Wilms tumor continues to be critically examined. Lung and mediastinal

Table 6.3 Radiation therapy recommendations for COG Wilms tumor protocols

Tumor stage/histology	RT dose and fields
Stage I and II FH	No RT
Stage III FH, Stage I–III focal anaplasia, Stage I–II diffuse anaplasia, Stage I–III CCSK[c]	10.8 Gy flank[a] RT[b]
Stage III diffuse anaplasia, Stage I–III RTK	19.8 Gy (infants 10.8 Gy) flank[a] RT[b]
Stage IV (lung metastases, FH)	12 Gy (whole-lung irradiation in children who are not in complete remission at week 6 after induction chemotherapy)
Stage IV (lung metastases, UH)	12 Gy whole-lung irradiation regardless of chemotherapy response
Stage IV (liver metastases)	No RT if resected before chemotherapy, all others 19.8 Gy
Stage IV (brain metastases)	21.6 Gy (whole brain) + 10.6 Gy (local boost) or whole brain 30.6 Gy
Stage IV (bone metastases)	25.2 Gy (tumor +3 cm margin)
Lymph node metastases not surgically resected	19.8 Gy
Relapsed Wilms tumor (flank/abdomen)	12.6–18 Gy (age < 12 months) and 21.6 Gy in older children if previous radiation dose is ≤10.8 Gy
	9 Gy boost to gross residual tumor after surgery

CCSK clear cell sarcomas of the kidney; *FH* favorable histology; *RTK* rhabdoid tumors of the kidney; *UH* unfavorable histology

[a]Whole-abdomen irradiation is indicated when there is diffuse tumor spillage, intraperitoneal tumor rupture, peritoneal tumor seeding, and cytology-positive ascites. When dose is >10.8 Gy, renal shielding is required to limit the dose to the remaining kidney to <15 Gy

[b]A boost of 10.8 Gy is to be administered to areas of gross residual tumor after surgery

[c]Patients with stage I CCSK will not receive flank irradiation if lymph node sampling and central pathologic review were performed

irradiation with or without doxorubicin has resulted in a higher incidence of cardiac complications such as congestive heart failure (CHF), myocardial infarction, pericardial disease and valvular heart disease in childhood cancer survivors (Green et al. 2001b; Pein et al. 2004; Tukenova et al. 2010). The demonstration of a threshold dose (>5 Gy) for cardiac mortality has highlighted the importance of delivering a lower dose to the heart (Pein et al. 2004). Dosimetry studies have shown several advantages for the use of whole-lung IMRT over standard AP-PA techniques. They include superior cardiac protection, superior four dimensional (4D) lung PTV dose coverage and superior dose-uniformity in the lungs with fewer hot spots (Kalapurakal et al. 2013c) (Fig. 6.4). Another report has shown that compared to standard AP-PA techniques, the use of whole liver IMRT in stage IV patients with liver metastases was associated with superior 4D–liver dose coverage and reduced dose delivery to the remaining solitary kidney (Kalapurakal et al. 2013b). Another finding of these reports is the importance of using 4D simulation to accurately determine the internal target volume (ITV) of the lung and liver after consideration for maximal organ movement during respiration. A prospective multi-center clinical trial has confirmed the dosimetric advantages of cardiac protection with IMRT and demonstrated the feasibility and safety of cardiac sparing whole lung IMRT in children with pulmonary metastases (Kalapurakal et al. 2014).

6.7 Radiation Therapy Planning

6.7.1 Flank RT

The flank treatment field is determined by the CT/MR scan volume of the tumor-bearing kidney at initial presentation before administration of chemotherapy and includes the outline of the kidney and associated tumor with a 1 cm margin. The superior, inferior and lateral borders of the radiation therapy field should be placed at the edge of targeted volume approximately 1 cm from the kidney volume at initial presentation. The medial border of the treatment field should be extended across the midline to include all of the vertebral bodies with a margin of 1 cm. In the presence of tumor thrombus involving the IVC, the treatment

volume should include the entire thrombus with a 1 cm margin. In the presence of lymph node involvement, the entire length of the paraaortic lymph node chain from the crus of the diaphragm to the lower border of L5 should be included in the treatment volume. The flank RT fields are delivered using AP-PA parallel-opposed beams (Fig. 6.3a).

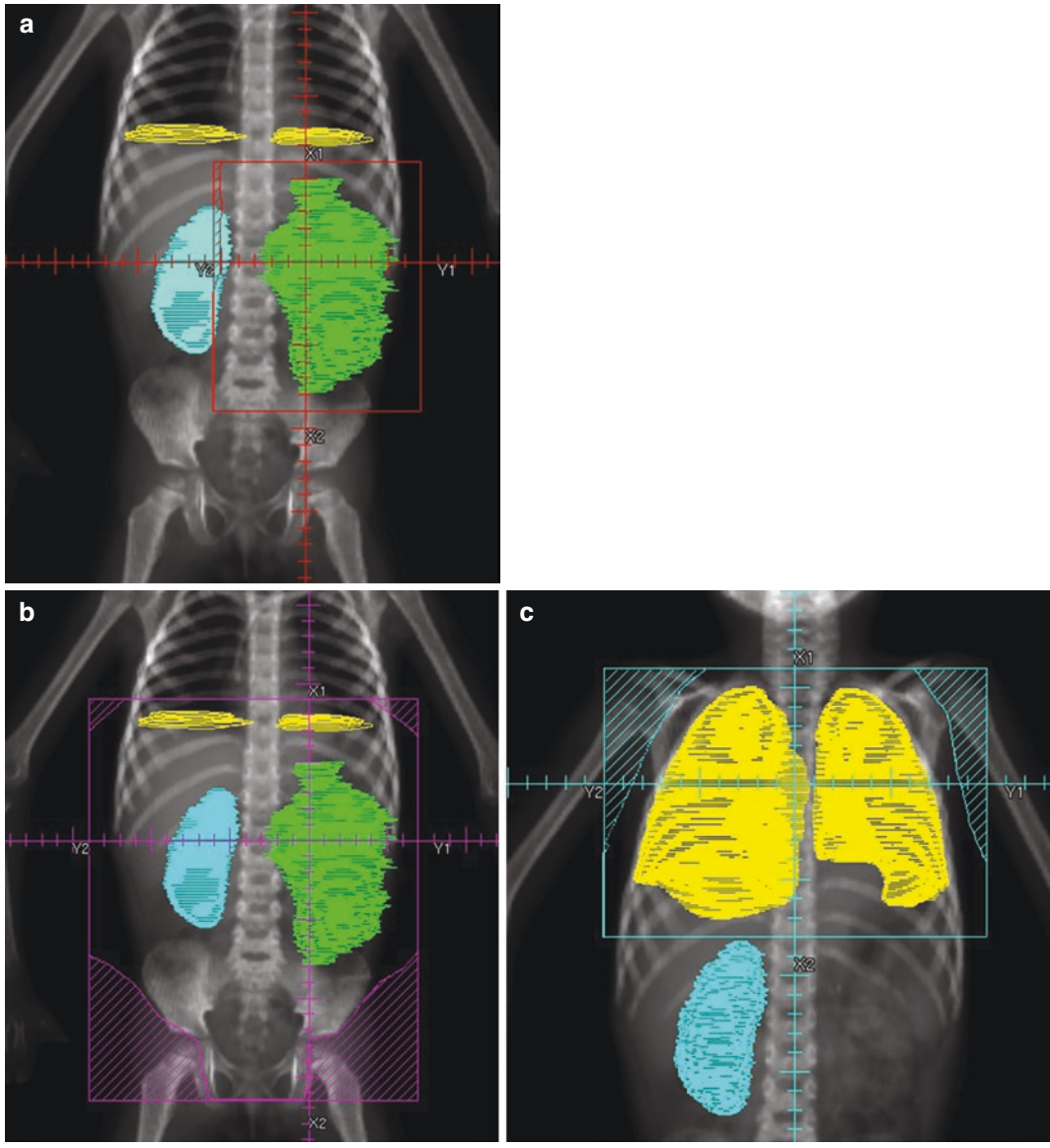


Fig. 6.3 (**a**) Anteroposterior left flank radiation portal in a child with a stage III favorable histology Wilms tumor. The superior and inferior field margins are placed approximately 1 cm from the preoperative Wilms tumor plus renal volume (*green*). The medial field margin should include the entire width of the vertebral body to irradiate the lymph nodes and avoid scoliosis. The normal right kidney (*blue*) and the domes of the diaphragm (*yellow*) are shown. (**b**) Anteroposterior whole-abdomen radiation portal. The upper margin of the abdominal field must include the diaphragm. The acetabulum and femoral head should be excluded from the irradiated volume to decrease the probability of slipped femoral epiphysis. The preoperative Wilms tumor plus renal volume (*green*), normal right kidney (*blue*) and domes of the diaphragm (*yellow*) are shown. (**c**) Anteroposterior whole-lung radiation portal. A review of the sagittal and coronal images during CT simulation, is required to ascertain inclusion of the anterior and posterior costophrenic angles with a 1 cm margin at the inferior edge of the treatment volume. The whole lung volume (*yellow*) and normal right kidney (*blue*) are shown

6.7.2 Whole Abdomen (WA) RT

The WART field should encompass the entire peritoneal cavity that extends from the dome of the diaphragm superiorly to the pelvic diaphragm inferiorly. The superior border should be approximately 1 cm above the dome of the diaphragm and the inferior border should be at the bottom of the obturator foramen. The lateral borders of the field will be placed approximately 1 cm beyond the lateral abdominal wall. The femoral heads and portions of the heart (beyond a 1 cm margin from the diaphragm) should be shielded using customized blocking (Fig. 6.3b).

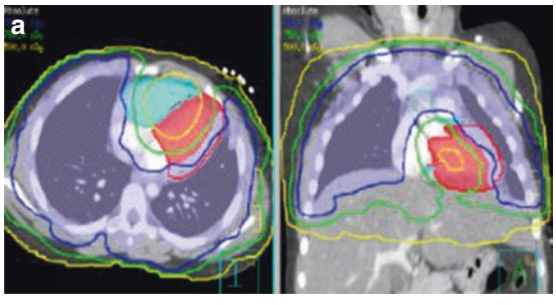
Supplemental boost RT Supplemental RT is required after flank or WART for gross residual tumor after surgery. The use of 3DCRT or IMRT is preferred. The GTV is the postoperative residual tumor and the CTV will be an anatomically confined margin of 0.5 cm surrounding the GTV. The PTV margin can range from 0.5 to 1 cm.

6.7.3 Whole Lung RT

The treatment fields should encompass both lungs regardless of the number and location of metastases. The target volume includes the entire lung volume, mediastinum and the pleural recesses especially the inferior-most extent of the anterior and posterior costo-diaphragmatic recesses as defined by 3D or 4D CT simulation scans (Kalapurakal et al. 2013c). The superior, inferior and lateral borders of the treatment fields should be placed 1 cm beyond this target volume. The humeral heads and associated joint spaces should be shielded. If a patient requires both whole lung and either flank or whole-abdomen RT, all treatment volumes should be treated concurrently. An AP-PA technique or cardiac sparing IMRT technique may be used for whole lung RT (Kalapurakal et al. 2013c) (Figs. 6.3c and 6.4).

6.7.4 Liver RT

The entire liver should be irradiated if the liver is diffusely involved with metastatic disease. If the entire liver volume is not involved, the individual metastases should be irradiated with a 2 cm margin based on the residual tumor at the time of treatment planning. The site(s) of resected metastases will require RT if the margins are positive. In the setting of complete response to chemotherapy, the investigator will be required to administer RT to the metastatic site using a 2 cm margin based on the pre-chemotherapy volume. While irradiating the liver, the dose to the upper pole of the remaining kidney should be monitored. A posterior kidney block may be inserted in order to limit the dose to the remaining kidney to ≤14.4 Gy. An AP-PA technique or IMRT technique may be used for



b LV Volume/%Dose Gy	Standard WLI	IMRT WLI	P-value
V95 (14.3Gy)	98.7%	33%	<0.0001
V83 (12.5Gy)	99.8%	61%	<0.0001
V67 (10Gy)	99.95%	82%	<0.0001
V50 (7.5Gy)	100%	95%	0.006

Fig. 6.4 Cardiac sparing 4-dimensional-based intensity modulated radiation therapy (IMRT) plan showing 95% isodose line (*blue*), 75% (*green line*), and 50% (*yellow line*) on CT images of left ventricle (*red*), right ventricle (*light blue*), and whole lung planning target volume (*purple*). (**a**) Axial image and (**b**) coronal image showing biventricular sparing with IMRT. The corresponding left ventricular (LV) volume doses received with standard and IMRT treatment plans are shown in the adjacent table (Kalapurakal et al. 2013c)

whole liver RT. The use of 4D CT simulation is encouraged to avoid geographic miss of the tumor due to breathing (Kalapurakal et al. 2013b). Liver regeneration occurs after surgery in patients who undergo hepatic resection. Regenerating hepatic tissues are especially vulnerable to radiation. Radiation therapy should be withheld in patients undergoing resection until Day 10 after surgery.

6.7.5 Brain RT

In patients with brain metastases, the whole brain is included in the irradiation field to a dose of 21.6 Gy or 30.6 Gy. When the whole brain dose is 30.6 Gy, no additional boost irradiation is required. However, if the whole brain dose is 21.6 Gy, a boost of at least 10.8 Gy is required. In patients with ≤3 circumscribed lesions especially in patients younger than 3 years, a limited volume (tumor, or tumor bed only with 0.5 cm margin) boost dose of 10.8 Gy in 6 fractions using 3DCRT or IMRT may be administered after whole brain RT to 21.6 Gy.

6.8 Chemotherapy

Single-agent chemotherapy has been used for Wilms tumor since the 1950s, when both dactinomycin and vincristine were found to be active. The interplay between chemotherapy and locoregional radiation was tested in the initial NWTS studies. NWTS-1 showed that RT conferred no advantage in children younger than age 24 months with group I tumors who also received 15 months of dactinomycin (D'Angio et al. 1976). NWTS-2 showed that RT could be avoided in all children with group I Wilms tumor if they received both vincristine and dactinomycin (D'Angio et al. 1981). The results of NWTS-3 showed that stage II tumors required only vincristine and dactinomycin without any RT. NWTS-3 also demonstrated an interaction between chemotherapy and RT: 10.8 Gy with three drugs (vincristine, dactinomycin, doxorubicin) was equivalent to 20 Gy with two drugs (vincristine, dactinomycin) (D'Angio et al. 1989). In NWTS-4, two questions were posed concerning duration of chemotherapy (6 vs. 15 months) and the delivery of dactinomycin and doxorubicin (pulse-intensive, single-dose vs. 5-day course of dactinomycin or 3-day course of doxorubicin). Results showed no advantage to prolonged therapy or divided doses, which actually proved to be more toxic; the consolidated 2-year, relapse-free rate and survival results were 90% and 97%, respectively, for the low- and high-risk patients. Thus the shorter courses of the pulse-intensive regimens are now considered standard, reducing both clinic time and cost for both parents and staff (Green et al. 1998). NWTS-5 asked whether young patients less than 24 months old with stage I favorable histology Wilms tumor weighing less than 550 g could be treated with nephrectomy only without adjuvant chemotherapy. The study was stopped early because the number of relapses observed exceeded the predefined stopping rule. However, nearly all patients with relapse were successfully treated, leading to 5-year EFS and OS rates of 84% and 98%, respectively (Green et al. 2001a; Shamberger et al. 2010). Based on the outstanding OS, the question of omitting adjuvant therapy was readdressed in the recent COG study.

6.8.1 Anaplastic Histology

In NWTS-3 and NWTS-4 the addition of cyclophosphamide to vincristine, dactinomycin and doxorubicin for stages II to IV diffuse anaplastic tumors resulted in significant improvement in 4-year relapse-free survival (27% vs. 55%) (Green et al. 1994a). Patients with all stages of focal anaplastic histology or stage I diffuse anaplastic histology had excellent outcomes, regardless of treatment regimen. Based on these results,

patients with stage I anaplastic tumors were treated with vincristine and dactinomycin for 18 weeks without RT. Patients with stage II to IV diffuse anaplastic histology were treated with vincristine, doxorubicin, cyclophosphamide, and etoposide for 24 weeks plus flank/abdominal RT. Among 2596 patients with Wilms tumor enrolled onto NWTS-5, 281 (10.8%) had anaplastic histology. The 4-year EFS and OS rates for stage I anaplastic tumors was 70% and 83%, respectively. These results were less satisfactory than expected and inferior to stage I favorable histology tumors. Therefore, the recent COG study augmented therapy for this group of patients to include doxorubicin and flank radiation. The 4-year EFS and OS in stages II, III, and IV diffuse anaplastic tumors were 83% and 82%, 65% and 67%, and 33% and 33%, respectively (Dome et al. 2006). These results form the basis for the recent COG study that recommended further augmentation of therapy for stage II-IV diffuse anaplastic tumors.

6.8.2 Clear Cell Sarcoma

Data from NWTS-1 to NWTS-4 suggested that the addition of doxorubicin to vincristine and dactinomycin improved relapse-free survival rates of patients with CCSK (Argani et al. 2000; Green et al. 1994b). NWTS-4 included a double-randomization that evaluated the effect of "pulse-intensive" dactinomycin and doxorubicin given over 1 day instead of 3–5 days (first randomization) and of total duration of therapy (second randomization). In patients with CCSK there was no significant difference in outcome between the standard and pulse-intensive chemotherapy regimens. However, there was a trend toward improved relapse-free survival with long duration therapy (additional 9 months) compared to standard chemotherapy with 8-year relapse-free survival estimates of 88% and 61%, respectively (P = 0.08). However, there was no difference in OS, with 8-year OS estimates of 88% and 86% for the long and short-duration therapy (Seibel et al. 2004). A group of patients with CCSK that fares particularly well are those with stage I disease. A recent analysis of patients enrolled on NWTS 1–5 with stage I CCSK based on the updated NWTS-5 definition of stage I disease showed that regardless of treatment regimen, the EFS and OS rates were 100% (Kalapurakal et al. 2013a).

6.9 Children's Oncology Group Studies

The COG is the successor of the NWTS. The COG risk-group classification for treatment assignment in the new generation of Wilms tumor protocols is shown in Table 6.2. This classification will, in addition to tumor stage, also consider patient's age, tumor weight, presence or absence of LOH at 1p and 16q, and response to chemotherapy in children with FH tumors and lung metastases. The main objectives of the first generation of COG protocols are listed below. The COG chemotherapy and radiation therapy regimens are outlined in Tables 6.2 and 6.3. All of these studies have completed accrual and are currently closed. While final results of these studies are awaited, some of these studies have preliminary outcome data that are shown below.

AREN03B2 This is a renal tumors classification, biology, and banking study. The main objectives were: to classify patients with renal tumors by histologic categorization, surgicopathologic stage, presence of metastases, age at diagnosis, tumor weight, and LOH for chromosomes 1p and 16q and to maintain a biologic samples bank to make specimens available to scientists to evaluate additional potential biologic prognostic variables and for the conduct of other research by scientists.

AREN0321 This was a study for the treatment of children with high-risk renal tumors. The main objectives were: to evaluate whether a regimen of cyclophosphamide/carboplatin/etoposide

alternating with vincristine/doxorubicin/cyclophosphamide improves the EFS and OS of patients with diffuse anaplastic Wilms tumor and malignant rhabdoid tumor of the kidney; to evaluate in a phase II "window" study, the antitumor activity of a combination of vincristine and irinotecan against metastatic diffuse anaplastic Wilms tumor; to maintain the excellent EFS of patients with stage I CCSK without the use of abdominal irradiation.

Preliminary Results: A total of 24 patients with stage IV diffuse anaplastic Wilms tumor were enrolled on the phase II window with vincristine and irinotecan. The partial response rate was 79% indicating that this regimen has high response rate in patients with diffuse anaplasia (Daw et al. 2014).

AREN0532 This was a study for the treatment of children with very low and standard risk FH Wilms tumor. The objectives were: to demonstrate that very low risk patients treated by nephrectomy and observation alone will have a 4-year EFS rate of ≥85% and 4-year OS rate of ≥95%; to improve the current 4-year EFS for patients with FH Wilms tumor with LOH of 1p and 16q by adding doxorubicin but not RT to the standard dactinomycin and vincristine regimen.

Preliminary Results: A total of 116 children with very low risk Wilms tumors were treated with nephrectomy alone on this study and their 4-year EFS and OS rates were 90% and 100%, respectively. Tumor 11p15 methylation status was highly predictive of relapse (Fernandez et al. 2015b). Among patients with stage I/II tumors with LOH at 1p and 16q the 4-year EFS after augmentation of therapy with DD4A was 84% compared to 75% with regimen EE4A (Fernandez et al. 2015a).

AREN0533 This is a study for the treatment of newly diagnosed higher risk FH Wilms tumors. The objectives were: to demonstrate that patients with stage IV FH Wilms tumor with pulmonary metastases only, who have complete resolution of the pulmonary lesions after 6 weeks of regimen DD4A chemotherapy (vincristine, dactinomycin, and doxorubicin) called rapid complete responders (RCR), will have at least an 85% 4-year EFS after therapy with additional chemotherapy (regimen DD4A) and without WLI; to demonstrate that stage IV FH patients who do not have resolution of pulmonary metastases by week 6, called slow incomplete responders (SIR), will have a 4-year EFS rate of 85% with the addition of cyclophosphamide and etoposide to a modified regimen DD4A (regimen M) and WLI; to improve the 4-year EFS rate to 75% for patients with stage III or IV FH Wilms tumor with LOH for chromosomes 1p and 16q.

Preliminary Results: Among patients with stage III/IV tumors with LOH at 1p and 16q the 4-year EFS after augmentation of therapy with regimen M was 92% compared to 66% with regimen DD4A (Dix et al. 2015a). Among 296 patients with lung metastasis 105 (39%) had a complete response at week 6. Their 4-year EFS and OS rates were 78% and 95%, respectively without WLI. While these results were inferior to the EFS of 85% with WLI and DD4A, the difference was not statistically significant (Dix et al. 2015b). Among patients who had a slow incomplete response (SIR) at week 6, the augmentation of therapy with regimen M and WLI resulted in a 3-year EFS and OS of 88% and 92%, respectively. These outcomes were significantly superior to the estimated EFS of 75% with regimen DD4A and WLI (Dix et al. 2014).

AREN0534 This is a study for the treatment for patients with bilateral, multicentric, or bilaterally predisposed unilateral Wilms tumor. The objectives were: to improve the 4-year EFS rate to 73% for patients with bilateral Wilms tumor; to prevent complete removal of at least one kidney in 50% of patients with bilateral Wilms tumor (BWT) by using prenephrectomy three-drug chemotherapy; to facilitate partial nephrectomy in lieu of nephrectomy in 25% of children with unilateral tumors and aniridia,

BWS, hemihypertrophy, or other overgrowth syndromes by using prenephrectomy two-drug chemotherapy; to have 75% of children with BWT undergo definitive surgical treatment by 12 weeks after initiation of chemotherapy. This study has just completed accrual and no data is available yet.

6.10 SIOP Wilms Tumor Studies

While the NWTS strategy is to avoid preoperative therapy and perform up front surgery in order to obtain the maximum amount of information concerning prognostic factors and tailor therapy accordingly, the SIOP strategy is to deliver upfront chemotherapy before surgery in order to facilitate easier surgical removal of tumor with a lower incidence of intraoperative rupture and down staging of the tumor to reduce treatment-related morbidity by reducing the total amount of treatment (De Kraker 1997; Lemerle et al. 1976, 1983). The revised SIOP renal tumor classification and SIOP staging system are shown in Tables 6.4 and 6.5.

Table 6.4 Revised SIOP classification of renal tumors (2001)

Low-risk tumors
Mesoplastic nephroma
Cystic partially differentiated nephroblastoma
Completely necrotic nephroblastoma
Intermediate-risk tumors
Nephroblastoma—epithelial type
Nephroblastoma—stromal type
Nephroblastoma—mixed type
Nephroblastoma—regressive type
Nephroblastoma—focal anaplasia
High-risk tumors
Nephroblastoma—blastemal type
Nephroblastoma—diffuse anaplasia
Clear cell sarcoma of the kidney
Rhabdoid tumor of the kidney

Table 6.5 SIOP Wilms tumor staging system

Stage I
(a) The tumor is limited to kidney or surrounded with a fibrous pseudocapsule if outside of the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated with the tumor but it does not reach the outer surface, and it is completely resected (resection margins 'clear')
(b) The tumor may be protruding ('bulging') into the pelvic system and 'dipping' into the ureter (but it is not infiltrating their walls)
(c) The vessels of the renal sinus are not involved
(d) Intrarenal vessel involvement may be present
Stage II
(a) The tumor extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into peri-renal fat but is completely resected (resection margins 'clear')
(b) Tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but it is completely resected
(c) Tumor infiltrates adjacent organs or vena cava but is completely resected
Stage III
(a) Incomplete excision of the tumor which extends beyond resection margins (gross or microscopical tumor remains post-operatively)
(b) Any abdominal lymph nodes are involved
(c) Tumor rupture before or intra-operatively (irrespective of other criteria for staging)
(d) The tumor has penetrated through the peritoneal surface
(e) Tumor implants are found on the peritoneal surface
(f) The tumor thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by surgeon
(g) The tumor has been surgically biopsied (wedge biopsy) prior to pre-operative chemotherapy or surgery
Stage IV
Hematogeneous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region
Stage V
Bilateral renal tumors at diagnosis. Each side should be substaged according to above classifications

SIOP 1: Children were randomized to receive 20 Gy preoperative RT or undergo primary nephrectomy. While there was no risk difference in OS, there was a significantly higher risk of tumor rupture after RT compared to primary surgery (4% vs. 32%). Also, the risk of recurrence was significantly higher at 51% after tumor rupture compared to 27% among those without rupture. Preoperative treatment was found to significantly downstage tumors compared to up front surgery. **SIOP 2** was a nonrandomized study comparing patients receiving 20 Gy of preoperative RT and actinomycin D compared to primary nephrectomy. Even though children with smaller tumors underwent primary nephrectomy, tumor rupture was significantly lower at 5% in the preoperatively treated group compared to 20% after up front surgery (De Kraker 1997, Lemerle et al. 1976, Lemerle et al. 1983). **SIOP 5** was designed to ascertain whether preoperative chemotherapy with actinomycin D and vincristine was as good as preoperative RT to 20 Gy and actinomycin D. Postoperatively RT was given for stage II and III tumors but omitted for stage I disease. There was no difference in the tumor rupture rate, postoperative stage, relapse-free or OS between the two arms. Following preoperative chemotherapy alone 43% had stage I disease and did not receive any RT (Jereb et al. 1994). **SIOP 6** adopted actinomycin D and vincristine preoperative chemotherapy for all patients. Patients who had stage I disease at the time of surgery were randomized to receive postoperative vincristine and actinomycin D for 17 or 38 weeks. All lymph node–negative stage II patients received 38 weeks of vincristine and actinomycin D and were randomized to receive or not receive 20 Gy of involved-field RT. There were eight relapses among 50 non-irradiated patients compared to only one local recurrence of the 58 patients given postoperative RT. However, there was no difference in the OS (Tournade et al. 2001; Tournade et al. 1993). **SIOP 9** had, as its primary question, the appropriate duration of prenephrectomy chemotherapy (4 weeks vs. 8 weeks). There was no difference between the two arms for the frequency of stage I tumors (64% vs. 62%), tumor rupture (1% vs. 3%), and 5-year OS (92% vs. 87%). Thus, 4 weeks of preoperative chemotherapy was established as the standard duration of induction chemotherapy (Boccon-Gibod et al. 2000; de Kraker et al. 2004). In **SIOP 93-**after standard preoperative chemotherapy, patients with stage I low-grade histology received no additional therapy. Patients with stage I intermediate or high-grade tumors were randomized to a 4-week postoperative program of vincristine and actinomycin D or a 6-week program. All stage II and III patients with intermediate grade tumors received therapy as in SIOP trial 9. Stage II and III high-grade tumors were treated with ifosfamide, etoposide, and carboplatin. Among 410 patients with stage I intermediate-risk and anaplastic Wilms tumor after 4 weeks of chemotherapy were randomized postoperatively to no further therapy or two additional cycles of chemotherapy. There was no difference in 2-year EFS between the no further therapy group (91%) compared to those who received additional chemotherapy (89%) (Ora et al. 2007; Vujanic et al. 2009). A diminishing number of patients have received RT in the sequential SIOP trials. The estimated percentages of patients who received irradiation are as follows: SIOP 1, 90%; SIOP 2, 90%; SIOP 5, 72%; SIOP 6, 34%; SIOP 9, 24% (Jereb et al. 1994). The current **SIOP 2001 trial** has closed. The current SIOP 2001 chemotherapy and radiation therapy guidelines are summarized in Tables 6.6 and 6.7. A recent report from SIOP 2001 showed that intensification of chemotherapy for blastemal type Wilms tumors resulted in improved 5-year EFS of 80% compared to 67% seen in SIOP93-01. There was no difference in OS. The benefit of

Table 6.6 SIOP 2001 protocol chemotherapy regimens for newly diagnosed localized Wilms tumors

Pre-operative treatment
Vincristine 1.5 mg/m^2 (maximum dose 2 mg) weekly for 4 weeks (4 doses in total)
Actinomycin D 45 μg/kg (maximum dose 2 mg) at week one and three (2 doses in total)
Post-operative treatment
Regimen AV-1
Stage I, Intermediate Risk Only
Vincristine 1.5 mg/m^2 (maximum dose 2 mg) weekly for 4 weeks (4 doses in total)
Actinomycin D 45 μg/kg (maximum dose 2 mg) at week two (day 7) of the post-operative regimen
Regimen AVD
Stage I, High Risk and Stage II/III Intermediate Risk Randomized to This Regimen
Vincristine 1.5 mg/m^2 (maximum dose 2 mg) weekly for 8 weeks (8 doses). Thereafter, 6 courses of Vincristine on day one and seven with a two week interval between courses (12 doses in total) to start at week 11
Actinomycin D 45 μg/kg (maximum dose 2 mg) at week 2, 5, 8, 11, 14, 17, 20, 23 and 26 (9 doses in total)
Doxorubicin 50 mg/m^2 in a 4–6 h infusion every 6 weeks to start in week two concurrently with the first dose of Actinomycin D and the second dose of Vincristine
The total duration of the post-operative chemotherapy is 27 weeks
Regimen AV-2
Stage II, Low Risk and Stage II/III Intermediate Risk Randomized to This Regimen
Vincristine 1.5 mg/m^2 (maximum dose 2 mg) weekly for 8 weeks (8 doses). Thereafter, 6 courses of Vincristine on day one and seven with a two week interval between courses (12 doses in total) to start at week 11
Actinomycin D 45 μg/kg (maximum dose 2 mg) at week 2, 5, 8, 11, 14, 17, 20, 23 and 26 (9 doses in total)
The total duration of post-operative chemotherapy is 27 weeks
Stage II, Intermediate Risk Randomization
R → **REGIMEN AVD** (the same as stage I high risk) **R** → **REGIMEN AV-2** (the same as stage II low risk)
'High Risk' Treatment Regimen
All high risk histology tumors of Stage II or III
There are two alternating courses of chemotherapy. Both combinations consist of 2 drugs.
Cyclophosphamide 450 mg/m^2 for 3 consecutive days with Doxorubicin 50 mg/m^2 on day one of this course (total of 6 courses) with a 6 week interval
Etoposide (VP16) 150 mg/m^2 for three consecutive days together with Carboplatin 200 mg/m^2 also for three consecutive days (a total of 6 courses) given every 6 weeks from week 4 on, i.e., on weeks 4, 10, 16, 22, 28 and 34
Stage III, Low Risk Receive Regimen AV-2 Without Radiotherapy
Stage III, Intermediate Risk Randomization
The same chemotherapy regimens are used as in stage II intermediate risk
Stage III, High Risk Receive the 'High Risk' Regimen with Abdominal Radiotherapy

augmented therapy for improved OS was only seen in stage I tumors by the addition of doxorubicin (Van den Heuvel-Eibrink et al. 2015). In another report from SIOP 2001, the omission of doxorubicin for children with stage II-III intermediate risk Wilms tumors without blastemal subtype tumors did not result in inferior outcomes. Following treatments with and without doxorubicin the 2-year EFS was 93% and 88% and 5-year OS was 97% and 96%, respectively (Pritchard-Jones et al. 2015).

Table 6.7 Radiation therapy recommendations for SIOP 2001 Wilms tumor protocol

Flank RT
Stage III intermediate risk: 14.4 Gy
Boost to the macroscopic residual disease after surgery: 10.8 Gy (total dose of 25.2 Gy). Patients with tumor positive lymph nodes should receive a boost to the para-aortic lymph nodes
Stage II, Stage III, high risk: 25.2 Gy
Boost to the macroscopic residual disease after surgery: 10.8 Gy
Whole abdominal RT
The entire peritoneal cavity should be irradiated to a maximum of 21 Gy, with consideration of a boost to a limited area (as for flank RT). Dose per fraction should be lowered to 1.5 Gy
In children under 1 year of age total dose should be reduced to 10–12 Gy
Brain RT
The whole brain is treated to a dose of 25.5 Gy. A small boost may be given (4.5 Gy)
Liver RT
A dose of 20 Gy may be given to the area of R1 resection of metastases
Bone RT
For bone metastases the metastasis may be treated with a dose of 30 Gy
Pulmonary RT
For whole lung RT the total dose is 15 Gy for both lungs (with correction of tissue heterogeneity). The dose per fraction is 1.5 Gy delivered within 10 treatment days. A boost of 10–15 Gy should be considered for areas of gross residual disease after surgery

6.11 Retrieval Therapy

Children with relapsed favorable histology Wilms tumor have a variable prognosis, depending on the site of relapse, the time from initial diagnosis to relapse, and previous therapy. Favorable prognostic factors include no previous treatment with doxorubicin, relapse more than 12 months after diagnosis, and intra-abdominal relapse in a patient not previously treated with abdominal irradiation (Green et al. 2007; Grundy et al. 1989; Malogolowkin et al. 2008). Patients with relapsed or progressive disease after initial chemotherapy with vincristine and dactinomycin and no RT were treated on a specific stratum in NWTS-5, consisting of alternating courses of vincristine, doxorubicin, cyclophosphamide and etoposide/cyclophosphamide, plus surgery and RT. The 4-year EFS and OS was 71% and 81% for all patients, 68% and 81% for those who experienced relapse in the lung only, and 78% and 83% for those who had relapse in the operative bed with or without lung metastasis (Green et al. 2007). Patients who had experienced relapse or whose disease progressed after initial chemotherapy that included vincristine, dactinomycin, and doxorubicin plus RT were treated with alternating courses of drug pairs (cyclophosphamide/etoposide and carboplatin/etoposide), surgery, and RT. The 4-year EFS and OS was 42% and 48% for all patients and 49% and 53% for those who had relapse in the lung only (Malogolowkin et al. 2008).

6.12 Late Effects

The types of late effects of treatment and their severity depend on the age and sex of the child, extent of surgery, chemotherapy drugs, and RT-related factors. The most common cause for renal failure in Wilms tumor patients is bilateral nephrectomy, whereas the second leading cause is RT-induced damage or surgical complications affecting the remaining kidney. The frequency of renal failure in bilateral Wilms tumor was 16.4% for NWTS-1 and NWTS-2, 9.9% for NWTS-3, and 3.8% for NWTS-4 (Ritchey et al. 1996). The incidence of scoliosis ranges from 40 to 60% with radiation doses of 25–40 Gy. However, the rate of scoliosis should be low with the current doses of 10.8 Gy (Paulino et al. 2000; Thomas et al. 1983). The cumulative frequency of congestive heart failure among patients on NWTS-1 to NWTS-4 was 4.4% at 20 years among patients treated initially with doxorubicin and 17.4% among patients treated with doxorubicin for first or subsequent relapse. Factors significantly associated with heart failure were female sex, cumulative doxorubicin dose, lung irradiation, and left-sided abdominal irradiation (Green et al. 2001b). Women who are Wilms tumor survivors have significantly higher rates of adverse pregnancy outcomes, such as malposition of the fetus and premature labor,

with the incidence greatest after flank irradiation to doses higher than 25 Gy. Their offspring more often are premature and of low birth weight compared with control cohorts; a trend toward an increased number of congenital malformations has been noted after flank irradiation (Green et al. 2010; Kalapurakal et al. 2004). The cumulative 15-year risk of second malignant neoplasms was 1.6% among patients enrolled on the NWTS, after a mean follow-up of 7.5 years per patient. Higher doses of abdominal RT and doxorubicin increased the risk of another neoplasm (Breslow et al. 1995). The standardized mortality ratio in an NWTS review was 24.3 within 5 years of diagnosis, 12.6 for the next 5 years, and more than 3.0 thereafter. The main cause of mortality within the first 5 years was related to the original disease. Beyond 5 years the mortality was equally related to the original disease and late effects of treatment including second malignant neoplasms, congestive heart failure, and end-stage renal disease. The risk of death particularly from treatment-related late effects remained elevated even 20 years after diagnosis (Cotton et al. 2009).

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Rare Tumors in Pediatric Oncology

7

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7.1 Introduction

We define rare tumors in pediatric oncology arbitrarily as including the following histologies: retinoblastoma, nasopharyngeal carcinoma, desmoid, non-CNS germ cell tumors, liver tumors, pleuropulmonary blastoma (PPB), chordoma, malignant peripheral nerve sheath tumors, and for some, the true connective tissue tumors. Relative to adult tumors, practically every tumor in this text could be considered rare but these histologies are rare even within the scope of pediatric care.

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Because radiation therapy is not typically used with non-CNS germ cell tumors, PPB and liver tumors, and because connective tissue tumors (sarcomas) will be the focus of Chapter 4, we will focus on retinoblastoma, nasopharyngeal carcinoma, and desmoid tumors. For diseases that occur commonly in adults but rarely in children such as breast cancer, we will not cover the diseases in detail. Adult techniques are used with special anatomic considerations that apply to children on a case by case basis. For even more rare tumors, a large number of registries exist worldwide (Rare tumor registries in the United States 2010; Rare Disease Registries in Europe 2015).

Because these tumors are so rare, the Children's Oncology Group (COG) established a committee dedicated to their study in 2002. No single institution in the world can accrue enough patients to study and make progress in the treatment of these "orphan" diseases. The COG formed in 2002 from the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG) and each of these smaller groups had established committees studying single classes of rare tumors. Other international organizations exist for the same reason. The first European meeting on rare pediatric tumors took place in Padua, Italy on June 26, 2008 and included teams from Italy (TREP, founded in 2000), the UK (founded in 1998), Poland (PRTS, founded in

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2005), Germany (German Rare Tumor Working Party, founded in 2008), and France.

7.2 Retinoblastoma

Retinoblastoma (RB) makes up less than 3% of the diagnosis of cancer in children less than 15 years of age in the United States (US). In the first year of life, however, it makes up 11% of cancer diagnoses. About two-thirds of all cases occur in those under the age of 2 years and 95% in those under the age of 5 years. In the US, incidence of RB remains relatively unchanged over the 20 year period from 1975 to 1995. In the US, the incidence remained balanced during this timeframe between whites and blacks and between males and females at about 3.7 cases per million children (Ries et al. 1999). In the US that equates to about 350 cases per year and about 5000–8000 cases worldwide.

7.2.1 History

The first known evidence of man knowing about ocular tumors may have come in the form of a sculpture found in Peru from almost 2000 years ago showing an ocular tumor. A terracotta figure from the Meyer-Steineg collection from the Island of Kos in Greece is thought by art historians to demonstrate retinoblastoma in the right eye of a child (Gmek and Gourevitch 2000). Meyer-Steineg found instruments of ophthalmological use from around the second century BCE from excavations on Kos (Jackson et al. 1913).

The first written, Western description of retinoblastoma is credited to the Dutch anatomist Peiter Pauw's notes from 1597 describing a 3 year old boy with a rapidly-growing, large ocular tumor (Kivela and Polkunen 2003). This same case was republished by Bartolini in 1657 and again in the nineteenth century by the German Julius Hirschberg, and then in the twentieth century by Edwin Dunphy as part of his 1963 Edward Jackson Lecture in Boston. Pauw was a professor of anatomy in the Academy in Leiden and the description came from a postmortem examination in the form of his autopsy notes.

Hayes then published an article about a bilateral case in 1767 entitled "The Case of a Diseased Eye Communicated to Mr. William Hunter by Mr. Hayes, Surgeon" (Hayes 1767). It was at about this time that the clinical sign we now associate with retinoblastoma, leukocoria, was first described in the literature. The first person to strongly correlate the clinical sign with the diseases strongly was Georg Joseph Beer in Vienna (Beer 1813). Around the same time a Scottish surgeon based in London named James Wardrop described retinoblastoma in a treatise that was focused on assembling all the known data on retinoblastoma at the time in one place. He concluded that because it was very different in terms of the age when it was found, being in children, that it was a different disease than that found in adults. He was likely the first to ascribe the source of the disease to the retina based on his dissections. His work summarized the natural progression of the disease in a manner that is felt to be essentially that of today's clinic. He is perhaps best known for being the first to champion enucleation (Wardrop 1809).

Enucleation was slow to become accepted because general anesthesia did not come into use until chloroform was discovered. Anesthesia in the form of chloroform and the invention of the ophthalmoscope in 1847 by Babbage (Lyons 1940) permitted a diagnosis at an early enough point to allow for enucleation. Surgical techniques evolved reflecting improved understanding of the natural patterns of spread of the disease with survival rates rising from 5% in 1869 (Hirschberg 1869) to 57% in 1916 (Leber 1911).

The first likely case of radiation's use for retinoblastoma was performed by H.L. Hilgartner in Austin, Texas in 1903 for a three and half year old with bilateral disease. He treated the patient with 84 fractions and the patient was lost to follow-up. The right eye was larger and "became shrunken" while the left eye lesion was smaller and was described as "resorbed" (Hilgartner 1903). Schonberg then presented a series of three papers looking at the long term outcome of a 2 year old girl with bilateral disease in which one eye was surgically managed and the less advanced eye was treated with radiation, a strategy still in

use today (Schoenberg 1927a). At 10 years the child had useful vision (Schoenberg 1927b) but at 25 years the child developed a sarcoma that ultimately spread and took her life (Reese 1951). Perhaps the most famous of the early reporters of radiation was Frederick Herman Verhoeff of the Massachusetts Eye and Ear Infirmary. He reported the case of a 17-month old boy treated in 1917 for a massive left sided lesion without success and then to the right side for an early lesion treated with an anterior chamber sparing technique. That child did well until 1977 when a basal cell carcinoma developed on the lid; it recurred and later a squamous cell carcinoma arose in the lid region as well.

Modern approaches to the treatment of retinoblastoma parallel the fields of surgery, pediatric oncology, and pediatric radiation oncology. The use of brachytherapy was first used in 1930 by Moore via a radon seed (Moore 1931). Kupfer used chemotherapy and radiation together for the first time in the treatment of retinoblastoma in 1953 (Kupfer 1953). Local and system therapy development continues unabated to this day.

7.2.2 Pathology

Retinoblastoma source, as noted above, was first described as arising from the retina by Wardrop in 1809 (Wardrop 1809). This was in debate until work from Paris by Robin and Nysten in 1815 confirmed the source to be the retina (Robin and Nysten 1815). In Berlin, Virchow theorized that the cell of origin was glial, but this was based on flawed Golgi staining techniques of the period (Virchow 1864). Other, more accurate methods of the time based on stains, were inconclusive. Despite an unclear link between retinoblastoma and glial cells, Bailey and Cushing described relationships between retinoblastoma cells and medulloblastoma and "neuro-epitheliomas" (Bailey and Cushing 1926).

Research expanded greatly with the development of cell line and placement of retinoblastoma cells into nude mice (Mcfall et al. 1977). Manipulation of retinoblastoma cells was able to achieve differentiation into different tissues of the retina making the source of the retinoblastoma cell uncertain, save to be pluripotent in nature (Kynthsis et al. 1984).

Retinoblastoma at surgery is soft and friable when resected and is often necrotic and calcified, suggesting that it rapidly outgrows its blood supply. Because of this, it often disseminates in the vitreous and retina and forms small white dots, or seeds, when visually examined in vivo. These cases can be difficult to tell apart from multifocal disease (Sang and Albert 1982). Under the microscope, distinctive Flexner-Wintersteiner rosettes can be seen. They are specific to retinoblastoma and consist of a circle of low columnar cells arranged around an eosinophilic membrane-defined lumen centrally. This membrane is similar to the normal membrane at the outer edge of the normal retina. Homer-Wright rosettes consisting of irregular circles of cells surrounding tangles of fibrils that are lacking the eosinophilic internal membrane can also be seen in retinoblastoma but are more commonly seen in neuroblastoma.

A variant of retinoblastoma made of cells that have a distinctive *fleur de lis* pattern of larger cells made up of abundant, eosinophilic cytoplasm. These are called retinocytomas or retinomas. Cells can exhibit more specific characteristics of cell types of the normal retina including photoreceptor-like 9-0 microtubules, neurosecretory granules, synaptic ribbons, and abundant cytoplasmic microtubules.

7.2.3 Genetics and Molecular Pathophysiology

The current understanding of retinoblastoma, that it has both a germ line and a spontaneous pattern of inheritance, was not understood in the nineteenth century because survival was uncommon. Cases exist with family histories suggestive of retinoblastoma's heritability, but as late as 1905 published essays suggest that no such proof of retinoblastoma being inherited existed (Owens 1905). As more patients survived, some had children, had offspring, and data was collected on the patterns of spread and presentation of the

disease. The real breakthrough in the understanding of retinoblastoma and to some degree in human cancer genetics came in 1971 when A.G. Knudeson, Jr. published his paper on the inheritance patterns seen in retinoblastoma using mathematical modeling based on Poisson distribution analysis. From this work came the now famous "two-hit" hypothesis that described the germ line and spontaneous mutation patterns of presentation and inheritance (Knudeson 1971). Knudeson's work fueled a search for the possible retinoblastoma gene that lasted until 1986 when RB1 (the gene's name) became the first cancer gene to be discovered existing on the long arm of chromosome 13, now known to be 13q14 (Friend et al. 1986).

The protein encoded by RB1 is a phosphoprotein expressed in all adult human tissues and consists of 928 amino acids and weighs 110 kDa. The protein is a regulator of the cell cycle at the transition from G1 to S-phase. Normal RB1 presumably is associated with regulation of the cell cycle where mutated RB1 cells lack control of entry into S-phase and more rapid cell cycling results. Normal RB1 is bound to the protein E2F and when it is phosphorylated, releases E2F allowing E2F to bind to DNA and stimulate DNA transcription (Goodrich et al. 1991).

The RB1 gene is large covering over 200 kilobases and containing 27 exons. Mutations have been described across the gene without clear hotspots being defined. Paternal allele's are more commonly involved in the first hit (Zhu et al. 1989). Penetrance of the trait is over 90%.

The second hit occurs in both germinal and non-germinal cases. It is usually chromosomal in nature and may reflect the effects of the first hit and reflects recombination errors. It occurs in much higher frequency than the first hit and appears to be more susceptible to environmental agents (Zhu et al. 1992). New methods are looking at peripheral blood in the diagnosis of RB1 and can tell if loss of heterozygosity has occurred (Ruiz Del Rio et al. 2015).

After both "hits" to the RB1 gene are present, the cells rapidly accumulate genetic damage and tumors develop. Not much is understood because no animal model for retinoblastoma exists at present. Pure knock-out mice for RB1 die at gestational day 14 due to hematopoietic and neuronal failure. A conditionally RB1-deleted p107-deficient mouse model does exist, but this is not like human retinoblastoma and is unlikely to reflect the clinical pathology seen in human retinoblastoma cleanly. The pathways involved downstream of RB1 include p14ARF, MDM2, MDM4). Human tumors express wild type p53, but changes to MDM2/MDM4 may lead to blockage of the p53 pathway (Laurie et al. 2006). RB1 cells typically show losses at 16q1 and amplifications and gains at 1q and 6p.

7.2.4 Genetic Counseling, Etiology, and Unusual Variants

Today patients are counseled that retinoblastoma comes in two main forms, an inherited or germinal form and a spontaneous or non-germinal form. In the inherited, germ-line form both copies of chromosome 13 harbor the mutated gene. Both eyes are affected in 85% of germinal cases and the presentation is in younger children, often under 1 year of age. When both eyes are affected, the mean number of tumors spread across both eyes is five. When in only one eye it is usually multifocal. Eight percent of those with a germ-line mutation have a positive family history of retinoblastoma. The spontaneous form of the disease always happens in one eye and it is uni-focal even if it can appear via instability to be multifocal due to tumor splitting apart and forming large numbers of "seeds" as noted above (Chintagumpala et al. 2007).

The following is a general map of risks based on class of family member:

1. Children of those with retinoblastoma
   (a) If a parent has bilateral disease the risk is 45%.
   (b) If the parent has unilateral disease, the risk is 5%.
      i. Family history positive: the risk remains 45%.
      ii. Family history negative, less than 2%.

2. Siblings of those with retinoblastoma
   (a) Bilateral sibling with a family history, the risk is 45%.
   (b) Unilateral sibling with a family history, the risk is 30%.
   (c) Without family history, the risk is 2% for those with siblings with bilateral disease and 1% with unilateral disease.

It is important to educate the family on the significance of each form of retinoblastoma, to understand the genetic consequences and to understand the risk to family members in the process of planning families. All patients should undergo genetic testing. Because testing is evolving, it is likely that at least two if not more different tests will be performed to analyze a patient's genetics. Additionally, screening for expected tumors associated with retinoblastoma and its treatment is important. Graphical tools have been developed to assist families in understanding the subtleties of a retinoblastoma diagnosis regardless of educational level.

Retinoblastoma is more frequent in Africa, India, and in Native Americans at about 6–10 cases per million) (Chantada et al. 1999). Most of these are unilateral. Most of the patients have the abnormality on the paternal chromosome. Even in wealthy, industrialized countries the disease is more common amongst those of lower financial class and educational status. These data suggest an environmental etiology, but it is unclear what environmental element is at work (Bunin et al. 1989). Hypotheses have been put forward involving diet, HPV virus exposure, and by extension the incidence of cervical cancer and HPV exposure at delivery (Orjuela et al. 2000). Mouse models support a possible HPV etiology (Griep et al. 1998) and about one-third of cases have detectable HPV detected upon genomic evaluation of tumor specimens. Other epidemiologic associations include *in vitro* fertilization (Moll et al. 2003; Cruysberg et al. 2002) and sunlight (Jemal et al. 2000) exposure.

The clinical picture of retinoblastoma is not limited to the development of tumors. Unilateral, non-inherited forms of the disease can present as phenotypically normal. Bilateral (inherited) cases usually present with small lesions in the RB1 gene than cannot be detected. In 5% of cases, however, karyotyping can detect areas of loss and larger areas of loss are correlated with more severe degrees of abnormality (Baud et al. 1999) in what is a constellation of a 13q-loss phenotype:

- Short nose
- Different degrees of mental retardation
- Anteverted ear lobes
- High and broad forehead (frontal bossing)
- Prominent philtrum
- Some have overlapping digits
- Some have microcephaly
- Some have bone growth plate fusion delay

A rare variant of retinoblastoma is the so-called "tri-lateral" retinoblastoma where lesions exist in both orbit and in the pineal region (75–80%) or another suprasellar or parasellar location (20–25%). The intracranial portion presents about 20 months after the bilateral disease is known. The patients have been treated as stage IV extra-ocular retinoblastomas on recent COG trials. They represent primitive neuroectodermal tumors (PNETs) with pathological finding suggesting a possible retinal germinal layer origin. It has been suggested that the decrease in diagnosis of trilateral retinoblastoma may be as a result of an increase in use of early chemotherapy for bilateral disease, making the development of the later-onset brain lesion less likely. Pineal cysts form in cases where chemotherapy has been used and this may represent treated sublinical disease (Popovic et al. 2007; Beck Popovic et al. 2006).

7.2.5 Diagnosis

The diagnosis if retinoblastoma is made initially via careful clinical examination. If a family history of retinoblastoma is known, screening is done so

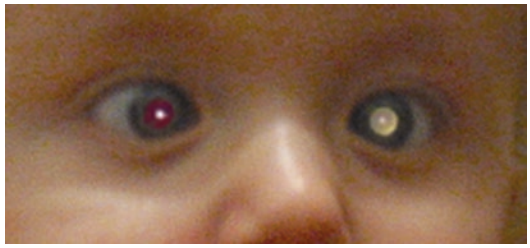


Fig. 7.1 Leukocoria in the left eye from retinoblastoma. Source: Wikipedia, public domain image, submitted by J. Morley-Smith. 2008

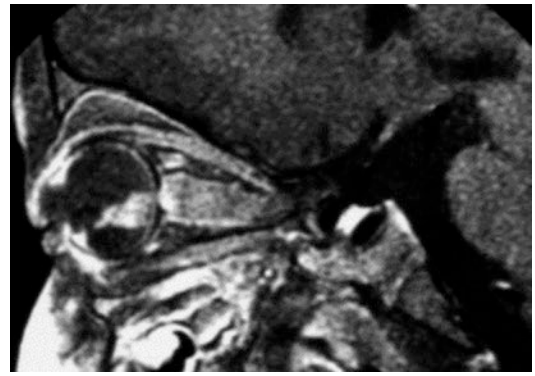


Fig. 7.2 This sagittal T1 enhanced MRI images shows involvement of the optic nerve by tumor. (Public domain Wikipedia)

as to capture the disease as early as possible so as to preserve vision for as long as possible. After an initial clinical exam is done, often driven by leukocoria (Fig. 7.1), examination under anesthesia with a fully dilated pupil is the standard approach used. Mechanical manipulation of the sclera (indentation) is necessary in order to fully visualize the complete retinal surface.

Tumors fall within one of two general categories: endophytic or exophytic. Endophytic tumors grow inward and may seed the vitreous cavity while exophytic tumors grow into the subretinal space causing detachment and can seed into this space. Ophthalmologists document their findings with very detailed hand drawings that to this day are really superior to anything developed in terms of compact documentation. Tumor size, number, location, retinal detachment, the presence and locations of seeds, and the degree of sub-retinal fluid are all part of complete documentation. Additionally, wide-angle retinal imaging, such as provided by the RetCam®, is currently is being used to capture up to 130° angles of view.

For staging purposes, multi-dimensional ultrasound, thin-slice computed tomography (CT), and thin-slice orbital magnetic resonance imaging (MRI) of the orbits are collected (Fig. 7.2).

Using these images, extra-ocular extension is evaluated and if seen, further directed studies are undertaken. Figure 7.2 shows a sagittal MRI from a patient with optic nerve involvement (Aerts et al. 2006). Because 10–15% of patients have metastatic disease, it can be necessary to perform full systemic workups. The findings typically seen with metastatic disease include invasion of the optic nerve beyond the lamina cribrosa, invasion of the iris or ciliary bodies, deep choroidal or scleral invasion, and other direct features of extra-ocular invasion. A full neck examination is indicated in all cases once disease outside of the orbit is suspected. Cerebral spinal fluid, bone scan, and volumetric imaging based on standard principles are indicated in the context of suspected extra-ocular disease.

A partial listing of the differential diagnoses for diseases of the orbit:

- congenital cataract (leukocoria can be present)
- hamartoma (endophytic), choroiditis (exophytic)
- Coat's disease (unilateral telangiectatic retinal blood vessels associated with retinal detachment causing leukocoria and a yellow exudate)
- retinopathy of prematurity (with retinal detachment causing leukocoria)
- retinal astrocytoma, retinoma (benign variant of retinoblastoma)
- persistent hyperplastic primary vitreous

- toxocariasis (associated with endophthalmitis with a resultant membrane formation that can make the pupil appear white)
- Bloch-Sulzberger disease (*incontinentia pigmenti*, and X-linked dominant disease that affects females and which is characterized by a vesiculobullous dermatitis and which may include deformities of the teeth and the CNS including retinal detachment which can cause leukocoria)
- retinal dysphasia (can be unilateral or bilateral)
- Patau's syndrome
  - Norrie's disease
  - Edward's syndrome
  - others
- metastatic disease

7.2.6 Staging

The staging of retinoblastoma that is most accepted currently is the Reese-Ellsworth (R-E) grouping system (Table 7.1). The system was originally used to predict the outcome after external beam radiation therapy and divides each eye into one of five groups based on tumor size, tumor locations, number of lesions, and the presence or absence of vitreous seeding.

Because treatment has shifted from external beam therapy, a new staging system has begun to be used that is simpler and more applicable to current therapy: the International Classification of Retinoblastoma system (Table 7.2). The basis of this system is the extent of seeding into the vitreous and the extra-retinal space rather than tumor size or tumor number and this system (Shields et al. 2006) is the system currently in widest use and is felt to be a better predictor of outcome than the previously used Reese-Ellsworth system. These staging systems are based on an intact eye.

If a patient has undergone enucleation, pathologic data unavailable otherwise are able to influence staging and management of the patient: choroidal involvement, optic nerve extension, and metastatic disease are examples of these data. Surgeons and pediatric oncologists collaborated to form a new, international staging system based on this more complete set of data (Chantada et al. 2006) (Table 7.3). The most common pattern of spread for retinoblastoma is as follows: intraocular, to scleral invasion, to orbital content invasion, to lymphangetic spread to the pre-auricular lymph nodes, to the cerebral-spinal spread, and finally to hematogenous spread.

Table 7.1 Reese-Ellsworth grouping system of retinoblastoma

Reese-Ellsworth classification for conservative treatment of retinoblastoma (Shields et al. 2006)		
Group	Likelihood of globe salvage	Features
I	Very favorable	(a) Solitary tumor, less than 4 disc diameters in size, at or behind the equator
		(b) Multiple tumors, none more than 4 disc diameters in size, all at or behind the equator
II	Favorable	(a) Solitary tumor, 4–10 disc diameters in size, at or behind the equator
		(b) Multiple tumors, 4–10 disc diameters in size, at or behind the equator
III	Doubtful	(a) Any lesion anterior to the equator
		(b) Solitary lesion larger than 10 disc diameters behind the equator
IV	Unfavorable	(a) Multiple tumors, some larger than 10 disc diameters in size
		(b) Any lesion extending anterior to the ora serrata
V	Very unfavorable	(a) Massive tumors involving over half of the retina
		(b) Vitreous seeding

Table 7.2 The international staging system for retinoblastoma

The international classification (staging) system for retinoblastoma (Shields et al. 2006)			
Group	Subgroup	Features	Details
A	A	Small tumor	Small tumors ≤3 mm in basal diameter or thickness and without Group B features
B	B	Larger tumor	Tumors >3 mm in basal diameter or thickness
		Near disc (Juxtapapillary)	Distance to disc ≤1.5 mm
		Macular (near fovea)	Distance to fovea ≤3 mm
		Subretinal Fluid	Clear subretinal fluid ≤3 mm to margin
C		Focal seeds	Tumor with
	C1		Subretinal seeds ≤3 mm away
	C2		Vitreous seeds ≤3 mm away
	C3		Both C1 and C2
D		Diffuse seeds	Tumor with
	D1		Subretinal seeds >3 mm away
	D2		Vitreous seeds >3 mm away
	D3		Both D1 and D2
E	E	Extensive disease	Occupying over 50% of the globe Neovascular glaucoma Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, or anterior chamber

Table 7.3 New international staging system of classifying retinoblastoma (Chantada et al. 2006)

International classification of retinoblastoma (Chantada et al. 2006)			
Stage	Likelihood of globe salvage	Features	
0	Treated conservatively		
I	Eye enucleated, completely resected histologically		
II	Eye enucleated, microscopic residual tumor		
III	Regional extension	(a) Overt orbital disease	
		(b) Preauricular or cervical lymph node extension	
IV	Metastatic disease	(a) Hematogenous metastasis (without CNS involvement)	1. Single lesion
			2. Multiple lesions
		(b) CNS extension (with or without any other site(s) of regional or metastatic disease)	1. Prechiasmatic lesion
			2. CNS mass
			3. Leptomeningeal and CSF disease

7.2.7 Treatment

Treatment is individualized based on stage (Chantada and Schaiquevich 2015). Focus is first paid to preventing loss of life and then it is paid to preventing loss of vision. The radiation oncologist extends this to think about avoiding second malignancy, avoidance of late effects with organs at risk and disfigurement. The extent of disease, whether one or both eyes are involved, and stage affect the overall approach used in a case. The overall approach to treatment is not dissimilar to that used with most primary brain tumors in that it is team-based. It is, however, different in that primary management of these tumors has historically been the domain of the ophthalmologists because the follow-up and evaluation of intact orbits demands a formal exam under anesthesia in the operating room.

1. Surgery

   For any patient with disease limited to the eye, enucleation is an option and when local options fail, or vision has been lost, and tumor is still limited to the eye this can often be the optimal salvage option in that it avoids the use of radiation with its inherent risk of subsequent second cancers. Enucleation should be performed in an oncologically experienced surgeon's hands in that the orbit should be kept intact if at all possible to avoid seeding. Additionally, for staging purposes, a long section of optic nerve should be removed intact. This is typically 10–20 mm in length. During enucleation, an implant for the orbit is fitted by the surgeon. Muscle attachment is performed in a fashion to optimize later placement of a more realistic, ceramic globe. Ocularists use digital technology mixed with hand painting to make ceramic implants that look extremely realistic. These are changed with time as a child grows.
2. Non-radiation local therapies

   When disease is limited to the contents of the orbit, saving useful vision is the goal of the team treating the child. This becomes crucial when one eye has already been enucleated. Therapy is typically reserved for small 3–6 mm lesions and is used in combination with chemotherapy.

   Cryotherapy is used for small peripheral and equatorial tumors that are less than 2 mm thick and typically under 4 mm in cross section at the base. Patients get 1 or 2 monthly sessions of triple freeze-thaw cycles and control is excellent. This is an approach used in many locations and is relatively well tolerated by patients.

   Photocoagulation using a laser such as an Argon laser treats tumors less than 2.5 mm high and 4.5 mm wide. It also can treat neovascularization induced by radiotherapy. Treatments take one, two, or three sessions typically. Complications can include focal scarring of the retina (Lavinsky et al. 2013).

   The use of heat is also used in the form of transpapillary thermotherapy. Temperatures of 40 to just under 60 C are used for 5–20 min (higher temperatures are used for shorter time periods). Lasers are typically used to deliver this energy. When used with chemotherapy for intraocular tumors, control rates can be as high as 80%. The drugs used include carboplatin, vincristine, and etoposide. Complications can occur and are related to destabilization (detachment) of the retina, local scarring, and retinal tearing (Schueler et al. 2003).
3. Chemotherapy

   Chemotherapy in the traditional intravenous sense is used with local therapy, when patients have bilateral disease, extra-ocular disease, or intra-ocular disease with high risk features. The agents in use include etoposide, cyclophosphamide, doxorubicin, vincristine, ifosfamide, and the platinums (Rodriguez-Galindo et al. 2007; Ghassemi and Khodabande 2015; Chantada and Schaiquevich 2015).

   Work pioneered in Japan evaluated the use of melphalan via intravitreal and intraarterial (IA) routes as a means to treat disease with chemotherapy while avoiding radiation therapy in the context of advanced or recurrent localized disease (Kaneko and Suzuki 2003). Preclinical data suggested that intravitreal

melphalan and thermotherapy interacted in a synergistic fashion (Inomata and Kaneko 1987). Responses with intravitreal chemotherapy and hyperthermia were confirmed in the clinic in patients with progressive disease (Kaneko and Suzuki 2003). Kaneko et al. moved toward IA delivery of melphalan into the ipsilateral carotid artery. This method was improved via the use of balloon catheter usage to direct the drug into the ophthalmic artery by the team lead by Mohri (1993). Abramson et al. reported a modification of this technique that involved cannulation of the ophthalmic artery via a microcatheter and high salvage rates have been reported by the group (Abramson et al. 2008). This last method is the current method being used on the open COG IA protocol for retinoblastoma (Abramson et al. 2010). Data regarding the toxicity of this approach is currently under active investigation (Rizzuti et al. 2008; Wilson et al. 2011). It has been shown in animal models that this approach, currently perhaps the most promising method that can treat advanced local disease successfully without external beam radiation therapy, may cause significant changes to occur in the tissues of the orbit (Steinle et al. 2012; Tse et al. 2013, 2015).

4. Radiation therapy

Radiation therapy has a long history in the treatment of retinoblastoma. The tumor is highly radiosensitive. The first patient treated with a linear accelerator (LINAC) had retinoblastoma and is still alive today with functioning vision. Traditional external beam radiation has fallen out of favor at this time because of the increase in the risk for local second malignancies in this population. It has, for the most part, become the mainstay of salvage if disease cannot be controlled via enucleation alone and of advanced disease (International Staging System stages II, III, and IV). The most common indication for radiation is vitreous and subretinal seeding, but IA therapy is currently being used in this situation on protocol and data from smaller phase I and II studies looks promising for this methodology if the toxicity doesn't turn out to be even worse than with radiation.

The historical dose used to control this disease is 45 Gy at 1.8 Gy per fraction and was the basis of the dose used in the recently closed international COG protocol for extraocular disease. It is likely that 36 Gy is sufficient when chemotherapy is employed and this is likely to be one possible starting point for the next trials in the COG.

There are two types of radiation that are still in common use for retinoblastoma: brachytherapy and proton beam therapy. Traditional photon therapy is still in use and is quite elegant in specialized settings, but it is less commonly used in North America at present due to concerns about integral dose. Electron beam therapy is in use as it has dosimetric advantages in terms of integral dose over photon beam use. Newer methods such as complex three-dimensional compensators can help to make electron beam therapy more conformal.

Brachytherapy in the form of intraocular plaques (Figs. 7.3, 7.4, and 7.5) and in some cases high dose rate brachytherapy using traditional afterloading catheters (Fig. 7.5) is used to keep the integral dose of radiation to a minimum. Brachytherapy has the advantage of being fast, accessible in many radiation centers, and affordable. Plaque therapy is the most common type of radiation used for intraocular disease at this time point in the COG and is a permitted option for local therapy on the current COG IA protocol. Plaque therapy can be used when tumors are 3–15 mm wide, thickness is less than 10–12 mm, and the location is more than 3 mm from the optic nerve and the fovea. The plaque is placed on the sclera in the operating room by the ophthalmologist. It is held in place via sutures. The muscles need to be detached to allow for this. Specialized planning software exists to support plaque brachytherapy including customized template construction for plaque placement via CT based treatment-planning software. The experience of the team is crucial to make this work well (Shields et al. 2001a). Subtle improvements in the process include self-collimating plaques that use clever placement of

sources into wells rather than "atop" the plaque material to decrease scatter and having notched plaques to get near but not "on" the nerve. Radio-isotope selection varies, but iodine is commonly used at present. Control rates in the literature hover between 85 and 90% using plaques (Shields et al. 2001b). Figure 7.3 shows a traditional plaque implant. Figure 7.4 shows a more unusual implant treating the whole eye via a series of four struts anchored to a sutured gold ring encircling the cornea. Figure 7.5 shows an afterloading procedure in sequence. Clearly the scope of options in brachytherapy is broad and crucial to the success of brachytherapy is physician training on the radiation team side and surgical skill and comfort with radiation devices on the surgical side. As is the rule in many parts of radiation oncology, teamwork is of paramount importance.

Proton beam therapy, the second type of common radiation therapy in use today is an improvement relative to other forms of exter-

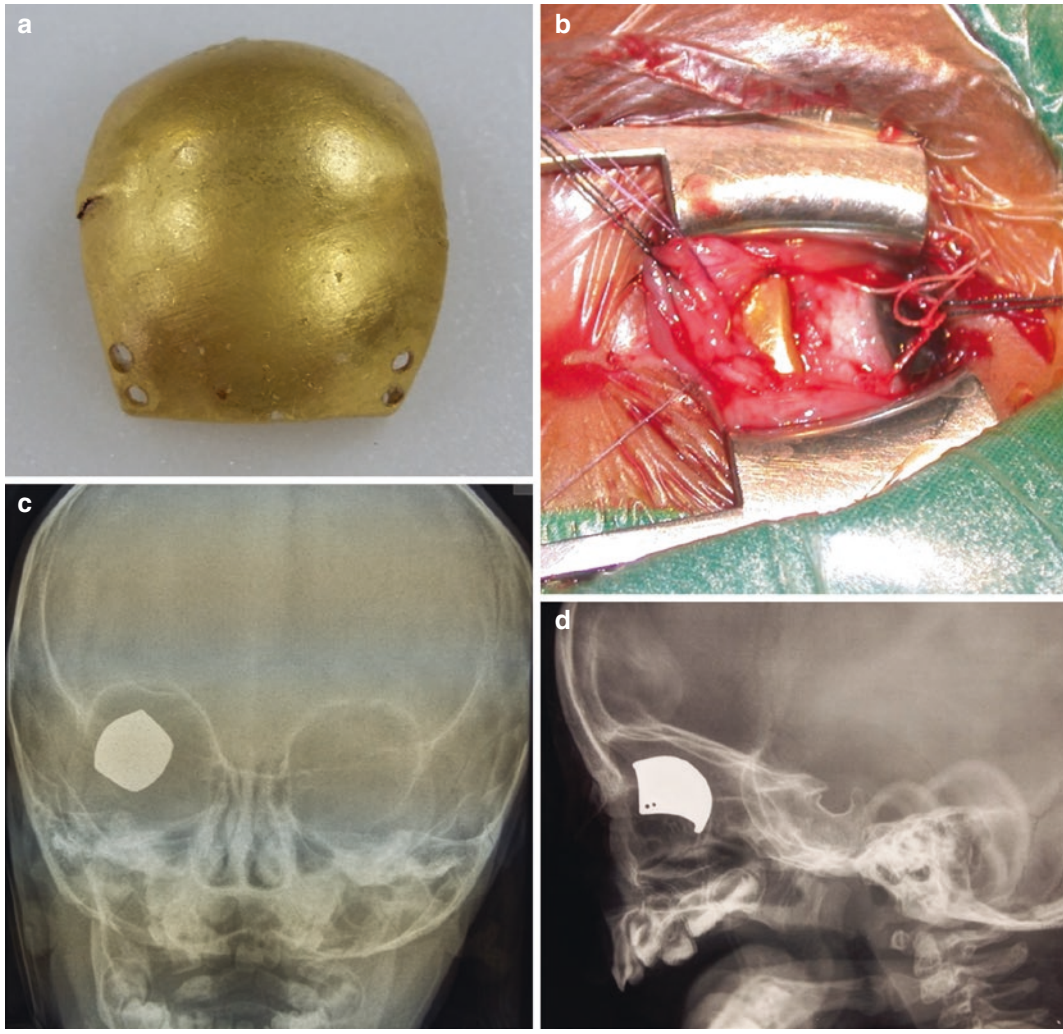


Fig. 7.3 (**a**) Shown is a typical gold plaque used for ocular brachytherapy. (**a**) Shows the outside surface of the plaque and the holes used to thread suture. (**b**) Demonstrates plaque placement in the operating room. (**c**, **d**) Show the placement of the plaque via orthogonal imaging. (**e**) Shows the radiation plan generated via source placement in the plaque. Sources are typically glued to the plaque. (Combined ocular tumor clinic, Groote Schuur Hospital, Cape Town, South Africa)

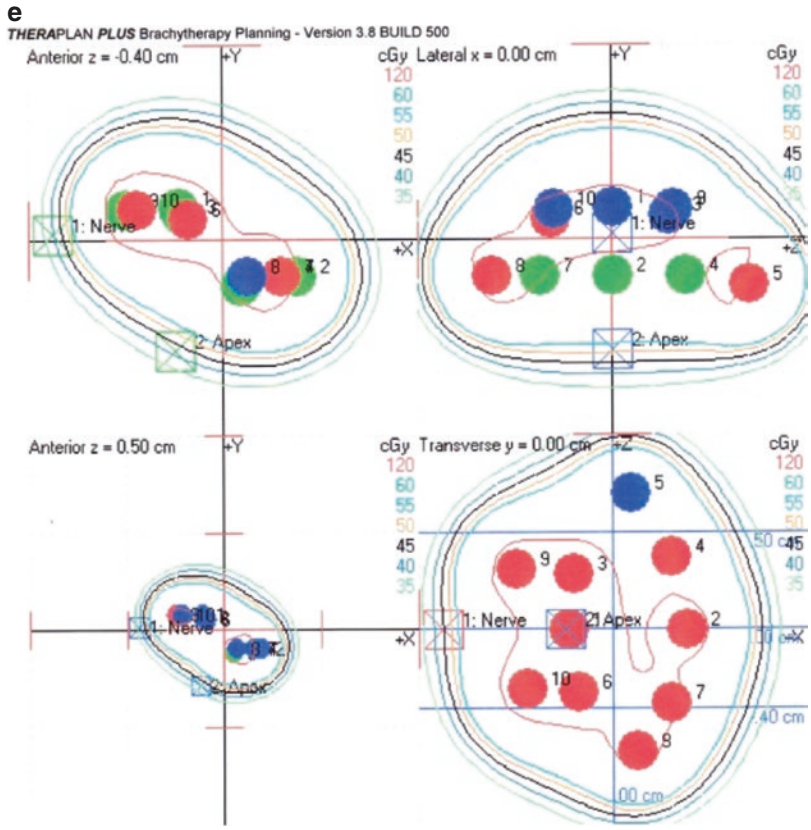


Fig. 7.3 (continued)

nal beam therapy, photons and electrons (Fig. 7.6), because it has a smaller integral dose (Krengli et al. 2005). It is not, however, without significant exposure to normal tissue and the same issues of lens sparing and careful use of ocular immobilization and lens blocking apply to the use of protons. While not a focus of literature to date (Krengli et al. 2005; Mafee et al. 1989), the move from passive scattering and uniform active scattering to spot scanning and intensity modulated proton therapy (IMPT) should, in theory, allow dose to be "wrapped around" the lens. This will require prospective analysis but might be a major indication for the use of IMPT over other forms of proton therapy in this population. Additionally, IMPT should allow lid and lacrimal gland sparing because it allows proximal blocking in addition to distal blocking. Even in the context of extra-ocular disease, given the typical age of the patients, the potential for craniospinal radiation, and the need to control integral dose, proton therapy is likely to be the first choice if any external beam radiation is to be used in a case (Sethi et al. 2014).

7.2.8 Treatment of Unilateral Disease

As noted, enucleation is curative and avoids radiation and systemic chemotherapy's toxicities, but at the cost of full vision. Because vision preservation success has been achieved in bilateral disease, these eyes are offered local therapies, noted above, and systemic therapy as a means to preserve the eye with enucleation being saved for salvage once vision is felt to have been lost.

Ocular preservation is increasingly being used as metachronous contralateral disease can occur, especially in very young children.

Adjuvant therapy is indicated when scleral invasion or tumor extends beyond enucleation along the nerve. Chemotherapy is considered an option rather than enucleation in these cases. In the absence of randomized studies, certain indications consistent with higher risk of extra-ocular disease have become associated with the use of chemotherapy and are currently being studied on active national protocols: retro-laminar and choroidal involvement and sometimes massive choroidal involvement. The standard approach is to use chemotherapy for about 6 months and to use multiple agents. Typical agent combinations include vincristine, doxorubicin, and cyclophosphamide (VDC); vincristine, carboplatin, and etoposide (VCE); hybrids of these two, and recently the use of IA generally with melphalan. On protocol, both local and national, other forms of chemotherapy administration are also under investigation in the unilateral eye.

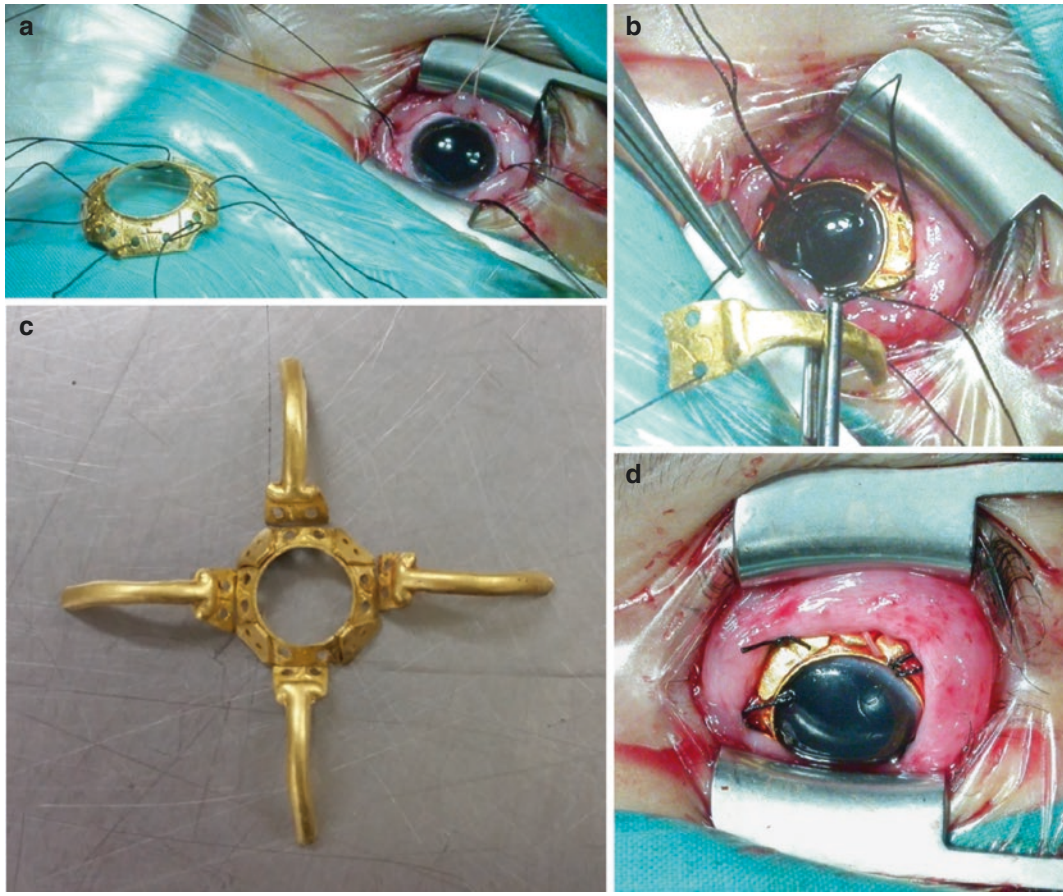


Fig. 7.4 This series of images demonstrates an extremely unusual plaque addressing the orbit volumetrically as a whole. (**a**) Shows the ring of gold that is places around the cornea first. Once the ring is sutured in place, one can see in (**b**) how each "strut" is placed along the curvature of the globe to cover the whole of the orbit. The complete assembly of this device is shown in (**c**). The dosimetry shown in (**d**) demonstrates the effects of the shielding the gold struts give to sources placed on the medial surface of each strut and shows the ability to spare the anterior chamber. In (**e**) the top dosimetry plot shows a "lateral" view of the orbit and the bottom part of the figure shows dose if one were to look right at the patient's pupil toward the fovea. (Combined ocular tumor clinic, Groote Schuur Hospital, Cape Town, South Africa)

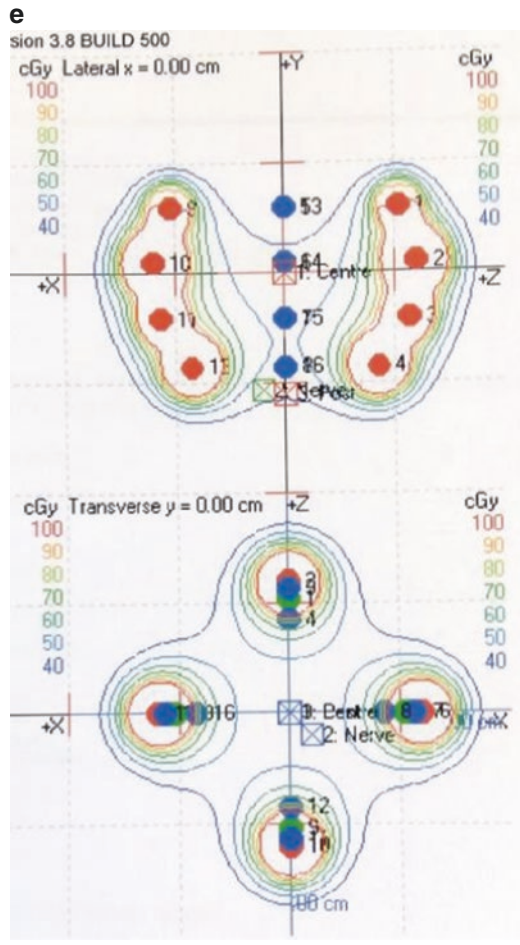


Fig. 7.4 (continued)

7.2.9 Treatment of Bilateral Disease

The current conservative approach using systemic chemotherapy and focal therapies to bilateral disease evolved from the historic approach of enucleation if vision was felt to be impossible to salvage, and external beam radiotherapy if vision might be able to be saved. The high rate of facial deformities in patients treated when very young and the risk of secondary malignancy in the area irradiated, and the advances in the use of chemotherapy and local methods have caused a major shift in the standard approach to these patients. This swing away from the use of radiation is also related to the fact that the risk radiation presents may be age-related and bilateral patients who harbour germline mutations, are typically very young (Abramson and Frank 1998).

The current standard approach in bilateral disease is, therefore, up-front chemotherapy and then sequential local therapy options to both eyes. Chemotherapy is optimized based upon stage with the intensity of therapy mirroring the level of disease. Combinations of vincristine, carboplatin, and etoposide make up the standard backbone of the more aggressive chemotherapy. When eyes are less involved, decreased levels of chemotherapy can be effective. The rates of ocular salvage historically were over 90% in the Group A and B eyes while it was typically over 50% in more advanced eyes with combined radiation therapy. This model may be shifting

toward IA chemotherapy and the early, single institutional data suggest at least equivalent outcomes using IA to these more traditional salvage approaches while fully avoiding radiation therapy and in some cases decreasing systemic toxicity. This is currently under investigation within the COG. Other areas of active investigation in this cohort of patients include intravitreal chemotherapy, subtenon chemotherapy, and other novel delivery approaches that might yield additional options beyond IA chemotherapy when interventional radiology is not available to a center, and when to use IA in combination with other mechanisms of chemotherapy delivery (Mulvihill et al. 2003; Lee et al. 2016; Shields et al. 2014; Seregard et al. 1995).

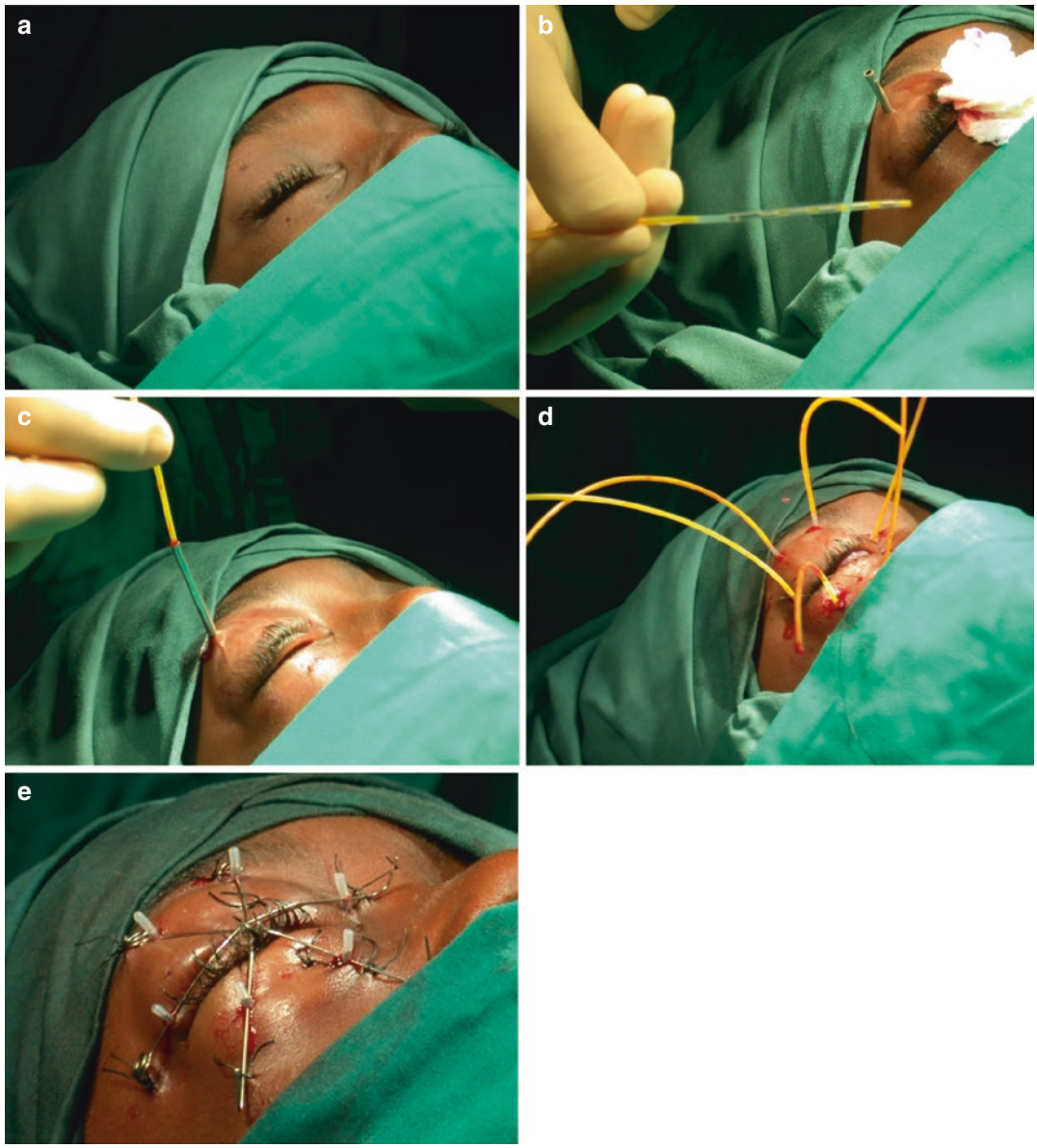


Fig. 7.5 In (**a**–**e**) an after loaded I-125 implant insertion is shown step by step. (**f**) Shows a lateral image of the implant in place and (**g**) shows the dosimetric plan employed in this particular case. (Combined ocular tumor clinic, Groote Schuur Hospital, Cape Town, South Africa)

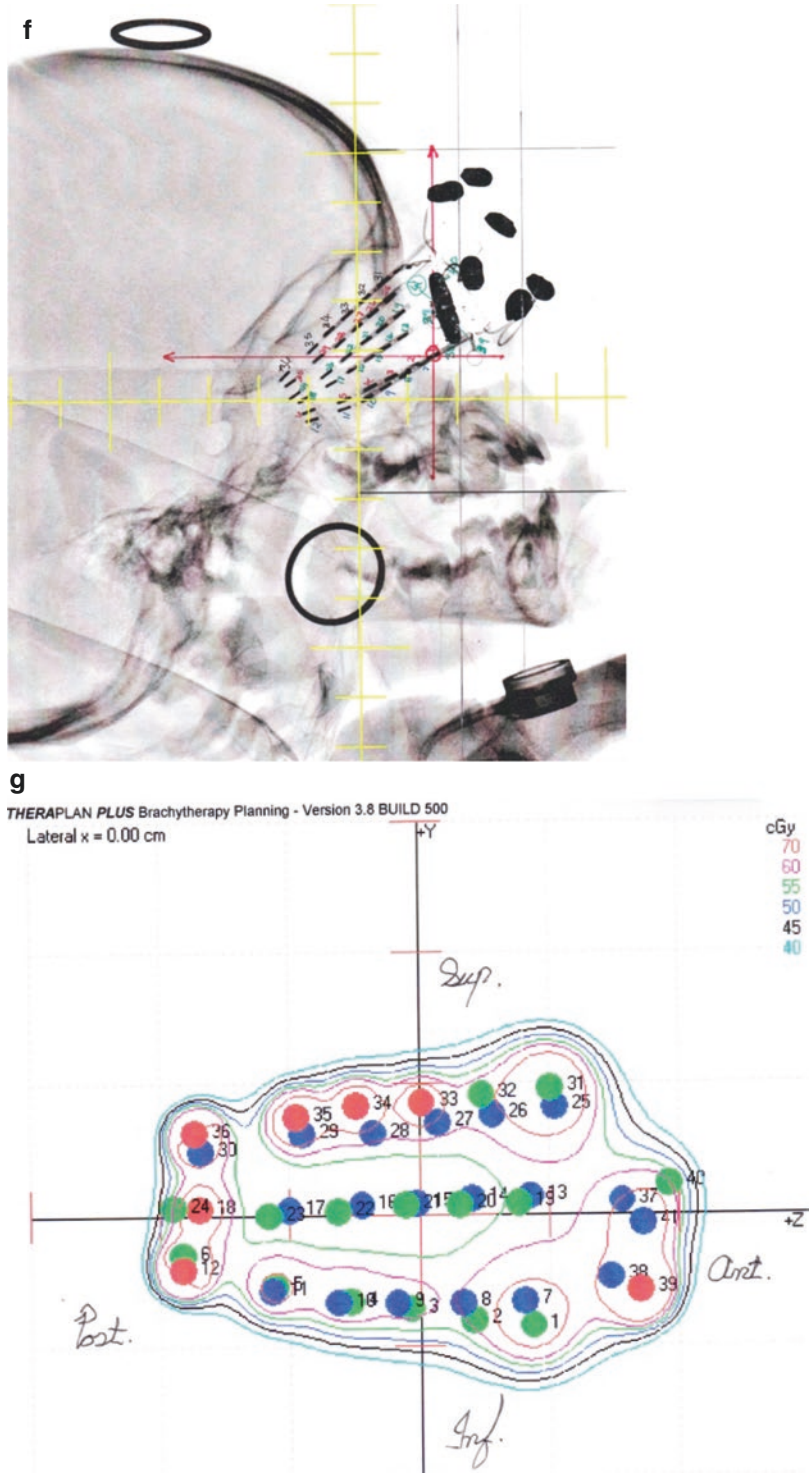


Fig. 7.5 (continued)

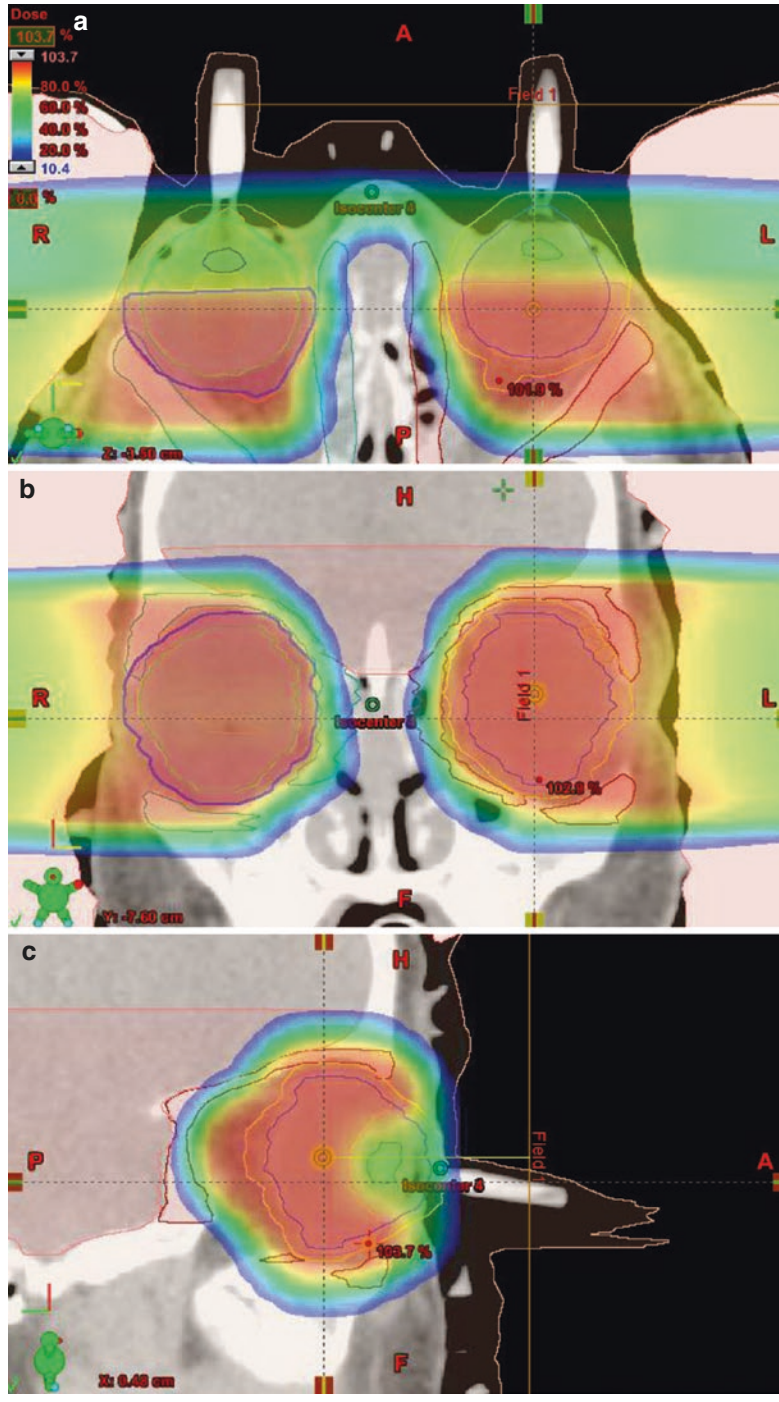


Fig. 7.6 Proton beam therapy to a bilateral case with extraocular, local involvement in each eye requiring radiation. Suction devices are being used to keep the globe still during treatment and are placed each day once the child is asleep. Memory and hormonal centers are able to be spared with the presented dose distribution. The particular case required that the anterior portion of the globes be covered. In this case, dose was limited so as to spare the lens via a cone-down from the entire orbit to the posterior aspect of the orbit as the colorwash demonstrates. Axial (**a**), coronal (**b**), and sagittal (**c**) planes are shown. (Indiana University Proton Therapy Center, Bloomington, Indiana)

7.2.10 Extra-ocular Disease

Four main patterns of spread exist for extra-ocular retinoblastoma "once extra-ocular": local-regional (including down along the optic nerve and the local lymphatics with the first location of drainage being the preauricular lymph nodes), CNS spread with the CSF space, classic metastatic disease via blood to any site in the body, and trilateral disease involving the orbits and the pineal region.

Treatment of extra-ocular disease correlates with two things: the use of external beam radiation and the income status of the population. Firstly, off protocol, the standard approach at this point in time is to treat areas of extra-ocular disease to 39.6–45 Gy at 1.8 Gy/fraction with a 5–10 mm CTV margin and an institutional PTV margin. This includes the use of CSI for CSF positive and trilateral disease with the CSI dose being 36 Gy in 20 fractions. In the recently closed protocol by the COG, ARET0321, patients were randomized to no radiation in stage IV if they had a CR to transplant based on preliminary data from Memorial Sloan Kettering suggesting doing such was safe. Those data are not yet published, so the standard of care is to use radiation, but there may be a move in extra-ocular retinoblastoma to slowly do away with radiation as the data become available.

Extra-ocular retinoblastoma is extremely rare in the United States, Canada, and much of Western Europe, making up less than 5% of all cases of retinoblastoma. In less developed countries, the incidence can be as high as 20–40%. Access to care and screening is felt to be the primary cause of this discrepancy. The difference is so extreme that the ability to conduct studies on this population was likely to have been impossible in the COG without the inclusion of centers in Asia, Africa, and South America (Menon et al. 2000; Antoneli et al. 2003).

1. Loco-regional extra-ocular disease

   Scleral disease is considered extra-ocular because it represents the primary means of tumor getting into the orbit from the globe. It is crucial to treat it as extra-ocular disease. About two-thirds of orbital disease is actually limited to the orbit while the other third represents disease that has spread further and can include the CNS, lymphatic, and hematogenous spread. The overall approach to these cases is to obtain baseline staging data (imaging, CSF status), employ chemotherapy for two to four cycles using a mixture of agents that penetrate the CNS, obtain response imaging data and then perform enucleation to better assess chemotherapy response, then deliver an additional four to six cycles of chemotherapy and complete the local control with radiation therapy at the end. The typical radiation approach is to use 39.6–45 Gy to the orbit. In the special case of local optic nerve involvement with surgical transection, the entire orbit is covered to at least 36 Gy and the optic nerve residual inclusive of the chiasm is treated to 45 Gy in a 9 Gy boost. Orbital exenteration typically is avoided in these cases helping to avoid complex reconstructive surgery (Chantada et al. 2003; Okumoto et al. 2014). Scleral disease is treated in the same way. This remains the standard of care but will likely change over the next several years if data suggesting that radiation may be avoided mature and remain valid.

   When preauricular disease is noted via clinical exam or imaging, coverage of the region takes on the approach used in standard head and neck radiation therapy. If irradiated, the 20% of patients with lymphatic spread have the same control and survival outcomes as those without if radiation is used to cover lymphatic spread (Doz et al. 1994). Data from a good clinical exam and staging imaging quality in this context is critical because one otherwise attempts to avoid excess radiation integral dose.

   Techniques to minimize integral dose are always very prominent in the thought process in this disease and referral to a proton therapy center is not uncommon in these cases. Electron beam therapy is used as well and recent developments in 3D attenuation devices and Monte-Carlo clinical calculation capacity has made this a reasonable option if heavier particle therapy is unavailable.

2. Extra-ocular disease in the central nervous system

   Spread into the CNS is via the optic nerve and outcomes for these cases are poor (Chantada et al. 2003). Protocol management of these cases is suggested given historically poor outcomes even with initial good responses to therapy and CSI is the normal approach taken. The dose employed has varied from 23.4 to 36 Gy with a boost typically up to 45 Gy to areas seen on MRI. The role of transplant has been explored on protocol (Dunkel et al. 2010a; Namouni et al. 1997). The most recent COG protocol allowed a randomization to no radiation use for stage IV cases if a complete response (CR) was observed after transplant using intensive chemotherapy. Until the results of that study are known, off-protocol the standard of care in terms of radiation therapy remains the use of CSI; and it is likely to remain a salvage modality even if the data from the trial support the avoidance of CSI during the initial treatment phase. The use of strategies to avoid integral dose such as the use of proton therapy is indicated in the case of CSI for retinoblastoma.
3. Hematogenous disease

   Much like spread to the CNS, the outcome for spread to areas via the blood such as bones and liver is poor; the literature has more long-term survivors in this category than in CNS spread (Dunkel et al. 2010c). The approach is similar in that chemotherapy is used intensively, but the volume of radiation is limited to the region of the spread plus a reasonable margin, typically 0.5–1.5 cm based on location and nearby organs of risk, to a dose of 45 Gy. Attention to integral dose in these patients still justifies the use of particle therapy in most cases if a good response to chemotherapy has been observed. These cases can be complex and if more than a few lesions are noted, the radiation oncologist may have to stage treatment. The overall approach to these patients is similar to neuroblastoma. Recently, high dose regimens with transplant as rescue have yielded surprisingly good results and some patients with non-skull region bone metastases may not need radiation based on recent work by Memorial Sloan Kettering (Dunkel et al. 2010c). Whether this can be translated into the worldwide community was the subject of COG study ARET0321. It is too soon to evaluate the results of this study but it may turn out that these patients as a group can avoid radiation in specific cases to some metastatic sites.
4. Trilateral retinoblastoma

   Trilateral retinoblastoma is defined as disease in the orbits and the pineal region. It can be seen with only one orbit being involved (Shah et al. 2013). The outcome of these patients is similar to those with more typical CNS metastases and is very poor. Survivors are typically caught early via screening and treated with intensive chemotherapy (Dunkel et al. 2010b). CSI is not always included in the treatment courses of those surviving trilateral disease although new imaging modalities suggest spinal spread is possible in these cases and CSI should be considered (Kamaleshwaran et al. 2014). It is estimated that 1 in 4 cases are found via screening (Kivela 1999). The interval between diagnosis of retinoblastoma and the development of trilateral disease is felt to be rapid, so screening for the first few years after diagnosis is something many groups practice via MRI. The typical approach used is to collect thin slice brain MRI scans every 6 months for 5 years (Pham et al. 2015). Currently the development of pineal gland cysts is being investigated in terms of its relationship with the RB-1 gene. It may be possible in the future to identify those with imaging based changes in the pineal region that do not have retinoblastoma (Pham et al. 2015; Ruiz Del Rio et al. 2014).

7.2.11 Late Effects of Treatment of Retinoblastoma

The immediate late effects of enucleation are loss of vision. The late effects of chemotherapy and radiation therapy are complex and there is a large

amount of data suggesting that both therapies can be quite harmful to this patient population.

Radiation therapy, which is associated with local growth abnormalities and localized secondary malignancies in this population has long been a modality that was targeted for removal from treatment algorithms due to a clear association with late effects (Larson et al. 1990; Newton et al. 1991; Ng et al. 2010). When it needs to be used, some have historically felt that waiting for patients to be over 12 months of age was a reasonable time point due to increased late effects seen in those younger than 12 months of age (Peylan-Ramu et al. 2001). The current use of radiation therapy is limited to plaque therapy and extra-ocular disease. Whenever possible, the use of integral dose variation is minimized via the use of particle therapy. Recent data analysis of the population of the United States supports this general approach (Tamboli et al. 2015).

Cataract in very young patients can be quite complex to manage and it is recommended that patients be referred to national centres of excellence where these patients are seen with regularity. The techniques for managing these cases are complex. It is not uncommon to need revisions of lens as patients age if the orbit grows normally, so using the largest lens possible is the approach typically used by those performing lens replacement surgery (Miller et al. 2005).

Some recently published data from long-term survivor studies in these cohorts suggest that children that are very young are able to re-organize their brains to address areas that may be exposed to low dose radiation and to the loss of visual data in the dimension of learning (Brinkman et al. 2015). Recent work in the study of late effects have seen significant risk to these patients from chemotherapy as well (Choi and Schmidt 2016; Schundeln et al. 2015). The side effects of chemotherapy and radiation are likely additive and the minimization of total exposure in this population is crucial (Shildkrot et al. 2011; Peretz et al. 2001). Even the most promising current management approach to retinoblastoma, the use of IA chemotherapy, may be toxic to these patients and after long term follow-up may be found to be inferior to other modalities (Tse et al. 2015).

7.2.12 The Future of Retinoblastoma Treatment

The focus for retinoblastoma in the future will likely be to use this tumor as a model system to develop and explore targeted therapies because, while complex, the genetics are felt to be far simpler than many other tumors. The RB-1 gene has been mapped and work by multiple labs around the world has synthesized an approachable "map" of genetic targets to test one at a time and in combinations that may allow the field to move away from the more toxic agents in use today. A summary of current concepts is shown in Fig. 7.7 demonstrates some of the signaling pathways active in retinoblastoma (Brennan et al. 2011; Zhang et al. 2012).

7.3 Nasopharyngeal Carcinoma

7.3.1 Introduction and Demographics

Pediatric nasopharyngeal carcinoma (NPC) is a rare disease with distinct differences from its adult counterpart. It is rarer in adolescents and children compared with adults, accounting for <2% of patients with NPC in the SEER registry of North America (Sultan et al. 2010) and <1% of children in the highest risk areas such as Southern China. In these areas there is a unimodal peak of incidence at 50–60 years, however, in Mediterranean countries and North Africa, a second peak in incidence is seen at 10–20 years of age, and in these areas 5–10% of NPC cases occur in children (Berry et al. 1980).

The epidemiology of NPC is complex and poorly understood, incorporating genetic, viral and environmental risk factors (Hu et al. 2013). Exposure to Epstein Barr virus (EBV) appears to be a strong predisposing cause, however, this is not the only risk factor, and genetic and dietary, as well as other factors may also play a role in pathogenesis of this disease.

There are early reports of documented NPC from China, and this region, together with Hong Kong, remains the area of highest worldwide

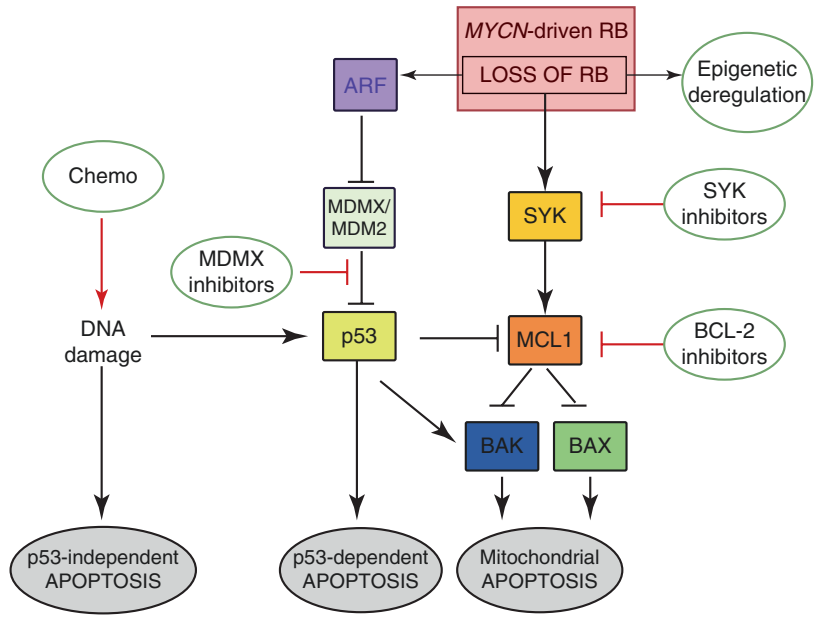


Fig. 7.7 Shown are the various targets that might be available to those seeking to target retinoblastoma in green ovals. (Figure kindly provided by Carlos Rodrigue-Gallindo, M.D. of St. Jude.) The sum of ideas in the figure represents work from multiple laboratories. The figure is relatively simple compared to many other cancers but to date has demonstrated extreme complexity nonetheless

incidence (Chang and Adami 2006). However, even in China, incidence varies greatly, with the highest incidence rates observed in Southern China (>20 per 100,000 person-years) compared with rates of <1 per 100,000 person-years in low incidence areas.

7.3.2 Classification of NPC

The WHO has classified NPC into three subtypes (Barnes et al. 2005) (Table 7.4):

In all geographical areas, there is a striking difference in gender distribution with males representing about 66–75% of cases (Sultan et al. 2010; Zheng et al. 1994). In contrast to adults, almost 90% of pediatric patients with NPC have Type III disease (Mertens et al. 1997; Ayan and Altun 1996). Even though children are more likely to present with advanced loco-regional disease, their prognosis is better. Reports from both endemic and non-endemic areas show overall survival rates of children with NPC of approximately 75–80% at 5 years (Sultan et al. 2010). This is despite being treated on a number of differing protocols, mostly adapted from adult treatment strategies (Ozyar et al. 2006).

Another difference between adult and pediatric NPC, is that pediatric survivors of NPC appear to be at a markedly increased risk of developing second cancers. In a SEER study, survivors of childhood NPC had a 41% increased risk of developing a second primary cancer. This concern has been raised in other studies previously (Scelo et al. 2007). Most of the cancers reported were solid cancers of the head and neck region. In addition, a higher than expected rate of late effects were also a concern in these children with xerostomia, deafness, subcutaneous fibrosis, endocrine problems and dental problems being described (Berry et al. 1980; Cheuk et al. 2011; Ozyar et al. 2006). Although some of the studies used less modern techniques of radiotherapy, there was sufficient concern to warrant that current studies look at ways to reduce radiation dose, as well as to employ techniques that limit morbidity (Sultan et al. 2010).

Table 7.4 WHO classification of NPC

Keratinising squamous carcinoma
Non-keratinising carcinoma • Differentiated • Undifferentiated
Basaloid squamous carcinoma

7.3.3 Genetics

1. EBV

The link between EBV and NPC was initially based on the finding of raised IgG and IgA EBV antibodies in NPC patients (Zeng et al. 1985). EBV has a geographical prevalence and primary infection ranges from a mild pyrexial, self-limiting disease in children, to infectious mononucleosis in adults. The virus infects the oropharyngeal epithelium, but also the B-lymphocytes, which act as a source of latent infection and allow dissemination of the virus to other epithelial surfaces (Vokes et al. 1997). Clonal EBV DNA has been shown to be present in NPC tumor cells, and has led to the hypothesis of the virus being the cause of malignant transformation in the cell.

As well as being a causative factor, levels of anti-EBV antibodies have been studied as a possible prognostic indicator in NPC (Neel et al. 1984; De-Vathaire et al. 1988). Twu et al. showed that EBV DNA in plasma may be a reliable indicator of prognosis and other studies have shown a correlation between levels of EBV DNA and staging, recurrence rates and survival in NPC patients (Twu et al. 2007; Ma et al. 2006; Leung et al. 2003).

Other genetic factors may also play a role in development of NPC. Genetic studies in high risk populations, such as the Cantonese people in Southern China and Hong Kong show a possible HLA-associated risk for NPC (Simons et al. 1976). In other high risk groups, such as the Aleut Indians, and North Africans, studies show genetic links to the population in Southern China, (Chang and Adami 2006; Zheng et al. 1994) strengthening this hypothesis.

Some studies also show a relationship between NPC and the consumption of certain preserved or smoked foods, especially in children (Ward et al. 2000).

7.3.4 Work-Up

Because of the anatomical location of the nasopharynx, patients tend to present late. This is particularly true of pediatric patients, many of whom may present with non-specific complaints such as recurrent otitis media (Martin and Shah 1994). However, the commonest presenting complaints in children tend to be neck masses (due to secondary lymphadenopathy) and headache. Due to an abundant lymphatic supply, NPC spreads early to the lymphatics and to bilateral regional lymph nodes which may be very bulky on presentation. Commonly involved are the internal jugular, posterior cervical and retropharyngeal chains of lymph nodes. Some would argue that children and adolescents with unilateral otitis media and significant cervical lymphadenopathy should be subjected to endoscopy if living in a high risk area (Martin and Shah 1994). All patients suspected of having a nasopharyngeal mass should have a complete general physical examination, as well as a detailed head and neck examination, including documentation of any enlarged cervical lymph nodes and careful evaluation for cranial nerve abnormalities. Cranial nerves III to VI are most commonly affected. Endoscopy with biopsy of a visualized lesion is required (Vokes et al. 1997), and in most children this entails an examination under anesthetic. In addition, cross sectional imaging is required to adequately assess extent of disease. EBV-related biomarkers may help in diagnosis but has a greater role in post-treatment surveillance (Lee et al. 2012).

Magnetic resonance imaging (MRI) is regarded as being superior to computed tomography (CT) scans for assessing the local tumor extent and nodal involvement. Fluorodeoxyglucose positron emission tomography (FDG-PET) combined with CT is also useful for assessing adenopathy in the neck, but MRI is superior for assessment of intracranial extent or involvement of the skull-base (Liao et al. 2008).

For the assessment of distant metastases, integrated FDG-PET has been shown to be superior to CT alone or conventional work-up consisting of CT, ultrasound and bone scan. Bone marrow biopsy is indicated in the presence of advanced loco-regional disease, and CSF cytology should be obtained for patients with intracranial extension. Systemic spread of NPC most commonly affects bone, lung, liver and bone marrow (Chua et al. 2009; Ng et al. 2009).

Staging of NPC is the most critical prognostic factor for both primary and recurrent disease in NPC (Lee et al. 2012). The current TNM staging system has been customized for NPC and has been adopted by both the American Joint Committee on Cancer (AJCC) (Edge and Compton 2010) and the Union for International Cancer Control (UICC) (Sobin et al. 2009; Greene and Sobin 2009; AJCC Cancer Staging Manual 2011) (Table 7.5).

In endemic areas, more than 90% of Pediatric NPC patients present with advanced stage disease (stage III and IV disease.) (Yan et al. 2013; Liu et al. 2014). However, in non-endemic countries like USA, this percentage is lower at approximately 77% (Sultan et al. 2010).

Table 7.5 American Joint Committee on cancer staging for NPC (2010)

	TNM staging of nasopharyngeal carcinoma
T1	Tumor confined to nasopharynx or extends to oropharynx and/or nasal cavity without parapharyngeal extension
T2	Tumor with parapharyngeal extension (i.e., posterolateral tumor infiltration beyond pharyngobasilar fascia)
T3	Involving bony structures and/or paranasal sinuses
T4	Intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit or masticator space[a]
N1	Unilateral nodes 6 cm or less, above the supraclavicular fossa, and/or retropharyngeal nodes 7 cm or less (may be uni- or bi-lateral)
N2	Bilateral nodes, 6 cm or less, above the supraclavicular fossa
N3a	Lymph node >6 cm
N3b	Extension to supraclavicular fossa
Mx	Distant metastases not assessed
M0	No distant metastases
M1	Distant metastases

Stage	
I	T1N0
II	T1-2 N1, T2N0
III	T3N0-2, or T1-3N2
IVa	T4N0-2
IVb	N3 disease
IVc	M1

[a]Note that definition of masticator space in this regard refers to tumors extending **beyond** the anterior surface of the lateral pterygoid muscle or lateral extension **beyond** the postero-lateral wall of the maxillary antrum and pterygomaxillary fissure (Lee et al. 2012)

7.3.5 Treatment

In all Pediatric patients with NPC, treatment is given with intent to cure. Because of the rarity of this disease, treatment has traditionally followed principles and guidelines established in adult NPC. However, in several studies, the outcome of children and adolescents with nasopharyngeal carcinoma appears to be superior to that of their adult counterparts with 5 year disease specific survival approximately 20% higher despite children presenting with advanced stage disease (Sultan et al. 2010; Liu et al. 2014).

Because of the anatomical location of NPC, almost all tumors are deemed irresectable at diagnosis and surgery is not indicated except for biopsy. Treatment, therefore, has been limited to radiotherapy and chemotherapy either alone, or in combination, and more recently with immunotherapy. Treatment regimens commonly used in the treatment of Pediatric NPC have generally used one of the following approaches:

1. Radiotherapy alone in early stage disease(unusual in children)
2. Neo-adjuvant(induction) chemotherapy followed by radiotherapy
3. Combined chemo-radiation with or without adjuvant chemotherapy
4. Induction chemotherapy followed by chemo-radiation
5. Chemoradiation followed by immunotherapy

7.3.6 Radiotherapy in NPC

The efficacy of mega-voltage radiotherapy in NPC has been well documented in many studies. In stage I disease, radiotherapy alone is adequate treatment. However, this applies to a very small percentage of children as by far the majority present with advanced disease. In stage III and IV disease, concurrent chemoradiation is the

established treatment regimen. However, treatment of stage II disease is more controversial (Lee et al. 2012).

Equally controversial is the dose of radiotherapy that is required to cure NPC in children. There appears to be a correlation between tumor burden and the dose required for local control, with an estimate of 1% increase in risk of local failure, for every 1 cm^3 increase in volume of tumor (Sze et al. 2004).

Recommended doses for the primary site and other involved nodal sites range from 59.4 to 70 Gy (1.8–2 Gy per fraction) and some studies have shown improved local control when doses >66 Gy are used (Ozyar et al. 2006). However, other studies have shown dose >70 Gy was not associated with a superior outcome, but did cause additional toxicity (Lee et al. 2009a; Hu et al. 2013). Several studies have looked at special techniques such as brachytherapy and stereotactic radiotherapy in an attempt to further boost dose to the gross tumor in NPC. In adults results are variable with some studies showing benefit while others (Rosenblatt et al. 2014) did not, but in children, profound additional toxicity was shown, most notably in terms of temporal lobe necrosis, catastrophic epistaxis (due to petrous internal carotid pseudo-aneurysm rupture) and osteoradionecrosis. Brachytherapy and stereotactic boost are, therefore, not recommended (Lee et al. 2012). Standard doses for the elective treatment of potential risk sites in the neck are treated to a dose of 50–60 Gy.

In the largest review of Pediatric NPC worldwide, the Rare Cancer Network looked at prognostic factors related to local control (LC), loco-regional (LRC) and distant-metastatic relapse-free survival (DMC) l. Multivariate analysis showed a statistically significantly poorer outcome for patients with T3/T4 disease (LRC), patients receiving a total nasopharyngeal dose of <66 Gy (for LC, LRC), age > 14 years (LRC), or male gender (DMC). Patients with N3 disease seemed to have a poorer DFS and OS with nodal bulk playing a major role. Patients who received radiotherapy alone also did worse in terms of DFS (Ozyar et al. 2006).

In contrast, other studies from France have shown that response-adapted, dose-reduced radiotherapy may be possible in about 50% of patients who have a favorable response to neoadjuvant chemotherapy. In these patients, dose reduction to the neck nodes of less than 50 Gy was not associated with an inferior outcome, and had less toxicity (Orbach et al. 2008). However, this is still not considered standard treatment, and at this time high dose radiotherapy (66–70 Gy) combined with chemotherapy is considered to be standard of care (Nasopharyngeal cancer: multi-disciplinary management 2010).

Technique of radiotherapy does seem to play an important role in toxicity of treatment, with several studies showing a reduction in acute grade 3 toxicity as well as a later onset of grade 2 toxicity when advanced treatment planning methods, such as intensity modulated radiotherapy (IMRT) are used (Laskar et al. 2008). IMRT allows better dose conformity and better protection of organs at risk with reduction in trismus and grade 2 xerostomia seen in some studies (Liu et al. 2014). Use of other advanced techniques of radiotherapy such as helical tomotherapy and proton therapy have been reported and may offer dosimetric advantages, but are not considered standard (Lee et al. 2008; Taheri-Kadkhoda et al. 2008).

However, in countries where advanced techniques are not readily available both 3-D conformal radiotherapy and 2-D radiotherapy can be adequately used to treat NPC. Despite the concern that use of IMRT may increase integral dose and therefore cause a greater risk for secondary malignancy, this risk has to be weighed up against the better acute side effect profile of advanced techniques (Hall 2006; Macklis 2006). Figure 7.8 shows an IG-IMRT treatment plan for a child and Fig. 7.9 shows a similar case in a different child where protons were employed.

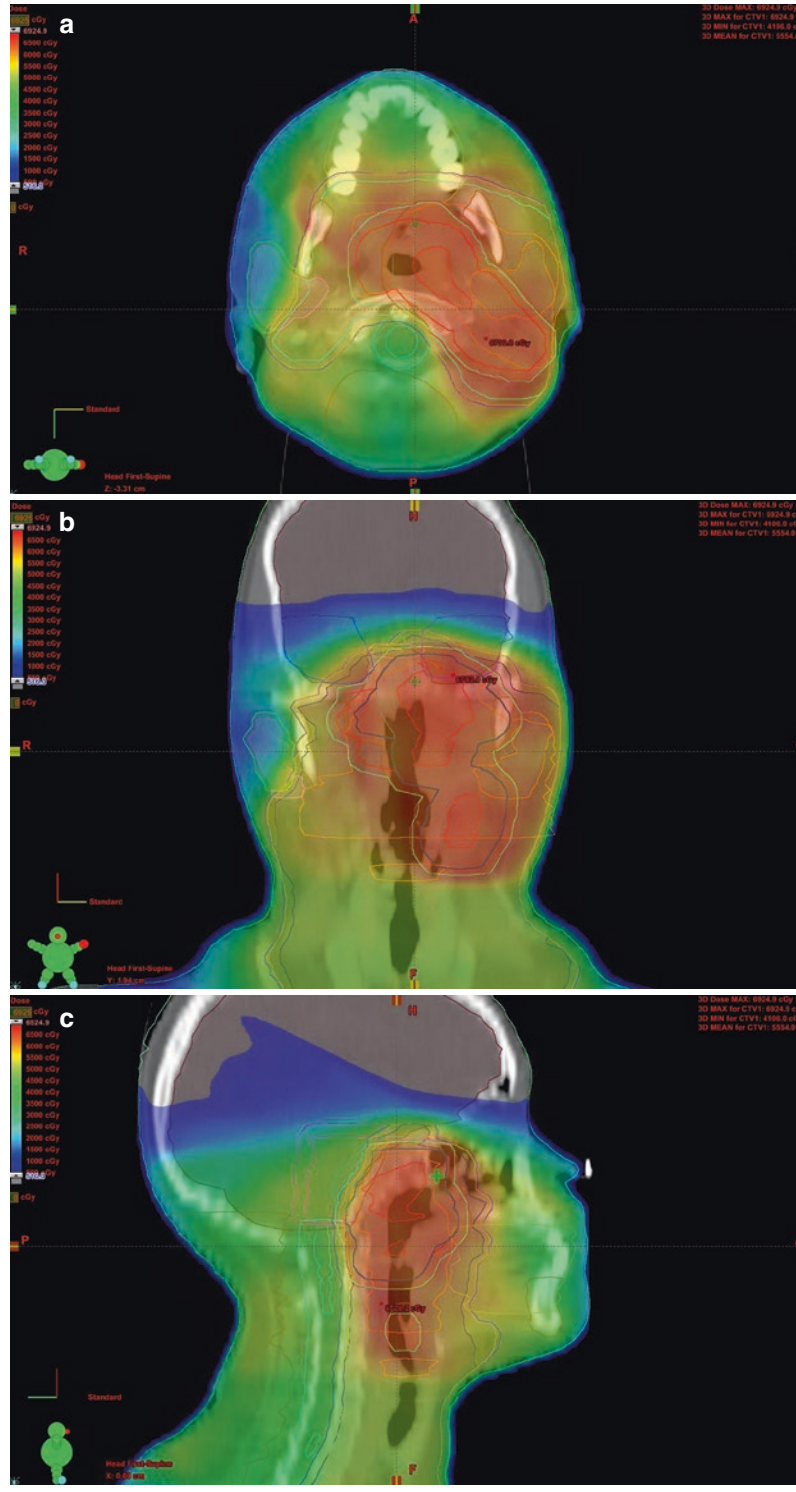


Fig. 7.8 This image-guided intensity modulated radiotherapy (IG-IMRT) plan shows the integral dose delivered with photons in this disease when the necks are treated. Shown are axial (**a**), coronal (**b**), and sagittal (**c**) views of the dose colorwash. (St Jude's children's research centre, Memphis, TN, USA)

Fig. 7.9 This image-guided intensity modulated proton therapy (IG-IMPT) plan shows the integral dose delivered with photons in this disease when the necks are treated. Shown are axial (**a**), coronal (**b**), and sagittal (**c**) views of the dose colorwash. This is a different patient than shown in Fig. 7.8. (St Jude's children's research centre, Memphis, TN, USA)

Table 7.6 Tumor volumes (Lee et al. 2009b) for RT in NPC

	Structures included in volume	Dose required (1.8–2 Gy/#)
Primary disease (GTV) =	Nasopharynx and all involved structures (lymph nodes > 1 cm on CT OR with necrotic centre OR FDG avid on PET OR clinically involved OR endoscopy findings	2.12 Gy per # to 70 Gy 59.4–74 Gy
CTV1 =	GTV+ 5 mm margin	
High risk areas (CTV2) =	CTV1+ 5 mm AND skull-base, clivus, pterygopalatine fossa, parapharyngeal spaces, retropharyngeal nodes, 1/3 to 1/2 of posterior nasal cavity, sphenoid sinus, maxillary sinuses, upper neck nodes to level of hyoid bone	1.8 Gy/# to 59.4 Gy 60 Gy
Prophylactic nodal irradiation (CTV3)	Lower neck and supraclavicular nodes	1.6 Gy/# to 50.4 Gy 50 Gy

7.3.7 Radiotherapy Planning

The treatment volumes required in NPC are extensive owing to the advanced local disease frequently encountered as well as the common involvement of bilateral neck nodes, right down to the supraclavicular nodes bilaterally. Radiotherapy volumes for areas at risk (CTV) are irrespective of planning technique to be used. However, margins applied to this for planning targets volumes (PTV) depend on the frequency and quality of portal imaging available during treatment, and are centre-specific (Table 7.6).

7.3.8 Tumor Volume Delineation

At critical areas e.g., brainstem, margin is reduced to 1 mm.

PTV = CTV2 + 3–5 mm to account for organ motion and set up error.

For IMRT volumes, Anne Lee suggests using the RTOG-0225 study radiotherapy guidelines (Lee et al. 2009b). In this study, radiotherapy was delivered using a simultaneous integrated boost technique, however, caution should be used in children where doses above 2 Gy per fraction, and accelerated fractionation have been related to a marked increase in late effects (Lee et al. 2009a).

Prolongation of treatment time for any reason has repeatedly been shown in several studies to adversely affect local control (Kwong et al. 1997).

7.3.9 Combination Chemotherapy and Radiotherapy in Pediatric NPC

Because the numbers of pediatric NPC are small when compared to the adult disease, many of the large studies are based on extrapolated results from adult studies, despite the histological differences.

In adults, the question regarding the benefit of adding chemotherapy to radiotherapy in treatment of locally advanced NPC was answered in a large meta-analysis where patients from endemic and non-endemic areas were included. The absolute survival befit for the addition of chemotherapy to radiotherapy was 6% at 5 years (improvement of 56–62% with HR = 0.82). The benefit for event-free survival (EFS) was slightly higher at 10%. The greatest effect was seen with concomitant chemoradiotherapy which was the only sequence that achieved significant survival benefit (Baujat et al. 2006).

Concomitant chemo-radiotherapy most frequently uses cisplatin with or without 5-fluorouracil together with radiotherapy in varying schedules (Lee et al. 2012). Controversy remains about the benefit of adding adjuvant chemotherapy to chemoradiation. Although concomitant chemoradiotherapy (CRT) is needed for local control and overall survival, there appears to be some indication that the addition of adjuvant chemotherapy is needed for distant control of NPC (Hui et al. 2009; Lee et al. 2011).

It must be noted that the addition of chemotherapy to radiotherapy is associated with a higher risk of acute toxicities, especially mucositis (Al-Sarraf et al. 1998). In addition, late toxicities such as sensorineural deafness may be worse with CRT compared with radiotherapy alone. Use of advanced radiotherapy techniques such as IMRT may improve this, allowing a lower dose constraint of <47 Gy to the cochleae. A further question surrounds the possible benefit of induction chemotherapy. The theoretical gains of tumor volume reduction, leading to increased minimum tumor dose and improved tumor control probability have been shown in some studies (Lee et al. 2009a). A further practical point in favor of induction chemotherapy in resource-limited settings is that dramatic changes in neck contours can be seen with this schedule prior to radiotherapy cast-fitting and planning, thereby avoiding re-casting and adaptive re-planning to account for this during radiotherapy.

In children, the benefit of concurrent CRT in advanced disease has also been shown in several studies (Bakkal et al. 2007; Cheuk et al. 2011). However, because study numbers are smaller, it is less clear as to whether the addition of adjuvant chemotherapy (or induction chemotherapy) confers any additional benefit (Yan et al. 2013).

7.3.10 Morbidities and Late Effects of Treatment

The commonest morbidities seen in survivors of Pediatric and adolescent NPC are xerostomia, neck fibrosis, hearing loss, trismus, glossolalia, encephalopathy and pituitary hormone deficiency (Yan et al. 2013). The incidence of these morbidities is dose–dependent, with a dose of >68 Gy to the primary associated with all of the above, except for neck fibrosis which was associated with a neck dose of >60 Gy.

7.3.11 Use of Novel Agents

Since routine use of CRT in NPC, distant failure has become the primary cause of death in patients who relapse. Apart from studies looking at improving radiotherapy techniques in order to limit late toxicities, other studies have investigated possible targets for novel therapies. Epidermal growth factor receptor and vascular endothelial growth factor receptor are overexpressed in the majority of NPC cancers (Chua et al. 2004). Studies investigating the possible benefit of the addition of biological agents to chemotherapy as well as immunotherapy and drugs targeting EBV gene products are ongoing (Buehrlen et al. 2012; Yoshizaki et al. 2012).

7.3.12 Recurrent Disease

The majority of recurrences of NPC in children occur within 2 years (Yan et al. 2013). This is earlier than in adult NPC, but in both, distant metastases are the most common pattern of failure, with bone being the commonest site involved. Treatment of recurrent NPC in children depends on the pattern of recurrence. Visceral metastatic disease is treated with chemotherapy whilst bone metastases are treated with concurrent or sequential chemo-radiation. Local recurrence carries a slightly better prognosis than distant metastatic recurrence and patients should be assessed for concurrent chemo-RT strategies. Prognosis after distant recurrence is poor (Yan et al. 2013).

7.4 Desmoid Tumors

7.4.1 Introduction

Desmoid tumors or aggressive fibromatoses are rare benign, non-metastatic but locally invasive tumors that arise from fascial or deep musculoaponeurotic structures in various locations in the body. They represent a monoclonal proliferation derived from mesenchymal stem cells (Wu et al. 2010).

They were first described by McFarlane in 1832 (Macfarlane 1832) but the name “desmoid” was coined by Muller in 1838 from the Greek word “desmos” meaning bond, fastening or tendon-like (Muller 1838). They occur in 2–4 new individuals per million per year and make up 0.03% of all neoplasms and 3% of soft tissue

tumors (Fletcher et al. 2013). Classically they are divided into juvenile and adult-type fibromatoses (Allen 1977) and make up 60% fibrous tumors in childhood (Ayala et al. 1986; Faulkner et al. 1995; Spiegel et al. 1999).

7.4.2 Epidemiology

Two relative incidence peaks are reported in the literature: a pediatric group at 6–15 years, and between puberty and age 40 years in women (Meazza et al. 2009). Up to 30% occur in the first year of life with a peak incidence at 4.5 years and a male predominance (Ayala et al. 1986; Faulkner et al. 1995; Spiegel et al. 1999; Schmidt 1995). They are mainly sporadic where the pathogenesis is most likely multifactorial including genetic predisposition, endocrine factors, trauma (including sites of previous surgery) and exposure to radiation (Meazza et al. 2009). The occasionally seen inherited cases (5%) have been linked to Familial Adenomatous Polyposis in Gardner Syndrome (autosomal dominant) often presenting with aggressive intra-abdominal mesenteric lesions (Lefevre et al. 2008). Most tumors in children tend to be extra-abdominal unlike their adult counterpart (Otero et al. 2015). They are usually solitary but may be multifocal where they tend to develop in the same limb or anatomical region (Häyry and Scheinin 1988).

Pediatric desmoids have a strong tendency to recur locally (24–77%) and may be fatal in abdominal locations or unresectable sites. Risk factors for local recurrence in children include young age, large size (>5 cm), presentation as recurrence, girdle/extremity/intra-abdominal location (abdominal/chest wall locations associated with better local control), involved surgical margins and B-Catenin-activating mutations. Whether local relapse affects survival remains unanswered (Meazza et al. 2011). OS is 90% at 10 years approaching 100% in extra-abdominal cases (16–22).

Historically the biologic and clinical patterns of AF in children have been considered the same as those in adults, and treatment recommendations have, therefore, been similar (Meazza et al. 2009). In an effort to standardize treatment specific to the pediatric population, identify risk factors associated with the abovementioned higher local recurrence rate as well as potential therapeutic targets for intervention, most of the international soft tissue sarcoma cooperative groups are now trying to register patients in databases and protocols. The European pediatric Soft Tissue Sarcoma Study Group (EpSSG NRSTS 2005 protocol) is strongly recommended and will be discussed below within the management section (Meazza et al. 2011).

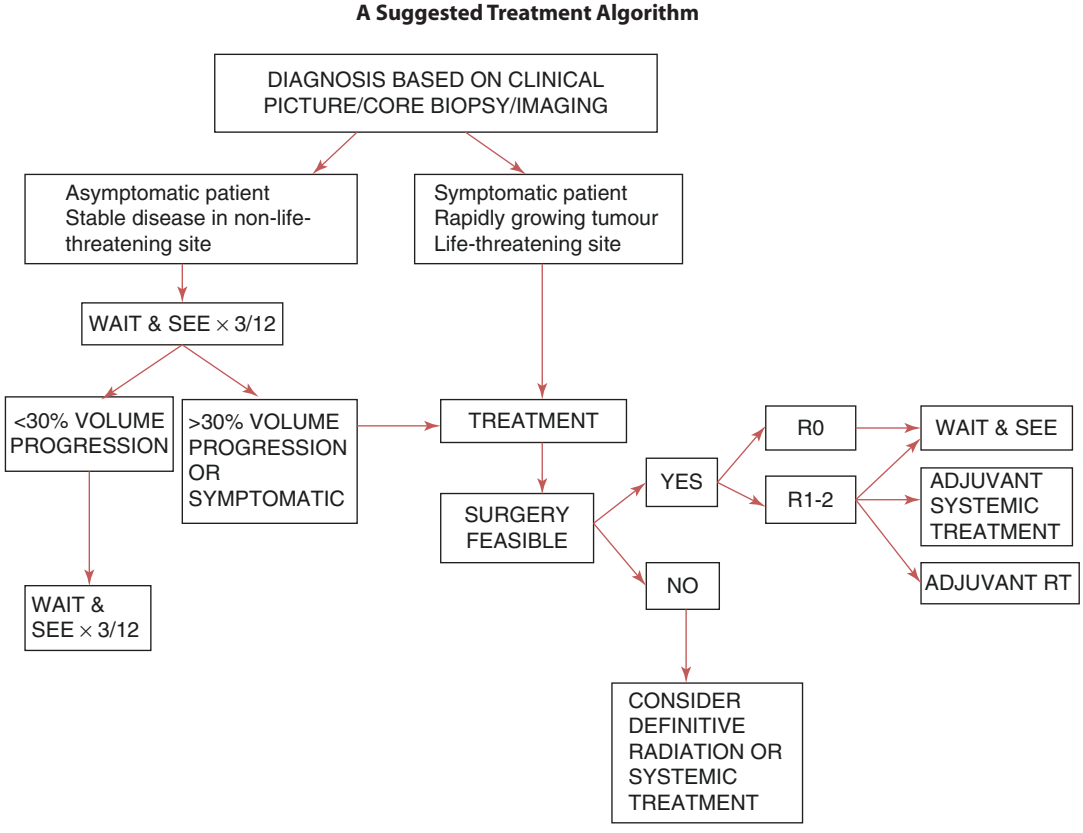
7.4.3 Diagnosis

1. Core biopsy—this is essential for diagnosis and shows an infiltrative lesion made up of uniform spindle cells (myofibroblasts) within a dense collagenous stroma. Tumors stain positive for vimentin with variable expression of muscle-specific actin, desmin and smooth muscle actin (Fletcher et al. 2013; Weiss and Goldblum 2001). Eighty percent express β-catenin, involved in promoting mesenchymal cell proliferation both in FAP-associated desmoids (through germline mutations in APC gene) and sporadic desmoids (through somatic mutations of the β-catenin gene CTNNB1) (Nieuwenhuis et al. 2008; Li et al. 1998; Iwao et al. 1999; Tejpar et al. 1999; Sakorafas et al. 2007). A stronger expression of β-catenin especially associated with p53 positivity may predict high recurrence rate: wild-type β-catenin tumors seem to have better relapse free survival compared to β-catenin mutated tumors (5-year RFS 75% vs. 43%) and may be a useful molecular biomarker of local recurrence (Dômont et al. 2010; Lazar et al. 2008). Gene alterations of chromosomes 8, 20, 6 and 5 are also reported. COX-2 increases growth factor expression e.g., PDGF in desmoids which may be mitogenic for fibroblasts and the tumor suppressor gene Rb1 is lower in this disease and may be involved in pathogenesis (Brandal et al. 2003; Poon et al. 2001; Kong et al. 2004). These molecular aberrations may guide new molecular targets in this disease (Meazza et al. 2011).

2. Imaging:
   (a) **Ultrasound**—findings are non-specific but may be used to direct core biopsy
   (b) **CT Scan**—tends to show a lesion isodense to skeletal muscle but also non-specific
   (c) **MRI**—used for primary diagnosis, to aid surgical staging and for follow up post treatment. The lesion may be well defined or have irregular infiltrative margins. A key diagnostic feature is hypointense bands representing collagen bundles on T2 W images. Moderate to marked gadolinium contrast enhancement is seen except in these collagen bundles. Other possible radiological findings include "split fat sign" which refers to a thin rim of fat surrounding the lesion or a "fascial tail" demonstrating infiltration along the fascia. The more infiltrative the lesion the higher the recurrence rate in children (Romero et al. 1995).
3. If a familial trait is suspected the following is suggested: skull x-ray, panoramic dental X-rays, fundus examination, colonoscopy and gastroscopy, dermatologic exam and referral for genetic counseling (Meazza et al. 2011).

7.4.4 Management

Management of these tumors is challenging and should be individualized. There is no "Gold Standard" strategy shown to lower recurrence rate and decrease long term toxicity yet. Due to the rarity of these tumors it is difficult to conduct randomized controlled trials needed to formulate evidence-based shared treatment guidelines. In children especially, there is a paucity of literature available, limited mainly to one prospective phase II trial (POG 9650 on 28 patients), reports on retrospective studies and review articles (Meazza et al. 2011). Options include surgery, radiation, systemic management or a combination of these, and observation ("wait-and-see" strategy).



7.4.5 Surgery

Surgery remains standard first line treatment and comprises wide local excision aiming for negative microscopic margins. Primary surgery is suggested if complete non-mutilating surgery is potentially feasible or in cases of tumor progression, symptoms or threatening site. Less than 25% microscopic complete resections are seen at diagnosis. Disease control is similar after marginal resection or intralesional surgery/biopsy. The following relapse rates have been reported:

Group I (Complete resections) 22%,
Group II (Marginal resections) 76% and,
Group III (Macroscopic residual disease) 76% (10)

Growth factors released during wound healing post-operatively may actually promote β-catenin activation helping to explain both the high relapse rate and role of surgery in stimulating the onset of desmoids. Because of wide margins, the need for reconstructive surgery is frequent and chronic pain and cosmetic sequelae are common.

7.4.6 Radiation Therapy

Most studies have shown that adjuvant radiation (post-operatively) confers a higher local control rate (Goy et al. 1997; Spear et al. 1998; Ballo et al. 1998). Surgery with adjuvant radiation has been compared to definitive radiation alone by the 2008 Guadagnolo et al. and the 2010 Rödiger et al. studies and reported no statistically significant difference in local control rates at 4 or 10 years (Guadagnolo et al. 2008). Postoperative radiotherapy raises local disease control to a level similar to complete resection (from 46 to 78% in primary tumors and from 18 to 76% in recurrent desmoids).

The decision to offer radiation should be made by both the treating clinician and patient/parents after weighing the potential benefits in local control against the potential toxicity associated with irradiating children. It is recommended that this treatment modality be used as sparingly as possible in children with desmoids tumors (Therasse et al. 2000). The optimal dose, whether definitive or adjuvant, has also not been defined. Total doses between 50–56 Gy in 2 Gy fractions, and fields covering the total tumor or surgical bed plus a margin of at least 5 cm have generally been recommended (Mendenhall et al. 2005; Spear et al. 1998; Ballo et al. 1998; Lewis et al. 1999; Plukker et al. 1995). Delayed second radiation may be considered at disease progression. The main complications of radiation include healing problems, fibrosis, edema, skin ulceration, pathologic fractures, cellulitis, growth abnormalities, neurologic deficits and secondary malignancy (Spear et al. 1998; Ghert et al. 2014). An increase in complications is noted above 56 Gy and in patients younger than 30 years (pediatric population) (Ballo et al. 1999). In contrast to adults, desmoid tumors in children are more likely to recur despite radiotherapy (Meazza et al. 2009; Therasse et al. 2000). The EpSSG guidelines recommend radiation only in select situations: failure to respond to chemotherapy, in unresectable cases, progression despite multiple surgical procedures or as an alternative to mutilating surgery. Figure 7.10 shows a case of a desmoid treated with proton therapy in a teen after multiple prior resections and progressive growth toward the spinal canal.

7.4.7 Systemic Therapy

Systemic treatment may shrink tumors to make them amenable to resection, stop growth or stabilize disease. It may be given upfront as neoadjuvant treatment prior to surgery or radiation (useful in very young children) or in previously treated patients e.g., failure after surgery, radiation or both. Experience is limited in prepubescent children. Due to the slow growth rate of the tumor and slow response to chemotherapy, at least 6 months treatment or up to 12–18 months treatment is recommended. Like adult sarcomas, a general chemo-responsiveness rate of about 40% is noted (Oudot et al. 2012). The Italian Pediatric Series observed an overall response rate of 49% to low dose chemotherapy, a further 38% achieved tumor stabilization and RR <30% with previous exposure to systemic treatment. Meazza et al. provided a useful table of available systemic options adapted below (Meazza et al. 2011).

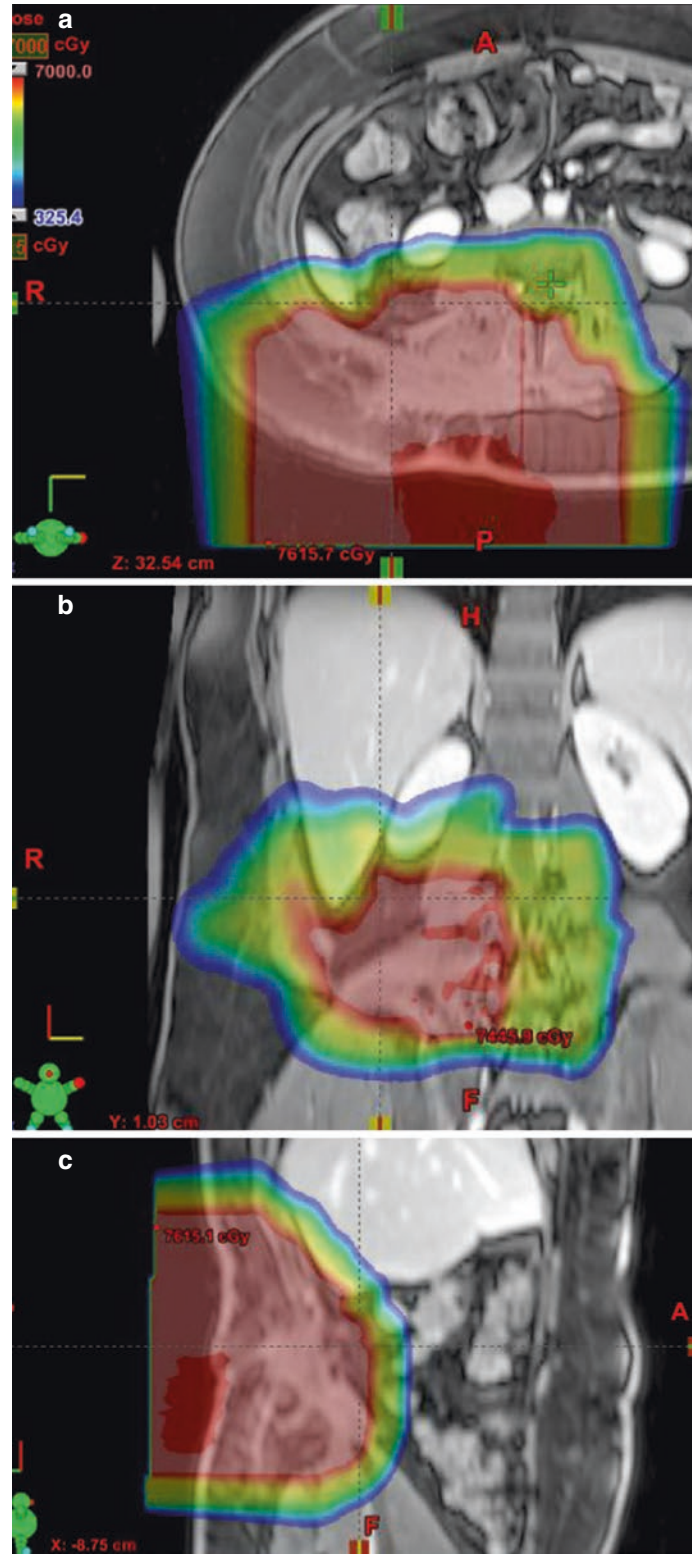


Fig. 7.10 Shown is a proton plan that addressed a desmoid that had recurred a total of four times and surgery options were exhausted given tumor spread to abut the spinal nerve roots and the bowel. A low dose was delivered to a larger volume while a higher dose, in a boost, was delivered to a smaller volume. The patient did not recur in the deep areas where dose was taken to the boost dose. Shown are axial (**a**), coronal (**b**), and sagittal (**c**) views of the dose colorwash. (Indiana University Proton Therapy Center, Bloomington, Indiana)

Serious side effects include fertility problems, cardiotoxicity and secondary malignancies. Wherever possible, children should be enrolled in clinical trials.

7.4.8 Systemic Treatment Options (Adapted from Meazza et al. 2011)

Chemotherapy

Regime	Response RATE
– Methotrexate 30 mg/m^2/week iv + Vinblastine 6 mg/m^2 (max 10 mg)/week iv – Methotrexate 30 mg/m^2/week iv + Vinorelbine 20 mg/m^2/week iv	58% Major/Minor response 42% Stable disease (Meazza et al. 2011, Skapek et al. 2007)
– Vinorelbine 25 mg/m^2/iv (or alternatively, 60 mg/m^2 oral) day 1,8,15 plus oral Cyclophosphamide 25 mg/m^2/day (every day)	
– IVA Regime (Vinc 1.5 mg/m^2 day 1, Actinomycin 1.5 mg/m^2 day 1, Ifosfamide 3 g/m^2 day 1–2) or VAC regime (Vinc 1.5 mg/m^2 day 1, Actinomycin 1.5 mg/m^2 day 1, Cyclophosphamide 1.2 g/m^2 day 1) or VA regime (Vinc 1.5 mg/m^2 and Actinomycin 1.5 mg/m^2) every 21 days	Response Rate 47% (Meazza et al. 2011)
– Pegylated liposomal doxorubicin (20–50 mg/m^2 iv every 3–4 weeks)	
– Hydroxyurea (20 mg/kg/day to start and then 30 mg/kg/day	Partial response 29%, stable disease 50% (preliminary results of N. American study underway) (Meazza et al. 2010, Takemaru et al. 2008)
Targeted therapy	
– Imatinib (400 mg × 2/day) (targets PDGFin desmoids)	Response Rate 10–20% (Heinrich et al. 2004)
– Sorafenib (400 mg day)	Partial Response 25% Stable disease 70% (Gounder et al. 2011)
Hormonal treatment	
– Tamoxifen 5 mg × 2/day if age < 10 years, 10 mg × 2/day if age > 10 years – Toremifene 60 mg × 3/day	Experience is limited in prepubescent children and caution is advised. Common side effects include growth abnormalities, teratogenicity and deep vein thrombosis
Non-steroidal anti-inflammatory drug	
– Sulindac (100–200 mg tablets) at the dose of 4 mg/kg × 2/day or 4 mg/kg twice daily – Celecoxib (100–200 mg capsules) 100 mg twice daily	Antacids, Proton Pump Inhibitors and monitoring of renal function advised in children

7.4.9 Observation

It has been observed that certain desmoid tumors may remain stable for long periods of time and even regress. This has prompted the use of a "wait-and-see" strategy that is more commonly used in adults but may be considered in children for asymptomatic tumors, in non-life-threatening sites, in the absence of marked progression (defined as >30% volume progression). This approach may also provide information on natural tumor biology and growth rate (Wu et al. 2010; Gronchi 2003). These patients should be strictly reviewed every 3–4 months with clinical examinations and MRI scans, preferably by a specialized pediatric sarcoma unit.

7.4.10 Other Options

These include radiofrequency ablation, cryoablation or limb salvage with isolated perfusion but are not widely used (Bocale et al. 2011).

7.4.11 Follow Up

In general this includes rehabilitation of children, aiming for maximal function. Regular physical examinations and appropriate imaging is mandatory.

Conclusions

Desmoids are rare tumors and, therefore, evidence is limited, especially in children. Treatment should be individualized ideally by a specialized pediatric sarcoma or oncology unit. Risks and benefits of each treatment modality should be thoroughly discussed between clinicians, patients and their parents. Future international prospective trials are awaited to further guide management of this chronic disease.

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Pediatric Glioma

8

Erin Murphy, Matthew Poppe, and Rakesh Jalali

8.1 Pediatric High Grade Glioma

8.1.1 Introduction

Tumors of the central nervous system (CNS) are the most common solid neoplasms in children. About 5% of all CNS tumors occur in the age group 0–14 years. Gliomas constitute approximately half of tumors in children, majority being low grade gliomas (LGG). The high grade gliomas (HGG) include ependymomas, anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), mixed gliomas—oligoastrocytoma, and glioblastoma (GBM) depending upon the astrocytic cell of origin (Louis et al. 2007). While HGGs represent one of the most common CNS tumors among adults, they comprise only 20% of all primary CNS tumors in the pediatric population. GBMs comprise only about 3% of all pediatric CNS tumors (Ostrom et al. 2015). Based on the recent CBTRUS data, HGG are the third most common histology in 0–4 years age group and second most common in 5–14 years age group. Age-adjusted incidence rates of HGG are 0.9 per 100,000 in 0–4 years age group and 0.5–0.9 per 100,000 in 5–14 years age group. Among HGG, supratentorial location constitutes 6–12% of all primary pediatric CNS tumors (Pollack 1994). If brainstem gliomas are excluded, then supratentorial is the most common location. Most supratentorial HGGs are located in cerebral hemispheres—35–50%, followed by 20–30% located in thalamus and basal ganglia (Fangusaro 2012).

Contrary to HGGs in adults where transformation from a low grade to high grade is a relatively common phenomenon, this phenomenon is exceedingly rare in pediatric patients (Broniscer et al. 2007) where tumors are *denovo* high grade. Molecular studies have shown that although histologically similar, pediatric HGGs are distinct from their adult counterparts (Jha et al. 2014; Pollack et al. 2006a; Ichimura et al. 2012). However, they both share aggressive clinical behavior resulting in significant morbidity and mortality among children with brain tumors. Despite decades of research and development of numerous treatment approaches, outcomes have remained fairly dismal with most series showing 3-year event free survival between 11–22% and the majority of children succumbing to their

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disease (Broniscer and Gajjar 2004; Cohen et al. 2011b). Pediatric HGGs remain the leading cause of childhood cancer mortality in children and young adolescents. A greater understanding of the biological mechanisms and driver mutations have led to the hope of novel treatment approaches using targeted therapies, immunotherapy and personalized approach and is the focus of the majority of ongoing phase-I and II studies.

8.1.2 Etiology

The etiological factors of the pediatric HGGs are not well studied. Various factors have been implicated including use of cell phones, smoking, infections, trauma and toxins. None have been consistently shown to be associated with tumorigenesis (Baldwin and Preston-Martin 2004; Vida et al. 2014; Swerdlow et al. 2011). One well understood risk factor is exposure to ionizing radiation, typically for the treatment of a previous acute leukemia. In a large cohort of patients of acute lymphoblastic leukemias treated with chemotherapy and cranial irradiation, there was a dose-dependent effect on tumor development from previous radiation exposure with children receiving radiation before the age of 6 years at the highest risk of developing a secondary malignancy (Walter et al. 1998; Neglia et al. 2006).

Genetic and familial syndromes are thought to be associated with childhood HGGs. Li-Fraumeni syndrome is genetic mutation of TP53 gene leading to suppression of p53 and predisposing to CNS tumors including HGG (Li and Fraumeni 1969; Birch et al. 1994). Other rare genetic disorders that increase the risk of CNS tumor development include Turcot's syndrome, Neurofibromatosis-1, and Tuberous sclerosis (Bondy et al. 2008; Poley et al. 2007; Hamilton et al. 1995; Melean et al. 2004).

8.1.3 Clinical Features

High grade gliomas have diverse clinical presentations that may vary with the location of the tumor. Constitutional symptoms such as fatigue, irritability, anorexia, loss of milestones, or failure to thrive can occur but are nonspecific in nature. There may be signs and symptoms of raised intracranial pressure such as persistent headaches, behavior changes, early morning nausea/emesis, diplopia, and papilledema. These can be seen regardless of histologic diagnosis or grade.

Seizures are rare in childhood HGG and are often partial; however, they are a common symptom in hemispheric lesions, especially when the tumor involves the temporal lobes. There is evidence to suggest that seizure on presentation is associated with better outcome (Walston et al. 2015). Lesions of dominant cortex especially around the speech areas tend to present with short history and profound deficits compared to subtle presentation of corresponding non-dominant cortex lesions.

Localizing focal neurologic deficits (motor or sensory) can occur in the deep-seated thalamic tumors.

Infants are a distinct population in whom signs and symptoms may be difficult to elicit and interpret. If the cranial sutures are still open, symptoms and signs of increased intracranial pressure may not be present; instead, the head circumference will increase, making room for the growing infiltrating tumor. A rapid increase in head circumference may be the first sign of a brain tumor in infants.

Nearly 10% have tendency to have leptomeningeal spread at presentation which may be asymptomatic or can have focal deficits resulting from involvement of spinal tracts (Heideman et al. 1997).

8.1.4 Diagnostic Imaging

A non-contrast computerized axial tomography (CAT) scan is commonly a first investigation to evaluate these children. It obviates the need to sedate, and is a good screen for hydrocephalus and hemorrhage. Magnetic resonance imaging (MRI) is, however, the gold standard in imaging brain tumors. It has unparallel resolution with multiplanar imaging capability. At a minimum, the following MRI sequences should be obtained:

T1-weighted, pre- and post-contrast administration, T2-weighted, and fluid-attenuated inversion recovery (FLAIR). Additional specialized magnetic resonance sequences include magnetic resonance spectroscopy (MRS), perfusion, diffusion-weighted imaging (DWI), and diffusion tensor imaging (DTI).

HGGs can have varying imaging features on MRI. These tumors are usually solitary but can be multifocal or multicentric. On pre-contrast T1-weighted sequences, these tumors are isointense or hypointense. After contrast administration, T1-weighted sequences typically show an irregular enhancing rim surrounding a non-enhancing area of central necrosis (Panigrahy and Bluml 2009). Alternatively, they can be poorly marginated with diffuse infiltration into white matter tracts such as the corpus callosum and anterior and posterior commissures. Hemorrhage is sometimes present within the tumor. The enhancing portion typically represents mitotically active proliferating tumor cells. T2-weighted and FLAIR sequences usually show a heterogeneous mass with variable signal intensity surrounded by a broad zone of vasogenic edema. Infiltrating malignant tumor cells extend far beyond the area of enhancement. These tumors have elevated choline level, lactate level, and lipid peaks and decreased N-acetylaspartate peaks on magnetic resonance spectroscopy (MRS) (Steffen-Smith et al. 2011). Because of the relatively high incidence of leptomeningeal spread, spinal MRI should be done at presentation and follow up.

8.1.5 Pathology and Molecular Biology of Pediatric HGG

A centralized histopathological review is frequently needed and recommended for appropriate diagnosis and grading of pediatric HGG, and is mandatory for patients being recruited in cooperative studies (Finlay et al. 1995; Pollack et al. 2003). The histomorphological features of pediatric HGG are no different from adult HGG, however, the difference lies in the molecular pathways of its tumorigenesis (Jha et al. 2014; Ichimura et al. 2012; Pollack et al. 2006a) (Table 8.1). With the increasing understanding of the molecular, biologic, and genetic make-up of pediatric HGG, it is often desirable to include molecular information in the "integrated diagnosis" in an attempt to define diagnostic entities as narrowly as possible. There is also a proposal for separating the pediatric HGGs as a separate entity from the adult ones in the upcoming revision of WHO classification of brain tumors (Louis et al. 2014).

One of the most common genetic abnormalities in adult HGG is the amplification of EGFR (Barker et al. 2001), which is associated with

Table 8.1 Summary of salient features comparing pediatric and adult HGG profiles

Characteristic	Pediatric HGG	Adult HGG	Adult secondary GBM
Median age	9–12 years	62 years	45 years
P53 mutation	33–74%	25–30%	60–65%
EGFR amplification	0–26%	20–50%	8%
PDGFR-A	12–14%	11%	NA
IDH-1/2 mutation	0–4%	10%	85%
MGMT methylation	37–50%	36%	75%
H3.3 K27 M	22–36%	3%	NA
ATRX/DAXX	31–34%	26–7%	NA
TERT, TERC	46%	10–100%	NA
Mismatch repair genes	27%	Rare	NA
Proliferative Index	Cut-off ranging from >25 to 36% correlates with survival	No cut-off defined correlate with survival	–

Please refer to text for relevant references

negative impact on survival. However, overexpression of the EGFR protein is uncommon in pediatric supratentorial HGG (Cheng et al. 1999). Platelet-derived growth factor receptor (PDGFR)-A on the other hand seems to be the predominant target of focal amplification in pediatric HGG (Paugh et al. 2010).

Pediatric GBM often demonstrate p53 mutations, similar to secondary adult GBM that evolve from LGGs. Over-expression of p53 protein has been reported in 63–74% of children in various studies (Pollack et al. 2002; Suri et al. 2009; Cheng et al. 1999). The CCG-945 study observed that overexpression of the p53 protein increases with tumor grade and is associated with reduced overall survival (Pollack et al. 2002). However, the prognostic significance of p53 expression has not been corroborated by others (Jalali et al. 2010). MIB labeling Index (LI) is an important marker for aggressiveness of childhood HGG. Studies have shown that children with high proliferation index have a poorer survival. The exact cut-off values above which there may be a negative impact on survival is not clearly defined with various studies defining different cut-off values (Pollack et al. 2006a).

Isocitrate dehydrogenase (IDH1) R132H point mutation—IDH1 is frequently mutated (>80%) in secondary adult GBMs (Nobusawa et al. 2009) and is a strong predictor of favorable outcome in adult GBM. However, IDH is very rarely mutated in pediatric GBM (Paugh et al. 2010).

MGMT (O(6)-methylguanine-DNA methyltransferase) gene encodes for a DNA repair enzyme and its overexpression in tumor tissue can reduce the efficacy of alkylating agents such as temozolomide. Promoter hypermethylation of the MGMT gene has been associated with prolonged survival in adult GBM patients receiving alkylating agents (Hegi et al. 2005; Pollack et al. 2006b). Frequency of MGMT promoter methylation status in childhood GBM has shown to be similar or lower as compared with adult GBM (Pollack et al. 2006b; Srivastava et al. 2010). The CCG-945 study showed lower expression levels of MGMT to be associated with better PFS (Pollack et al. 2006b).

Abnormal expression of Telomerase Reverse Transcriptase, TERT, has been demonstrated in children with HGG, including DIPG, which have increased *hTERT* and TERC levels compared to normal controls. More importantly, increased *hTERT* mRNA and TERC RNA expression are associated with worse OS in children with non-brainstem HGG. It has been suggested that the alternate lengthening of telomeres (ALT) in human glioma stem cells confers radiation resistance (Dorris et al. 2014). The therapeutic application of this finding is yet to be fully explored—both in terms of predicting response to existing therapeutic modalities and developing newer drugs for this target pathway.

Mutations have been described in genes involved in the H3.3-ATRX-DAXX chromatin remodeling pathway, almost exclusively in pediatric HGGs. The H3 histone, family 3A (H3F3A) gene, encoding the replication-independent histone 3 variant H3.3, is mutated in about 60% of DIPG and 30% of non-brainstem pediatric gliomas (Schwartzentruber et al. 2012; Wu et al. 2012; Sturm et al. 2012). H3.3 mutations are found mutually exclusively to IDH1 mutations. The therapeutic and prognostic relevance of these mutations is yet to be fully understood. In addition, *ACVR1* or *FGFR1* mutations have been described to co-exist with H3.3 mutations exclusively in midline (thalamus and brainstem) HGGs rather than cortical HGGs suggesting different oncogenesis and biologic behavior (Fontebasso et al. 2014).

8.1.6 Prognostic Factors

The extent of surgical resection is the most important independent prognostic factor (Wisoff et al. 1998). Supratentorial tumors located in the cortex do well compared to deep seated midline structures like thalamus and basal ganglia (Eisenstat et al. 2015). In addition, grade of tumor and age at presentation are inversely correlated with prognosis (Finlay et al. 1995; Wolff et al. 2002, 2008).

8.1.7 Management of Pediatric HGG and Their Outcome

Multimodality approach is the standard of care with maximal safe resection followed by adjuvant conformal radiation therapy and/or chemotherapy. The evidence for chemotherapy in pediatric HGGs is somewhat debatable unlike in adults where there is clearly a benefit of adding chemotherapy on progression free survival (PFS) and overall survival (OS) (Stupp et al. 2005; Finlay et al. 1995; Cohen et al. 2011b). The proponents for adding chemotherapy for children cite the strong adult evidence.

8.1.8 Surgery

The goals of surgical resection are to provide initial decompression improving neurological symptoms and to provide material for tissue diagnosis and molecular characterization. Maximal safe resection should be attempted while minimizing the risks involved for neurological deficits. It has been proven that extent of resection (EOR) is a strong, independent prognostic variable (Cohen et al. 2011b; Wisoff et al. 1998). In the CCG-945 experience, with gross total resection (GTR) compared to less aggressive resection, the 5-year PFS in anaplastic astrocytomas was 44% and 26%, respectively and for glioblastomas was 22% and 4%, respectively, with less aggressive resection (Wisoff et al. 1998). Gross or near-total resection (>90% resection) was achieved in 49% of lesions in superficial cerebral hemispheres and only 8% of those arising in the central structures (diencephalons, midbrain). Midline structures are less amenable to complete resection for fear of precipitating life threatening neurological deficits (Finlay et al. 1995). However, recent analysis of a separate cohort of midline patients from the CCG 945, aggressive resection in these group of patients may have a positive impact on long term survival and outcomes (Eisenstat et al. 2015).Although this data represents the era before there was wide availability of MRI scanning, stereotactic navigation and functional intraoperative monitoring, it is likely that more aggressive neurosurgical management backed with advanced stereotactic localization and intra-operative navigation techniques can have a positive impact on long term survival and outcomes especially in this group of patients. There is significant progress in image guided surgery techniques for intra-operative localization of tumor. This can be achieved by intra-operative MRI (iMRI), 5-aminolevulinic acid (5-ALA) fluorescence guidance, neuro-navigation including diffusion tensor imaging (DTI), and ultrasound. With better tumor localization there may be an improved extent of resection and better sparing of normal brain parenchyma leading to decreased post-operative neurological deficits. Whether it actually impacts the outcomes needs to be further explored in properly designed studies (Barone et al. 2014).

8.1.9 Radiation Therapy

Radiation forms an important component of treatment of HGGs. It is mostly employed as postoperative adjuvant treatment. Rarely, it may be used in the primary setting where the lesion is seated near critical structures. There have been no randomized studies between surgery alone versus surgery and radiotherapy for HGGs in children. The impact of adequate radiation therapy on survival is extrapolated to pediatric population from adult studies.

Treatment involves focal radiation to tumor and surgical cavity with adequate margins to include microscopic extension of disease and peritumoral edema. Studies in adults have shown infiltration of the malignant cells well into the perilesional low-density areas on CT or areas of abnormal signal on T2 MRI (Halperin et al. 1989). There is no role for whole brain radiotherapy in patients with localized HGG (Buckner et al. 2007).

Three-dimensional conformal radiation techniques are well tolerated and may reduce the sequelae of radiation by decreasing the exposure of adjacent normal brain. Target volumes are

defined preferably by co-registering the planning CT with MRI. Generally, the post-operative tumor cavity along with any enhancing lesion and surrounding low-density change (on CT) is taken as the gross tumor volume. If MRI is available then, contrast enhanced lesions on T1 and signal abnormality on T2/FLAIR weighted images is taken as initial GTV. This is then expanded to 2–2.5 cm to define the clinical target volume, CTV. This is then expanded to PTV to cover the set-up errors and uncertainties.

Dose levels used are 56–60 Gy in conventionally fractionated regimens with 6 MV photons. There is no role of dose escalation beyond 60 Gy (Halperin et al. 1989; Chan et al. 2002). Altered fractionation such as hyper- and hypofractionation have been tried without significant benefit (Fallai and Olmi 1997).

Proton radiotherapy has a property of depositing most of energy at depth due to the Bragg peak phenomenon. Dosimetric studies have shown a reduction in integral dose with protons compared with external-beam photons (Macdonald et al. 2008; St Clair et al. 2004). Many centers also use protons as a boost after conventional photon based conformal RT techniques. There is an ongoing phase 2 study comparing carbon ion therapy with protons for boost to macroscopic disease in newly diagnosed adult HGGs (CLEOPATRA trial, NCT 01165671). Because of the inherent infiltrative nature of gliomas in general and relatively sharp fall off of particle beams, it remains to be seen whether they offer a clear cut advantage over photons in terms of clinical outcomes. There is evidence to suggest that the dosimetric advantage of protons may translate into clinical benefit in terms of better QOL due to sparing of critical structures (Kuhlthau et al. 2012).

8.1.10 Chemotherapy

The role of chemotherapy has evolved from vincristine and procarbazine based regimens to the currently favored temozolomide. The first study involved all types of CNS tumors including HGGs, medulloblastomas and ependymomas among others and compared MOPP vs. OPP (Cangir et al. 1984). The study was marred by poor follow-up and underpowered data and therefore, unable to make any meaningful conclusions. The first landmark study was CCG-943, which evaluated the role of adding pCV to standard fractionated RT. It consisted of 8 cycles of lomustine, vincristine and prednisolone adjuvant to surgery and was followed by conventionally fractionated RT at 54 Gy along with weekly Vincristine. The study demonstrated a 5-year PFS advantage of 21% and established the role of surgery, radiation, and chemotherapy as the standard approach for these tumors in children (Sposto et al. 1989). CCG-945 compared a more intense chemotherapy protocol—so called "8-in-1" regimen that includes 8 drugs: lomustine, vincristine, hydroxyurea, procarbazine, cisplatin, cytarabinoside, dacarbazine and methylprednisolone—all given in 1 day versus pCV chemotherapy. Two cycles of 8 in 1 were administered after surgery followed by conventionally fractionated RT alone at 54 Gy (Finlay et al. 1995). The PFS and OS at 5 years were 33% and 36%, respectively. There was no difference in the outcomes between the two regimens.

Interestingly, the control arm treated in CCG-945 with pCV had an inferior outcome to that of children treated with pCV in CCG-943. One explanation for this observation could be more stringent histopathologic criteria of a true HGG in CCG-945. A significant proportion of children treated in CCG-943 turned out to have LGGs.

The Pediatric Oncology Society of the Germanic language group (GPOH) undertook a series of pilot trials—the HIT-GBM trials. These trials explored various chemotherapy regimens in induction, concurrent and maintenance phases with radiation. The HIT-GBM A regimen used oral trofosfamide and etoposide and was not proven useful (Wolff et al. 2000). The next regimen tried early, intensive chemotherapy consisting of ifosfamide, etoposide, methotrexate, cisplatin, and cytosine arabinoside followed by irradiation. This was followed by interferon maintenance therapy (Wolff et al. 2006). The induction regimen appeared superior. The third protocol—HIT-GBM C—replaced interferon

with valproic acid, a histone deacetylase inhibitor (HDAC), for maintenance (Wolff et al. 2010). This was shown to be superior to historic controls. In the HIT-GBM D, the same intensive chemotherapy is combined with methotrexate with encouraging results. This has led to mounting of a phase 3 trial (Wolff et al. 2011).

Temozolomide (TMZ) has been studied in concurrent and adjuvant setting along with RT. The results are not robust enough to either accept or refute its use unequivocally. After the landmark paper by Stupp in 2005, addition of TMZ to RT has become the standard of care in adult GBMs. This was confirmed by others worldwide in adult GBMs and was extended to the pediatric population. TMZ was not shown to be of benefit in ACNS0126 study by Cohen et al. when compared with retrospective results of pCV (Cohen et al. 2011b). A multi-institutional study by Walston et al., including all HGGs showed benefit in PFS with complete resection and use of TMZ (Walston et al. 2015). Most studies on concurrent chemotherapy have a heterogeneous group of tumors comprised of WHO grade 3 and 4. Data for a pure cohort of pediatric GBM's only is relatively sparse. In a large such series of 66 patients with pediatric GBMs a benefit rate of TMZ similar to adult trials was reported with similar toxicity rates (Jalali et al. 2010). Until more robust data are available, it seems appropriate to encourage use of TMZ along with RT.

In the ongoing ACNS0822 study, by the Children's Oncology Group (COG), Vorinostat (HDAC inhibitor) is used for radiosensitization along with RT and compared with Bevacizumab and temozolomide separately in a 3-arm study. Combination of Bevacizumab and TMZ for radiosensitization as well as adjuvant to RT is under study in the ongoing HERBY trial (NCT-01390948).

8.1.11 Special Cases: Infants and Young Children

There is a valid concern regarding neurocognitive effects of radiation especially in very young children (Merchant et al. 2009a). It may be argued that HGGs have a relatively poor outcome and therefore it is okay introduce RT upfront. However, it has been seen that children <3 years may do a little bit better as compared to older children (Finlay et al. 1995), possibly due to good responses to chemotherapy alone (Geyer et al. 1995; Duffner et al. 1996; Dufour et al. 2006). In such cases it may be prudent to reserve radiation for later date or for salvage of recurrence (Vanan et al. 2014).

8.1.12 Treatment of Relapses

The most common recurrence is at local site alone in about 2/3rd cases. Nearly 10% fail in the leptomeninges with the remaining showing combination of both (Heideman et al. 1997; Lindsay et al. 2002). Autopsy studies have confirmed the most common pattern of recurrence to be local with nearly 80% recurrences occurring within 2 cm of the initial contrast enhancing disease on CT (Liang et al. 1991).

Re-irradiation using highly conformal stereotactic radiation can be considered for relapsed cases. Small case series have reported re-irradiation using hypofractionated stereotactic radiation with various dose/fractionation schedules (Muller et al. 2014; Ciammella et al. 2013; Fogh et al. 2010). Median time from second RT to death is reported at 6–11 months. Generally, palliative re-irradiation in relapsed cases helps by improving symptom control, but its impact on extending survival is not yet established (Vanan et al. 2014). There is an ongoing phase I/II clinical trial evaluating the role of carbon-ion therapy in adult patients with recurrent HGG (CINDERELLA trial, NCT-01166308). Similar studies are expected in near future in pediatric HGG. TMZ has been tested in the past in phase II trials in relapsed setting with median OS has reported as 4–6 months and objective response rates of 10–12% (Lashford et al. 2002; Ruggiero et al. 2006).

Bevacizumab in combination with irinotecan has been tried in a pediatric Brain Tumor Consortium (PBTC) phase II trial in relapsed HGGs. Stable disease was reported in one-third of

cases with median OS ranging from 30 weeks to 6 months (Gururangan et al. 2010; Narayana et al. 2010; Parekh et al. 2011). However, there were no sustained responses once the chemotherapy was stopped. Generally, response rates and overall outcome has been perceived to be somewhat lower than seen in adult counterparts. Similarly, phase II studies combining O6-benzylguanine, an MGMT inhibitor with TMZ and the anti-integrin agent Cilengitide for recurrent disease have not shown encouraging results (Warren et al. 2012; MacDonald et al. 2013).

Dose escalation of chemotherapy with ASCR (autologous stem cell rescue) has been tried in smaller studies in recurrent setting. The long-term survival rates remain poor with significant long term toxicity from the chemotherapy (Finlay et al. 2008).

8.1.13 Survival and Outcomes

In a trial for conformal RT for malignant gliomas, Vern-Gross reported median OS of 16 months with range of 3–88 months with 6 children alive at the time of analysis (Vern-Gross et al. 2014). Finlay et al. (1995) report the CCG-945 outcomes of 5-year PFS 33% and OS 36% in the overall group. For the entire midline tumor group, 5-year PFS and OS were 18.3 ± 4.8 and 25 ± 5.4%, respectively (Eisenstat et al. 2015). Of note, pathology review strongly influenced survival distributions that were calculated for each treatment arm (Eisenstat et al. 2015; Pollack et al. 2003). Recent studies with RT with concurrent and adjuvant TMZ in GBM have shown median OS of 15 months (Jalali et al. 2010).

8.1.14 Quality of Life (QoL) and Neurocognitive Outcomes in Pediatric HGG

Limited data is available on QoL with treatment of pediatric HGG in sharp contrast with the adult data. Partly, this can be attributed to the poor outcome of these children. Two prospective studies provide the most of available data. In the first study, long-term survivors of CCG 945 were recruited into a prospective study. It has been observed that non-hemispheric location—midline or infratentorial, younger age at diagnosis and female sex are associated with poor outcome in terms of social, emotional, and behavioral functioning. Patients with these characteristics have a significantly lower neuro-cognitive score and a poorer QoL (Sands et al. 2012). The invasiveness of surgery and the effects of radiation impact long-term cognitive function in pediatric patients with HGG. However, better outcomes have been demonstrated with those able to achieve a greater maximal safe resection. Patients with minimal surgical morbidity who have a stronger cognitive function prior to the initiation of RT are more likely to be spared the detrimental decrease in IQ scores as outcome toxicity (Vern-Gross et al. 2014). This has a strong implication challenging the dogma that RT alone is a major contributor to long-term neuro-cognitive dysfunction.

The second study showed significant decline in global intellectual ability and adaptive functioning over follow-up time. Surprisingly, no significant change occurred on measures of academic or social-emotional/behavioral functioning (Vern-Gross et al. 2014). Future studies are needed to evaluate this with a more comprehensive neurocognitive battery of tests. Hydrocephalus and shunt placement as a consequence of tumor obstruction have been well reported as risk factors for developing adverse cognitive effects (Ralph et al. 2000; Reimers et al. 2003). Requirement of shunts is also associated with a negative impact on PFS (Vern-Gross et al. 2014).

8.1.15 Summary and Future Directions

Pediatric high-grade gliomas continue to pose formidable challenges and tend to be aggressive with poor outlook. They are currently treated similar to adult counterparts. In view of distinct genomic and molecularly identified pathways, there is a tremendous interest in identifying

appropriate driver mutations and appropriate therapies. Several targeted therapy agents including tyrosine kinase inhibitors such as erlotinib, gefitinib and imatinib are being developed in phase I/II studies for relapsed cases (Rizzo et al. 2015). There is some evidence from pre-clinical studies that the combination of erlotinib and imatinib may be supra-additive (Bax et al. 2009). H3.3K27M mutations have been shown to be more frequent in subcortical regions such as the thalamus and brainstem, whereas H3.3G34R/V lesions tend to be in hemispheric locations of HGGs. Availability of an antibody against the H3.3K27M-mutant is being investigated. Of great interest is the fact that BRAF mutations, such as BRAF V600E, are also present in 10–25% of these pediatric HGGs. The next decade is likely to focus on this targeted approach to improve outcomes for these challenging tumors.

8.2 Brainstem Gliomas

Brainstem tumors account for 3.6% of all malignant brain tumors, as per the latest CBTRUS data. About 12.4% of all CNS tumors in the age group of 0–14 occur in the brainstem (Ostrom et al. 2015). Median age of presentation for all brainstem gliomas is 6–7 years, with equal male-to-female ratio. Despite aggressive treatment approaches, outcome of diffuse intrinsic gliomas of brainstem (DIPG) remains poor with long-term survival rates of <10%. In contrast, prognosis for patients with focal, exophytic brainstem tumors is relatively good, with survival reported to be between 50 and 100% (Barkovich et al. 1990; Molloy et al. 1995).

8.2.1 Etiology, Pathology and Classification

Exact etiology remains largely unknown. Patients with neurofibromatosis-1 (NF-1) may have an increased risk of having brainstem gliomas, whether diffuse or focal, which however, display a generally indolent biologic behavior (Molloy et al. 1995; Walker et al. 2013). Since these tumors may stabilize in size or regress without intervention, intervention should be limited to those lesions that exhibit progressive growth on serial neuroimaging or lesions that produce significant clinical deterioration (Broniscer and Gajjar 2004).

Brainstem gliomas can be classified as "focal" or "diffuse" depending upon the pattern of involvement. Focal brainstem tumors are discrete, well-circumscribed tumors without evidence of infiltration or edema. These tumors may occur in any level in the brainstem but are most frequently seen in the midbrain or medulla rather than the pons. More often, focal tumors are dorsally exophytic to the brainstem, sometimes effacing the fourth ventricle. These tumors are amenable to biopsy. Histopathology reveals that focal brainstem tumors are most commonly pilocytic astrocytomas or, rarely, gangliogliomas, both WHO Grade I (Fisher et al. 2000; Khatib et al. 1994).

Most pontine lesions are diffusely invasive in nature causing diffuse enlargement of the structure. Neoplastic infiltration commonly extends into the midbrain, cerebral peduncle, cerebellum, or medulla. These are often histologically high-grade anaplastic astrocytoma (Grade III) or glioblastoma (Grade IV) (Fisher et al. 2000) and may show disseminated neuraxis spread (Donahue et al. 1998; Sethi et al. 2011).

8.2.2 Clinical Findings, Imaging, Diagnosis

Duration of symptoms often correlates with the type of brainstem glioma (BSG). Children with DIPG usually present with a brief history of neurologic symptoms, almost uniformly measured in weeks and certainly less than 6 months.

The most common clinical presentation includes the triad of cranial neuropathies, ataxia, and long tract signs. Presence of at least two out these three signs is required for diagnosing pontine gliomas clinically. Elevated intracranial pressure (secondary to obstructive hydrocephalus) is present in fewer than 15% of children with pontine gliomas. Midbrain (tectal plate) tumors and

dorsally exophytic tumors of the pons or pontomedullary junction typically present with elevated intracranial pressure caused by obstruction at the aqueduct of Sylvius or the fourth ventricle, respectively. The more focal, less aggressive brainstem tumors often are associated with prolonged symptoms, typically confined to deficits in one or two cranial nerves alone, ataxia, or gradual onset of elevated intracranial pressure.

It is standard practice to diagnose DIPGs based on magnetic resonance imaging (MRI) findings in the context of a typical clinical presentation. Biopsy is not routinely obtained due to the critical location of these tumors (Rao 2008; Leach et al. 2008). Biopsy is recommended if there is atypical presentation and for recruiting in clinical trial protocols (Walker et al. 2013).

8.2.3 Imaging

MRI is considered to be the gold standard in characterizing BSG and is the preferred investigation modality to assess response to therapy and prognosis. MRI findings include a large expansive pontine lesion that is hypointense or isointense on T1-weighted imaging, hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging, and of variable enhancement with gadolinium-based contrast agents (Leach et al. 2008; Hayward et al. 2008).

Radiological criteria of diagnosing conclusively include diffuse involvement of the brainstem (>50% involvement of a brainstem segment or involvement of >2 of these segments with or without enhancement on injection of intravenous contrast material). Engulfment of the basilar artery by tumor is specific for the diagnosis of diffusely infiltrative brainstem glioma but is not seen in all cases (Fisher et al. 2000). Conventional MRI sequences showed low sensitivity and specificity in correctly diagnosing high- and low-grade gliomas. Various multiparametric MR prediction tools have been developed to predict survival and clinical outcome. These await validation in large prospective studies (Jansen et al. 2015; Poussaint et al. 2015; Goda et al. 2013). Two clinical factors are strongly prognostic—time between onset of symptoms and presentation; and presence/absence of florid neuro deficits (Broniscer and Gajjar 2004).

8.2.4 Treatment

Surgical intervention is often avoided due to fear of precipitating severe life-threatening neurodeficits. Biopsy is attempted in few cases with exophytic component. Recently, there has been interest in considering routine biopsy after its safety has been demonstrated in several series (Roujeau et al. 2007; Cartmill and Punt 1999).

8.2.5 Radiation

In patients with focal, exophytic lesions, radiation therapy (RT) can be given for postoperative residual disease. Alternatively, RT can be reserved for disease progression (Khatib et al. 1994). For DIPG, RT in primary or definitive setting is the mainstay of treatment. Usually it is given as conventionally fractionated doses of 54–60 Gy. This produces a clinical improvement of neurological symptoms in up to 85% and radiological response in 50% patients (Hargrave et al. 2006). Poor or no response to RT is an adverse prognostic feature. Altered fractionation has been studied extensively in various cooperative group trials. Dose escalation by hyperfractionation has been explored either alone or in combination with chemotherapy. In a series of trials reported on dose escalation using hyperfractionation has resulted in median OS of 8–13 months (Packer et al. 1994; Mandell et al. 1999; Allen et al. 1999; Jennings et al. 2002; Edwards et al. 1989; Prados et al. 1995). In the largest of the hyper-fractionation trials (POG-9239), a dose of 70.2 Gy delivered in twice daily fractions of 117 cGy yielded no additional benefit in OS over standard fractionation arm (Mandell et al. 1999). Increased long term toxicities in terms of steroid dependency, radiation necrosis, vascular events, hormone deficiencies and hearing loss were seen in these trials (Freeman et al. 1996).

Hypofractionated RT has a potential advantage of shorter treatment duration in a set of patients with already poor outcome often requiring anesthesia for delivering radiation adding to burden of the patients and their parents. Two pilot studies and a randomized controlled trial provide the evidence for equivalence of results in terms of OS and PFS rates (Negretti et al. 2011; Janssens et al. 2013; Zaghloul et al. 2014). Hypofractionation can be considered as an excellent alternative in children with poor performance status to achieve quicker palliation and decreased hospital visits. Radio-sensitization has been attempted with cisplatin, carbogen and motexafin gadolinium without any success (Mandell et al. 1999; Bradley et al. 2008, 2013; Aquino-Parsons et al. 2008). In addition, concomitant tamoxifen and beta-interferon has been tested in phase I/II studies (Broniscer et al. 2000; Michalski et al. 2010; Packer et al. 1996).

Re-irradiation can be particularly challenging in DIPG since the typical time to progression is less than a year (Freeman and Farmer 1998). Re-irradiation has been explored in DIPG based on evidence to tolerate it in posterior fossa ependymomas with the second course of RT delivered as early as 7.5 months from the completion of the first course. Evidence for feasibility of re-irradiation in DIPG comes from recently published case series (Fontanilla et al. 2012; Khatua et al. 2014; Massimino et al. 2014). Time to progression from first RT has been reported from 4 to 18 months. Time from initial RT to second course ranged between 8–28 months. Median OS after re-RT is 6 months (6 weeks–14 months).

8.2.6 Chemotherapy

Pre–irradiation chemotherapy has been tried to improve the outcome. Most have used multiple-agent platinum-based regimens including autologous stem cell rescue, although vinorelbine and irinotecan have been used as single agents. The highest median OS has been reported to be 17 months using carmustine, cisplatin, tamoxifen, high dose methotrexate (Frappaz et al. 2008). None of these regimens could achieve meaningful responses before radiation with nearly one-third patients showing progressive disease on chemotherapy (Doz et al. 2002; Frappaz et al. 2008; Jennings et al. 2002; Kretschmar et al. 1993; Massimino et al. 2008).

Temozolomide (TMZ) has been explored after the robust adult HGGs experience much to the dismay. Two phase II trials combining RT and TMZ in concurrent and adjuvant settings have failed to show any improvement in OS (Jalali et al. 2010; Cohen et al. 2011a; Bailey et al. 2013). In a prospective study, the angiogenesis inhibitor thalidomide was combined with TMZ with OS of 12 months (Kim et al. 2010). Other studies including combination with triple anti-angiogenic agents (thalidomide, etoposide and celecoxib; ANGICOMB protocol) have reported similar survival rates (Kivivuori et al. 2011; Porkholm et al. 2014; Turner et al. 2007). The major toxicity reported with this combination is myelosuppression. Trials with other conventional cytotoxic agents in various combinations and dose intensities have shown no benefit compared to radiation alone (Korones et al. 2008; Bouffet et al. 2000). Temozolomide is further being explored in metronomic doses and in combination with other agents like cilengitide in relapsed setting (NCT01517776). Capecitabine is being tried as a radiosensitizer based on in vitro and phase I studies (Glynne-Jones et al. 2006; Kilburn et al. 2013; Sawada et al. 1999).

8.2.7 Biological Advances and Targeted Therapy

The lack of tissue diagnosis has limited our understanding of molecular pathways of brainstem gliomas. Recently, case series have demonstrated a relatively lower risk of permanent neurological deficits and no mortality in attempting a stereotactic biopsy (Puget et al. 2015; Roujeau et al. 2007; Cartmill and Punt 1999). In an ongoing trial, tumor biopsy is being obtained at the time of diagnosis and subjected to molecular analysis to guide an individualized treatment strategy based on EGFR and MGMT expression status in newly diagnosed DIPG (clinicaltrials.

gov; NCT01182350). Autopsy studies can be another major source of tissue material although it will be admixed with treatment related changes (Angelini et al. 2011).

EGFR over-expression but not amplification, has been reported in 27–40% cases. PDGFR amplification is observed in up to 36% cases. The humanized monoclonal anti EGFR antibody, nimotuzumab was found to be encouraging in pre-clinical and phase I studies (Massimino et al. 2011). However, a subsequent phase II study demonstrated median OS of 10 months without any significant benefit. Phase I studies of tipifarnib, imatinib, gefitinib and erlotinib report 1-year survival rates from 30 to 50% with intra-tumoral hemorrhage (ITH) raising some concern (Broniscer et al. 2010; Geoerger et al. 2011; Geyer et al. 2010; Haas-Kogan et al. 2008; Pollack et al. 2007). VEGFR inhibition by bevacizumab or vandetanib is in investigational phase (Broniscer et al. 2010). PARP-1 amplification is reported in up to 27% cases with veliparib, olaparib, and niraparib being studied to target this pathway.

Histone proteins, H3.3 and H3.1 are mutated in up to 70% and 20% respectively (Ichimura et al. 2012; Wu et al. 2012; Schwartzentruber et al. 2012). Epigenetic modification of histone coding genes is being extensively studied in preclinical studies and various drugs have been developed. Panabinostat showed a dose-dependent increase in H3 acetylation and H3K27 trimethylation in these studies and is currently being developed in phase I studies (Bagcchi 2015; Grasso et al. 2015). The dose finding phase I/II trial by COG (ACNS 0927, NCT01189266) of vorinostat has closed accrual and results are awaited. Lastly, valproic acid is also being explored modulating the same pathway yielding median PFS of 9.5 months in a study.

A major hurdle in the delivery of chemotherapeutic drugs to the local site is intact blood-brain barrier in DIPG. Penetration can be achieved by convection enhanced delivery of drugs using subcutaneous pumps to deliver drugs intra-tumorally (Vanan and Eisenstat 2015).

Significant interest has been developed in the immunotherapy in gliomas in general and more so in DIPG due to failure of almost all strategies to improve survival beyond that achieved with RT alone. Several glioma-associated antigens, which can be targets for antigen-directed immunological therapy, are currently being explored in clinical trials (NCT00880061, NCT01130077). A peptide-based vaccine approach is also being explored targeting novel GAA [Glioma associated antigens—EphA2, interleukin-13 receptor alpha2 (IL-13Rα2), and survivin]-derived epitopes in children with DIPG and HGGs (Pollack et al. 2014). EGFRvIII is also targeted by using a peptide vaccine and is undergoing a phase III trial in the treatment of newly diagnosed GBM in adults.

8.2.8 Survival and Outcomes

Focal tumors of the midbrain or medulla show a relatively better long-term survival after irradiation of 50–70% (Farmer et al. 2001; Barkovich et al. 1990; Freeman and Farmer 1998; Prados et al. 1995; Albright et al. 1986). Survival at 10 years for dorsally exophytic brainstem gliomas after surgery even without radiation approaches 75% (Freeman and Farmer 1998; Hoffman et al. 1980; Farmer et al. 2001; Pollack et al. 1993). Similarly outcomes are reported for the focal pontine lesions of limited size after localized irradiation (Farmer et al. 2001; Freeman and Farmer 1998). For DIPG, reported median OS is 7–14 months, median PFS 5–9 months, 1-, 2- and 3-year OS ranged from 14–70%, 0–25% and 0–10%, respectively. Brainstem tumor of any morphology occurring in setting of NF-1 has a better outcome compared to similar tumors occurring without NF-1 (Molloy et al. 1995; Walker et al. 2013).

8.3 Low-Grade Glioma

8.3.1 Introduction

Pediatric low-grade glioma (LGG) is the most common Central Nervous System (CNS) malignancy in pediatrics and represents a heterogeneous

group of histologies and locations. LGG accounts for approximately 26% of childhood CNS malignancies in the United States (CBTRUS 2010: Statistical Report: Primary brain tumors in the United States 2010). Low-grade gliomas are found in the cerebral hemispheres, cerebellum, and deep midline structures of the brain (hypothalamus, thalamus, ventricles, visual pathways, and brainstem), and the spinal cord. Symptoms tend to be present for many months to years, and vary with tumor location, including: fatigue, headache, nausea, seizures, vision difficulties, weakness, numbness, behavior changes, or any number of other neurological symptoms. Current treatment recommendations vary according to location, resectability, severity and progression of symptoms and patient age. In the majority of cases, patients undergo surgical resection followed by observation. Observation after gross total resection is the standard of care and can produce progression-free survival rates of 80% for Grade II tumors and more than 90% for Grade I tumors (Gajjar et al. 1997; Merchant et al. 2009b). Tumor that undergo less than a gross total resection have a significantly higher progression rate (Wisoff et al. 2003). Evaluation of 5- and 10-year progression free survival rates is often inadequate, as patients can progress and die from their disease 20 and 30 years from diagnosis (Bloom et al. 1990). Adjuvant therapy recommendations are controversial and include observation, chemotherapy and radiation (RT).

8.3.2 Pathology and WHO Grade

LGG is a term used to describe a heterogeneous collection of CNS tumors with relatively indolent clinical behavior. The World Health Organization (WHO) has categorized CNS tumors into grades I-IV, of which LGGs are considered Grades I and II, and HGGs grades III and IV (Louis et al. 2007) (Table 8.2). Roughly half of LGGs are juvenile pilocystic astrocytomas (JPA) followed by non-pilocytic or diffuse astrocytomas (fibrillary, protoplasmic, gemistocytic, giant cell, pleomorphic xanthoastroctoma), and non-astrocytomas (oligoastrocytoma, oligodendroglioma, gangliomas, glialneuronal).

Table 8.2 LGG tumor histologies (Louis et al. 2007)

WHO I	WHO II
Pilocytic Astrocytoma (JPA)	Diffuse Astrocytoma (fibrillary, gemistocytic or protoplasmic)
Subependymal giant cell astrocytoma (SEGA)	Pilomyxoid astrocytoma
Ganglioglioma	Pleomorphic xanthoastrocytoma
Gangliocytoma	Oligodendroglial
Desmoplastic infantile ganglioglioma	Glioneuronal
Dysembryoplastic neuroepithelial tumor	

WHO Grade I JPAs are typically nonaggressive, occur predominantly in young children and occur most commonly in patients with Neurofibromatosis Type-1 (NF-1) disease. They are described as well-circumscribed, often cystic in appearance, and typically enhance on both CT and MR. The majority of JPAs, unfortunately, occur in locations that are unresectable, such as the optic tracts, diencephalon, or brainstem. Optic pathway, chiasmatic and hypothalamic (OHG) gliomas are often grouped together for analysis. They are most commonly pilocytic astrocytomas and usually unresectable at diagnosis. The 15-year survival rate for completely resected tumors is greater than 90%. Children with unresectable tumors have an inferior survival rate of 64% and are often treated with surgery and radiotherapy (West et al. 1995). A SEER analysis of gangliogliomas/gangliocytomas from 2015 shows a 5-year survival rate of >92% for all ages groups with 68% achieving an upfront GTR (Dudley et al. 2015).

WHO Grade II gliomas include diffuse astrocytoma, pleomorphic xanthoastrocytoma, oligodendroglioma, oligoastrocytoma, pilomyxoid astrocytoma and glialneuromas, such as neurocytoma. Non-pilocytic astrocytomas typically occur in older children, are often

grossly infiltrative, usually do not enhance, and are best imaged with T2 and FLAIR MRI sequence. These are more prone to malignant degeneration than JPAs. Oligodendroglial tumors tend to have a better prognosis than their astrocytic counterparts. They are felt to be more sensitive to systemic chemotherapy, especially in the presence of a 1p/19q co-deletion (Leeper et al. 2015). A 2014 Surveillance, Epidemiology and End Results Program (SEER) analysis demonstrates WHO Grade II with a 20 and 30 year cause specific survival (CSS) to be 81% and 77% respectively, compared to WHO Grade I tumors with 87% and 81% (HR 1.71, 1.35–2.17) (Poppe et al. 2011) (Fig. 8.1). In the same analysis, overall survival (OS) for WHO Grade II tumors at 20 and 30 years is 78% and 70% respectively, compared to WHO Grade I tumors with 84% and 72% (HR 1.60, 1.28–1.99) (Poppe et al. 2011) (Fig. 8.2). Who Grade II tumors are more commonly associated with malignant transformation with a reported 15 year cumulative incidence of malignant transformation of 6.7%, not correlating with the use of radiotherapy (Broniscer et al. 2007).

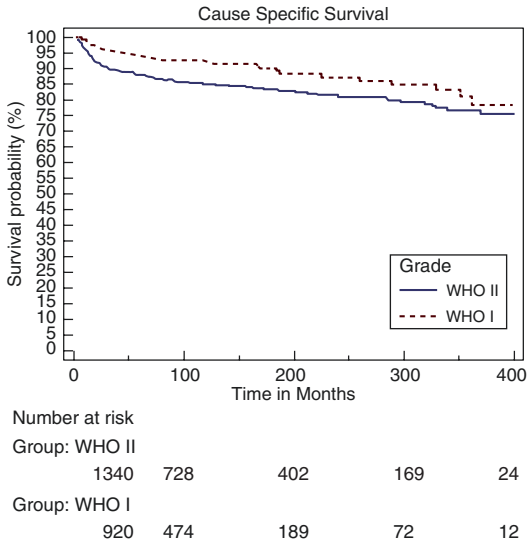

Fig. 8.1 CSS by WHO grade (Poppe et al. 2011)

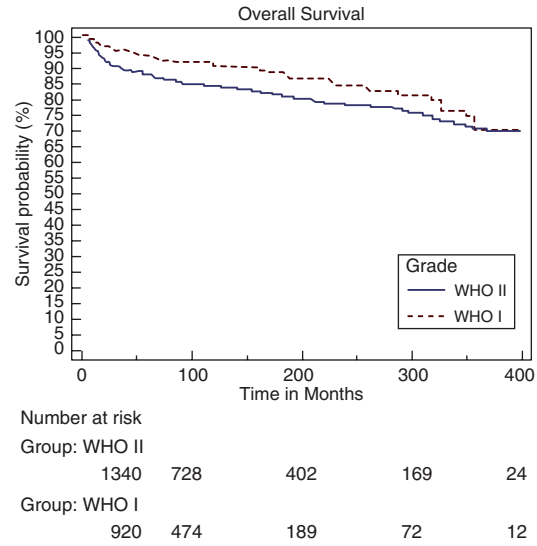

Fig. 8.2 OS by WHO grade (Poppe et al. 2011)

8.3.3 Etiology

The causation of LGG tumor development has not been well understood until recent genome analysis reveals a few consistent abnormalities. There is published work demonstrating BRAF oncogene mutations and BRAF gene fusions are frequently seen in pediatric LGG specimens. BRAF is a gene that gives rise to a protein called B-Raf which regulates the MAP kinase pathway, thereby affecting cell growth (Bar et al. 2008; Pfister et al. 2008; Sievert et al. 2009; Sithanandam et al. 1990). Other less common MAP kinases pathway alterations have also been described included SRFAP3-RAF1 and FAM131B-BRAF fusions, as well as FGFR1, NTRK2 and MYB/MYBL1 alterations (Eisenhardt et al. 2011; Jones et al. 2009; Bergthold et al. 2015). BRAF V600E mutations have been seen in cerebral pilocytic astrocytomas and pleomorphic xanthoastrocytomas, as well as gangliogliomas (Schindler et al. 2011; Gajjar et al. 2015). KIAA1549-BRAF gene fusion has been identified in pilocytic astrocytomas in the cerebellum, brainstem, spinal cord and optic pathways, but not the cortex (Lin et al. 2012; Sievert et al. 2009; Gajjar et al. 2015). Unlike adults, pediatric LGG patients are felt to have a lower frequency of IDH-1 mutations (Leeper et al. 2015; Buccoliero et al. 2012).

Tuberous Sclerosis (TS) and Neurofibromatosis Type-1 (NF-1) are two autosomal dominant inherited conditions that have a predisposition to LGG. TS is associated with an increased risk of subependymal giant cell astrocytomas and NF-1 is associated with JPAs, mainly of the optic pathway apparatus and hypothalamus.

8.3.4 Diagnostic Imaging

MRI with and without gadolinium infusion is the gold standard for imaging pediatric LGGs. LGGs can be difficult to see on CT images, as they often appear as isodense or hypodense regions of the brain, usually without enhancement, sometimes only seen as a mass effect. In general, LGGs share MRI characteristics of hypointensity on T1-weighted sequences and hyperintensity on T-2 weighted sequences with variable gadolinium enhancement. Tumors tend to stay confined to the white matter of the brain with local expansion of the cortex. When MR spectroscopy is performed, the tumors will often demonstrate an elevated choline peak, low NAA peak and an elevated choline:creatine ratio, distinguishing themselves from HGGs (Herminghaus et al. 2003). JPAs tend to appear well-circumscribed and often have a visible cystic component. WHO II tumors are more likely to appear infiltrating and be less circumscribed. Biopsy is recommended, when feasible, to establish a diagnosis as an imaging differential diagnosis can also include: infection, infarction, HGG, and germ cell tumor. Upfront imaging of the spine (without spinal symptoms) is controversial, as CSF dissemination is thought to be a rare event. A retrospective study from St. Jude from 1990 to 2010, however, found a 6% metastasis rate from a cohort of 599 LGG patients (Chamdine et al. 2015). Follow up after radiation can be difficult, as pseudoprogression has been documented in over 50% of patients at a median of 6 months after RT (Lassen-Ramshad et al. 2015; Naftel et al. 2015). Pseudoprogression is defined as a temporary increase in size or development of an imaging finding, characteristic for tumor recurrence that resolves without therapy.

8.3.5 Management of Pediatric LGG

Pediatric LGG management can include surgery, chemotherapy, and radiation therapy. The sequencing of therapy is affected by physician bias, patient age, tumor location, WHO grade, severity and velocity of symptoms, risks associated with progression and number of recurrences. Surgery provides the best therapy to prevent recurrence with no prospective randomized data in the pediatric population on the use of radiation vs. chemotherapy vs. observation after subtotal surgical resection or unresectable disease.

8.3.6 Surgery

Surgery comprises the mainstay of treatment for pediatric LGG. Data from CCG-981/POG-9130 has demonstrated the importance of a gross total resection (GTR), when safe and feasible. From 1991 to 1996 pediatric LGG patients were prospectively evaluated to determine the value of aggressive surgical resection. Five-hundred and eighteen eligible patients were followed with 64% considered to have a GTR (no residual disease by surgical report and post-operative imaging). Results reveal little difference in patients with $<1.5\ cm^3$ or $>1.5\ cm^3$ of residual disease after surgery, and both groups performed significantly worse than those with a GTR in terms of progression free survival (PFS) and OS (Wisoff et al. 2011). Patients in the < GTR group experienced a 50% progression of disease at 8 years compared to 7% in patients with a GTR. On multivariate analysis, tumor location and histology appeared to impact OS greater than the degree of surgical resection, as tumor location is the greatest predictor of extent of resection. Given this knowledge of the importance of surgical resection, management of children with a subtotal resection has been researched and debated. If the risk of functional impairment is minimal and the surgeon determines that a GTR is achievable, than further surgery should be considered. For patients not candidates for additional surgery, they are considered for observation, chemotherapy or radiation. As mentioned earlier, the decision for post-surgical adjuvant

therapy depends on patient age, tumor location, WHO grade, severity and velocity of symptoms, risks associated with tumor progression and frequency of recurrences.

8.3.7 Chemotherapy

Chemotherapy can allow for a delay or avoidance of radiation therapy in patients requiring tumor control with limited surgical options. In infants and young children <8–10 years old, chemotherapy can theoretically decrease late effects from radiation, by allowing for growth and brain development before radiation is initiated. As was demonstrated in CCG-981/POG-9130, a prospective phase II study, the 5- and 8-year PFS rates for incompletely resected LGG patients was 53–63% and 41–58%, respectively, depending on site and histology (Wisoff et al. 2011). This is the best prospective information we have for PFS rates without the use of adjuvant therapy.

Patients who receive adjuvant chemotherapy and radiation are often more challenging patients with s younger age, multiple tumor recurrences, WHO II histology and tumors in deep midline, unresectable locations. It can be difficult to compare this patient population with that of the CCG/POG dataset. That being said, Table 8.3 demonstrates the reported PFS rates achievable with chemotherapy, with an average of 45–50% PFS seen at 5 years. The majority of the published regimens are carboplatin/vincristine based, which can be problematic as up to 50% of children have been reported to eventually develop a hypersensitivity reaction to repeated doses of carboplatin, although many patients can still be continued despite hypersensitivity (Lafay-Cousin et al. 2005, 2008; Yu et al. 2001; Gnekow et al. 2012) On HIT-LGG 1996, a prospective phase II trial with 105 participating

Table 8.3 Chemotherapy in LGG

Publication	Year published	Chemotherapy	# Patients	Progression-free survival			
				2 years	3 years	5 years	10 years
Prados (Prados et al. 1997)	1997	TPVC	42	50%			
Packer (Packer et al. 1997)	1997	CV	78		68%		
Massimino (Massimino et al. 2002, 2010)	2002/2010	CisVP	31/37		78%/65%		
Gnekow (GPOH) (Gnekow et al. 2004, 2012)	2004/2012	CV	198/216			47%	44%
Khan (Khaw et al. 2007)	2007	TMZ	13		57%		
Ater (COG) (Ater et al. 2012)	2008	CV	137			35%	
		TPCV	137			48%	
Scheinemann (Scheinemann et al. 2011)	2011	Various	118			37%	
Bouffet (Bouffet et al. 2012)	2012	Vinblastine	50			42%	
Dodgshun (Dodgshun et al. 2015)	2015	Carbo	104			51%	
Gururangan (Gururangan et al. 2007)		TMZ	30	49%			

CV carbo and vincristine, *TPCV* thioguanine, procarbazine, lomustine, and vincristine, *CisVP* cisplatin and etoposide, *TMZ* temozolomide

European centers and 1182 registered LGG patients, 216 patients with progression or incomplete resections received carboplatin and vincristine for a 5-year EFS of 47% with over one half of these patients experiencing a Grade III or IV hematological toxicity (Gnekow et al. 2004). Unfortunately, published data describing the long-term cognitive, hearing and behavioral effects after chemotherapy is lacking. Dodgshun et al. recently reported their experience in Australia with single agent Carboplatin and it appears to provide similar effectiveness compared to multi-agent regimens with less toxicity (Dodgshun et al. 2015). Bevacizumab, a VEG-F inhibitor, has been evaluated with some success in a small number of patients. A retrospective review of 14 patients demonstrated that 12 had a response to therapy, but 13/14 patients progressed at a median of 5 months off therapy (Hwang et al. 2013). Lenalidomide, a derivative of thalidomide, is currently being investigated in a phase II trial by the COG as ACNS1022 (NCT01553149).

Regarding chemotherapy's potential effect on future radiation, there is a small series of 17 children with optic pathway and hypothalamic gliomas reported by Janss et al. that suggests PFS rates may deteriorate in patients receiving chemotherapy prior to radiation, potentially through the development of radiation resistance (Janss et al. 1995). In contrast to that small dataset, HIT-LGG 1996, determined that chemotherapy used before radiation did not decrease PFS over radiation alone, but also did yield improved outcomes (Gnekow et al. 2004, 2012; Muller et al. 2013).

8.3.8 Radiation Therapy

No published data has demonstrated an overall survival benefit with the use of chemotherapy or radiation therapy versus observation in the pediatric population. Several retrospective reviews, as well as a large prospective multi-institutional trial, have demonstrated long-term improved outcomes with radiation therapy, resulting in PFS ranges of 62–82% at 10 years (Table 8.4). Although radiation has not been found to increase overall survival, one can speculate that an improvement in progression

Table 8.4 Radiation in LGG

Publication	Year	Radiotherapy	# Pts	NF1 included	5 years	10 years
Wallner (Wallner et al. 1988)	1942–1985	45–60 Gy	36			74%
Pollack (Pollack et al. 1995)	1956–1991	>50 Gy	50	Yes		82%
Erkal (Erkal et al. 1997)	1973–1994	40–60 Gy	33	Yes	82%	77%
Grabenbauer (Grabenbauer et al. 2000b)	1975–1997	45–60 Gy	25			69%
Marcus (Marcus et al. 2005)	1992–1998	45–58 Gy[a]	50	Yes	82%	65% (8 years)
Oh (Oh et al. 2011)	1987–2008	54–57 Gy	50	Yes		89% (7 years)
Merchant (Merchant et al. 2009b)	1997–2006	54 Gy	78	Yes	87%	74%
Gnekow (GPOH) (Gnekow et al. 2004, 2012; Muller et al. 2013)	1997–2009	39.6–61.2 Gy[b]	147	Yes	65%	62%
	(JPA only)		75		76%	76%
Paulino (Paulino et al. 2013)	1996–2012	45–60 Gy	39			78% (8 years)

[a]Stereotactic radiotherapy (≤2 Gy/day)
[b]Radiation EBRT median 54 Gy, Brachy with I-125

free survival can lead to an improved quality of life and neurocognitive function. Currently, radiation is reserved for inoperative symptomatic patients or patients after resection with evidence of recurrence, or progression after chemotherapy. Investigators at the University of Michigan and San Francisco have both reported that the outcomes for patients treated up front with radiation after an incomplete resection was the same as RT used for salvage upon progression (Oh et al. 2011; Mishra et al. 2006). For patients with unresectable disease, radiation is used based on the velocity and severity of symptoms. Although patients at any age may require the use of radiation based on symptom progression, the decision to initiate radiation is often based on patient age, as the long-term cognitive effects of radiation decrease significantly after 8–10 years of age (Merchant et al. 2009a).

8.3.9 Radiation Dose

The current standard of care is to deliver 50.4–54 Gy of radiation, when feasible, although this dose has not been rigorously established. Grabenbauer evaluated 77 patients treated with 45–61 Gy of radiation and determined that PFS was affected by dose, with an improvement seen in patients receiving ≥52 Gy (Grabenbauer et al. 2000a). In a separate study by Grabenbauer evaluating optic pathway and hypothalamic glioma patients, RT doses ranged from 44 to 60 Gy, based on age. Sixteen patients received doses of radiation >45 Gy with a 10-year PFS of 85% compared to 9 patients receiving 44–45 Gy with a PFS of 36% at 10 years (Grabenbauer et al. 2000b). On the German HIT-LGG 1996 trial, children older than 5 years received 50.4–54 Gy and younger children received 40–45.2 Gy. In their modeling, RT doses of more than 50.4 Gy did not appear to improve PFS rates (Muller et al. 2013).

8.3.10 Radiation Volume

HIT-LGG 1996 used a 1 cm "safety," margin for tumors treated with MRI planning and a 2 cm margin if CT planning (Muller et al. 2013). Merchant et al. from St. Jude utilized 1 cm clinical target volume (CTV) margin added to the gross tumor volume (GTV) with an additional 3–5 mm planning target volume (PTV) expansion with 1 marginal failure in 78 patients after 10 years follow up (Jones 1994). This occurred near the optic chiasm in the only optic nerve case in the series who received 50.4 Gy instead of 54 Gy, due to the location (Merchant et al. 2009b). COG ACNS0221 used the same margin expansion as Dr. Merchant in a multi-institutional prospective trial which closed in 2010 and their data too is still maturing. Paulino et al. at Texas Children's Hospital used intensity modulated radiotherapy (IMRT) with a 1 cm CTV margin for tumors in 16 children, a 5 mm margin in 6 children and 14 children received a dose painting combination of 45–54 Gy to the GTV with 40–45 Gy to a 1 cm expanded volume (Paulino et al. 2013). With a median follow-up of 81 months they reported an 18% progression rate at a median of 37 months and all failures were considered infield with no marginal misses. Dr. Marcus at Massachusetts General Hospital has published the smallest margins to date, utilizing stereotactic fractionated radiation in which GTV = CTV and only a 2 mm PTV margin was added (Marcus et al. 2005). PFS results of 65% at 8 years and no marginal recurrences would suggest that tighter margins may in fact be adequate in the setting of high quality MRI.

8.3.11 Prognostic Factors

It appears that factors negatively affecting PFS would include young age, optic pathway and hypothalamic location and surgical resection less than a gross total. Achieving less than a GTR and young age (<age 5, and more so age < 1) also appear to negatively affect overall survival. Tumor location, presence of NF-1 and WHO grade appear controversial in their prognostic significance (Table 8.5). In the University of Michigan experience, optic pathway and hypothalamic location negatively affected PFS but overall survival was favorable (Oh et al. 2011).

Table 8.5 (a) Prognostic factors and (b) prognostic factors after RT

	Year	# Pts	Significant		Not significant	
			Worse PFS	Worse OS	PFS	OS
(a) *Prognostic factors*						
Oh (Oh et al. 2011)	1984–2008	181	Age ≤ 5 OHG < GTR No RT < GTR	<GTR Younger Age Other than OHG	Grade Gender Seizure sx	Location
Dudley (Dudley et al. 2015)	2004–2010	348		Age < 1 Brainstem		Gender
Gnekow (Gnekow et al. 2012)	1996–2004	1031	< GTR Location Diencephalic	Age < 1 Age > 11 Disseminated < GTR	Age NF-1 Hist	
Pollack (Pollack et al. 1995)	1956–1991	71	< GTR No RT < GTR	< GTR Histology	RT < GTR	
(b) *Prognostic factors after RT*						
Gnekow (Gnekow et al. 2012)			Nonpilocytic WHO I Non-diffuse WHO II Age < 1 Disseminated @ dx < GTR		Gender NF-1 Location GTR	
Erkal (Erkal et al. 1997)			NF-1			NF-1
Merchant (Merchant et al. 2009b)					NF-1 Grade	

8.3.12 Special Cases: Optic Pathway and NF-1

NF-1 associated LGGs appear to respond to adjuvant treatment with similar effectiveness to non-NF-1 patients (Jenkin et al. 1993; Listernick et al. 1997). In the University of Michigan experience, 32/34 patients with NF-1 presented with optic pathway/hypothalamic gliomas and 71% had no initial therapy with a 7-year PFS of 73% and no deaths (Oh et al. 2011). In the series published by Merchant et al., 13 of their 78 patients were documented to have NF-1 and none of these patients progressed after radiotherapy, nor developed a secondary malignancy. RT for these children may result in a slight increased risk of cognitive decline and vascular complications (Merchant et al. 2009a).

8.3.13 Vision Preservation

In the publication by Erak et al., 33 children were assessed for visual function after the completion of radiation, 2 of 4 patients with one optic nerve involved had improved vision and 9 of 26 (34%) patients with chiasmatic involvement had improvement with 14 (54%) showing stable vision, and only 3 (12%) experiencing deterioration (Erkal et al. 1997).

8.3.14 Quality of Life (QoL) and Neurocognitive Outcomes in Pediatric LGG

Dr. Merchant from St. Jude Children's Hospital has been carefully evaluating cognitive, endocrine and hearing effects from kids receiving

radiation with LGG for the past 20 years. From 1997 to 2006, 78 patients were prospectively evaluated after receiving 54 Gy of conformal radiation with 5 year changes to IQ, memory, verbal & auditory learning, and behavior carefully evaluated. Factors negatively affecting cognitive function include patient age, presence of NF-1, tumor location and volume, extent of resection and radiation dose, with the greatest effect based on patient age. Children under the age of 5 at the time of radiation experienced the most significant cognitive effects, while children over the age of 12 experienced no noticeable decline (Merchant et al. 2009a) (Fig. 8.3).

Learning and memory were not significantly affected by radiation; however pre-treatment with chemotherapy was found to be associated with a more significant decline than kids treated with radiation alone (Di Pinto et al. 2012) (Fig. 8.4). The risk of endocrine dysfunction is related to tumor location by proxy of the mean dose to the hypothalamus. The most sensitive hormone is growth hormone, with a mean hypothalamus dose of only 5 Gy required to show long-term deficits, and a mean dose of 16 Gy resulting in a 50% rate of growth hormone deficiency (Merchant et al. 2009a, 2011). Hearing loss was documented to be significantly increased in patients who received over 45 Gy to the cochlea. The use of IMRT or proton therapy has been demonstrated to safely allow a dose reduction to these critical structures, thereby reducing the potential risk of late effects in certain cases (Paulino et al. 2013; Greenberger et al. 2014).

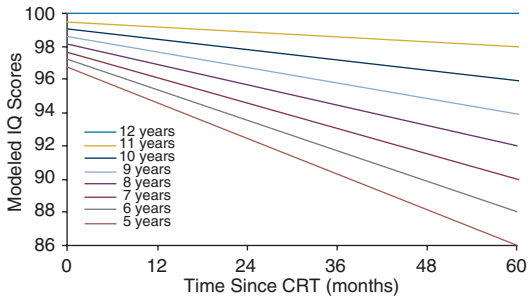

Fig. 8.3 Modeled IQ after radiation by age (Merchant et al. 2009a)

8.3.15 Summary and Future Directions

Pediatric LGG represents a diverse disease group, based on a variety of histologies and tumor locations, with 30–40 year overall survival rates of >70%. When surgically resectable, a GTR results in the best PFS and OS; however, tumors

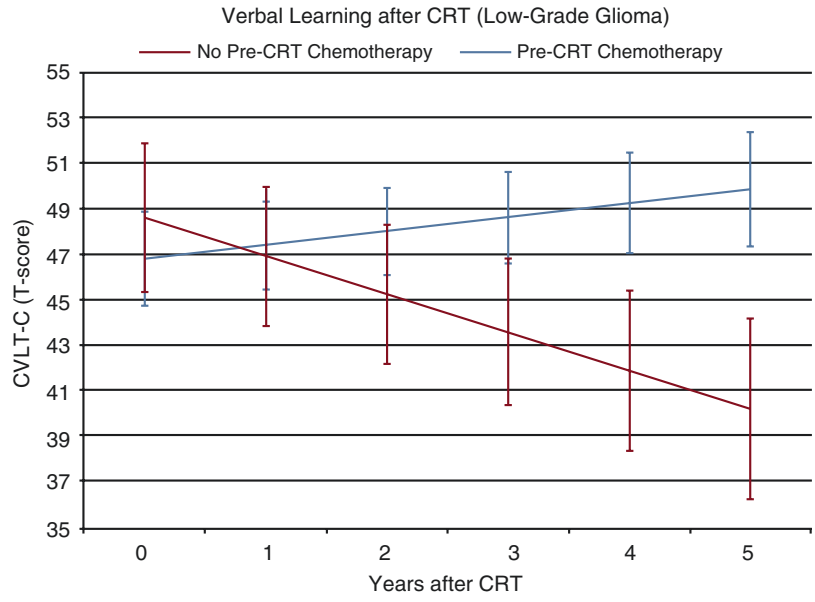

Fig. 8.4 Effect of chemotherapy prior to radiation (Di Pinto et al. 2012)

in unresectable locations can still do well and often demonstrate indolent behavior. Tumors that are subtotally resected tend to recur in greater than 50% of patients; however, adjuvant treatment is often delayed until evidence of tumor progression. Patients who require treatment due to recurrence, symptom progression or risk of significant symptom development are often stratified for treatment by their age. For patients under the age of 8–10 years, chemotherapy is often used to delay the use of radiation with a 5-year EFS rate of 30–50%. For patients over the age of 10–12 years, radiation is the preferred initial treatment with PFS rates of 60–80% at 10 years. IMRT and proton therapy may allow the safe delivery of radiation with a decrease in toxicity. Radiation can be delivered with a 5–10 mm CTV expansion without a significant risk of marginal failure, however, future radiation prescriptions may only include a 0–2 mm expansion based on emerging research. A radiation dose of 50.4–54 Gy appears to be the most common prescribed; however, a dose of 45 Gy may be sufficient based on the limited data currently available. As we learn more about the biology of LGG, a targeted approach, such as BRAF inhibition, may yield improved results over cytotoxic systemic agents.

8.4 Technical Advances

8.4.1 Radiosurgery

Radiosurgery has the benefit of using precise immobilization, high definition imaging, multiple intersecting beams to create an extremely conformal radiotherapy plan consisting of 1–5 high-dose treatments with rapid dose fall off, and sparing of adjacent normal tissues. It is a standard treatment approach for adults with brain metastases and intracranial benign brain lesions (Chang et al. 2009; Kondziolka et al. 1998; Murphy and Suh 2011). Indications for radiosurgery for pediatric LGG have included surgically inaccessible tumors and adjuvant treatment for incompletely excised or recurrent tumors. The available series of radiosurgery for pediatric LGGs comprise both Grade I and Grade II tumors and demonstrate local control in the range of 70.8–100%, with follow-up ranging from 19 to 144 months (Barcia et al. 1994; Boethius et al. 2002; Hadjipanayis et al. 2002; Kano et al. 2009; Kida et al. 2000; Somaza et al. 1996; Weintraub et al. 2012). Many of these patients also had prior radiotherapy. Radiosurgery was found to be safe and well tolerated with smaller tumors having improved local control (Kano et al. 2009; Weintraub et al. 2012). The main treatment related complication was transient symptomatic tumor edema, which was reported in several series of radiosurgery for pediatric LGG, (Boethius et al. 2002; Hadjipanayis et al. 2002; Kida et al. 2000; Weintraub et al. 2012) otherwise no additional toxicity was reported, including radiation necrosis.

Several series demonstrate utility of radiosurgery for adult recurrent HGG with median survival ranging from 5.3 to 18 months after radiosurgery (Sminia and Mayer 2012; Cabrera et al. 2012; Cuneo et al. 2012; Park et al. 2012). There is suggestion that the use of concurrent and or adjuvant bevacizumab can decrease adverse radiation events for these patients (Sminia and Mayer 2012; Cabrera et al. 2012; Cuneo et al. 2012; Park et al. 2012). This approach can be considered in children with small volume recurrence after an appropriate interval from initial radiotherapy.

8.4.2 Proton Therapy

Proton therapy has a dosimetric benefit of reduce normal tissue radiation exposure which can benefit pediatric glioma patients in particular with the goal of reduced impact on hearing, endocrine deficiencies and second malignancy. Data is available investigating the impact of proton radiotherapy for glioma patients, but long-term efficacy data is not yet available. Health related quality of life (HRQoL) has been reported for 142 pediatric patients with brain tumors treated with proton radiation at Massachusetts General Hospital from 2004 to 2010 (Kuhlthau et al. 2012). This report included 31 patients with ependymoma/malignant glioma and 20 patients with LGG. HRQoL was assessed

during and after proton radiotherapy up to 3 years. They found that disease type and intensity of treatment correlated with baseline HRQoL. The overall HRQoL score at the beginning of radiation treatment (67.0) was considerably lower for the entire cohort of patients with brain tumors treated with proton radiation than for the normative populations of children overall (82.3). However, overall HRQoL rose to 76.5 at the 3-year follow-up. Similarly, data from an adult prospective proton therapy trial for LGG with 5-year follow up showed no evidence for neurocognitive or quality of life decline in 20 patients, but potential for endocrine deficiencies was present (Shih et al. 2015).

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9 Medulloblastoma/Non-Medulloblastoma Embryonal Tumors

Stephanie M. Perkins, Efrat Landau, and Christine Hill-Kayser

9.1 Introduction

Medulloblastoma and non-medulloblastoma embryonal tumors (NMBET) are embryonal brain tumors and are the most common malignant brain tumors in the pediatric population. Notably, NMBET includes the diagnosis of atypical teratoid/rhabdoid tumor (AT/RT) which will be discussed in a separate chapter. Current therapy for medulloblastoma and NMBET most often includes a multi-modality approach including surgery, radiation and chemotherapy. With modern therapy, overall survival for medulloblastoma is approximately 80% while survival for NMBET is 30–50%. Factors associated with prognosis include the presence of disseminated disease, extent of surgical resection and patient age, with children <3 years categorized as high risk patients given the inability to deliver high dose radiation at this young age due to significant long term effects. Increasingly, there is great interest in further sub-grouping patients based on molecular profiling which is highly predictive of outcome. While four molecular subgroups have emerged for medulloblastoma, the sub-grouping of NMBET has proved more challenging with an increasing awareness that this is a heterogeneous group in which histological diagnosis is challenging. The current challenges for both medulloblastoma and NMBET include the determination of optimal therapy for children such as decreased therapy for favorable risk groups and intensification and targeted therapy for high risk groups. Additionally, data are now available for long-term survivors which detail the significant effects of therapy in this young population.

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9.2 Epidemiology

Annually, there are approximately 500 new cases diagnosed in the United States each year and approximately 70% occur in patients under the age of 18 years. The most recent publication of the Central Brain Tumor Registry of the United States (CBTRUS) estimated 320 new cases

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predicted for children age 0–14 years in 2015 (Ostrom et al. 2014). The median age at diagnosis is 6 years with the majority of cases in children ages 5–9 years. There is a male predominance with average annual age-adjusted incidence rate of 0.60 cases per 100,000 males age 0–14 years and 0.38 cases per 100,000 females age 0–14 years. For the years 2007–2011, the average annual age-adjusted incidence rate of medulloblastoma was higher for white children than black children (0.53 cases per 100,000 versus 0.30 cases per 100,000, respectively) (Ostrom et al. 2014).

The majority of medulloblastoma cases are not associated with an underlying genetic syndrome. However, known genetic predispositions do exist and are present in <5% of medulloblastoma cases. Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is the most common syndrome present in medulloblastoma patients. The phenotype for this autosomal dominant disease includes basal cell carcinomas, odontogenic tumors, rib anomalies and medulloblastoma, among others (Gorlin 1987). Up to 5% of patients with Gorlin syndrome are diagnosed with medulloblastoma (Cowan et al. 1997). The majority of patients with Gorlin syndrome have germline mutations in *PTCH1* chromosome 9 which is involved in the sonic hedgehog (SHH) signaling pathway (Taylor et al. 2000). However, germline mutations of *SUFU*, also a member of the SHH signaling pathway, are also associated with patients meeting criteria for Gorlin syndrome (Smith et al. 2014). Turcot syndrome is another familial syndrome associated with medulloblastoma secondary to mutations in the *adenomatous polyposis coli* (*APC*) gene. Other more rare genetic predisposition syndromes associated with medulloblastoma include Li-Fraumeni syndrome and Rubinstein-Taybi syndrome (Taylor et al. 2000). NMBET can be associated with germline mutations in the *Rb* tumor suppressor gene. This mutation can lead to the diagnosis of trilateral retinoblastoma featuring pineoblastoma (Blach et al. 1994).

NMBET are a rare diagnosis accounting for 2–3% of childhood brain tumors with an estimated 80 new cases predicted for children age 0–14 years in 2015 (Ostrom et al. 2014). Unlike medulloblastoma, the median age at diagnosis for NMBET is younger at 3.5 years and there is no difference in average annual age-adjusted incidence rates for males and females age 0–14 years (0.13 cases per 100,000 versus 0.11 cases per 100,000, respectively) or for white and black children (0.12 cases per 100,000 versus 0.10 cases per 100,000, respectively) (Ostrom et al. 2014).

9.3 Presentation and Radiographic Findings

Both medulloblastoma and NMBET patients often present with signs and symptoms related to intracranial pressure including headaches, lethargy and/or morning vomiting. Medulloblastoma patients often present with cerebellar symptoms including ataxia and impaired balance in addition to cranial nerve palsies (i.e., diplopia). NMBET patients usually present with nonspecific symptoms caused by mass effect, including headaches, vomiting, seizures and occasionally, hemiparesis.

Imaging studies of medulloblastoma most often demonstrate a midline cerebellar mass commonly involving the fourth ventricle. However, medulloblastoma arising in the more lateral cerebellar hemispheres do occur and appear to be most often associated with the sonic hedgehog (SHH) molecular subtype (Perreault et al. 2014). Magnetic resonance imaging (MRI) demonstrates contrast enhancement for the vast majority of cases (Fig. 9.1). MRI imaging of the spine is required for all cases and evidence of distant disease can manifest as contrast enhancing masses or contrast enhancing leptomeningeal disease in the brain and/or spine. On imaging NMBET appear rather large with a heterogeneous signal in unenhanced T1WI and T2WI MRs. Intratumoral hemorrhage and necrosis are quite frequent. Tumor borders tend to be sharp with minimal to absent edema. Contrast enhancement is usually variable and heterogeneous. Tumors show diffusion restriction (Nowak et al. 2015).

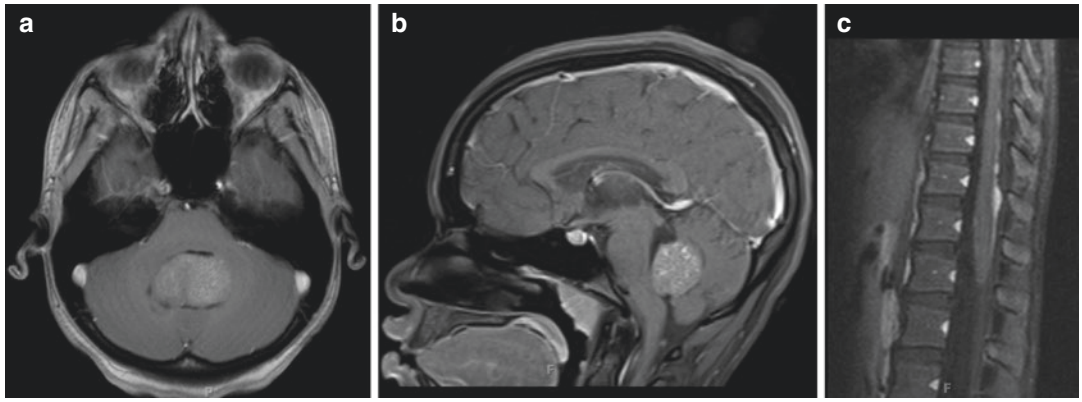

Fig. 9.1 T1 axial gadolinium-enhanced MRI (**a**) and T1 sagittal gadolinium-enhanced MRI (**b**) of a 13 year old girl with medulloblastoma. A T1 sagittal gadolinium-enhanced MRI of the spine (**c**) in a 7 year old with spinal disease from medulloblastoma

9.4 Histology/Molecular Profile

Medulloblastoma is characterized as a highly cellular with high mitotic index and presence of Homer-Wright rosettes in some cases. It is an embryonal tumor categorized as a World Health Organization (WHO) grade IV neoplasm. In the 2007 WHO classification, there were four recognized subtypes based on histology (Louis et al. 2007). These subtypes included desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity (MBEN), anaplastic medulloblastoma and large cell medulloblastoma. The WHO 2016 classification system now defines medulloblastoma either histologically or genetically (Louis et al. 2016). Histologically defined medulloblastomas include classic, desmoplastic/nodular, extensive nodularity or large cell/anaplastic. The majority of medulloblastoma cases are categorized as classic histology with desmoplastic/nodular medulloblastoma as the next most common sub-type comprising approximately 15–20% of new diagnoses (Kool et al. 2012). Medulloblastomas meeting criteria for desmoplastic/nodular or MBEN sub-types are known to have a favorable prognosis whereas anaplastic and large cell subtypes demonstrate worse overall survival (Eberhart et al. 2002; Giangaspero et al. 1999; Massimino et al. 2013). Additionally, the subtypes are not evenly represented across the age spectrum with desmoplastic tumors commonly represented in infants and adults but rare in children.

Although the morphology of medulloblastoma can be predictive of outcome, in the last 5–10 years, work from several groups began to identify molecular subgroups of medulloblastoma that were highly predictive of outcome. These data also demonstrated that once patients were categorized by molecular subgroup, the histologic features of the tumor were less predictive of survival. In 2010, a consensus was reached regarding the four recognized medulloblastoma molecular subgroups: WNT, SHH, Group 3 and Group 4 (Taylor et al. 2012) (Fig. 9.2). Genetically defined medulloblastoma is now recognized within the WHO 2016 classification with these 4 sub-categories: WNT-activated, SHH activated and TP53-mutant, SHH activated and TP53-wildtype, non-WNT/non-SHH which includes group 3 and group 4 patients.

WNT tumors are the least common subgroup occurring in approximately 10% of cases. WNT subgroup patients demonstrate classic histology and have an excellent prognosis with greater than 90% cause-specific survival (Kool et al. 2012; Ellison et al. 2011). This subgroup is present in adults and children but rarely in infants. Approximately 30% of medulloblastoma cases are categorized as SHH tumors. SHH tumors occur in infants and adults and are associated with desmoplastic histology. However, in

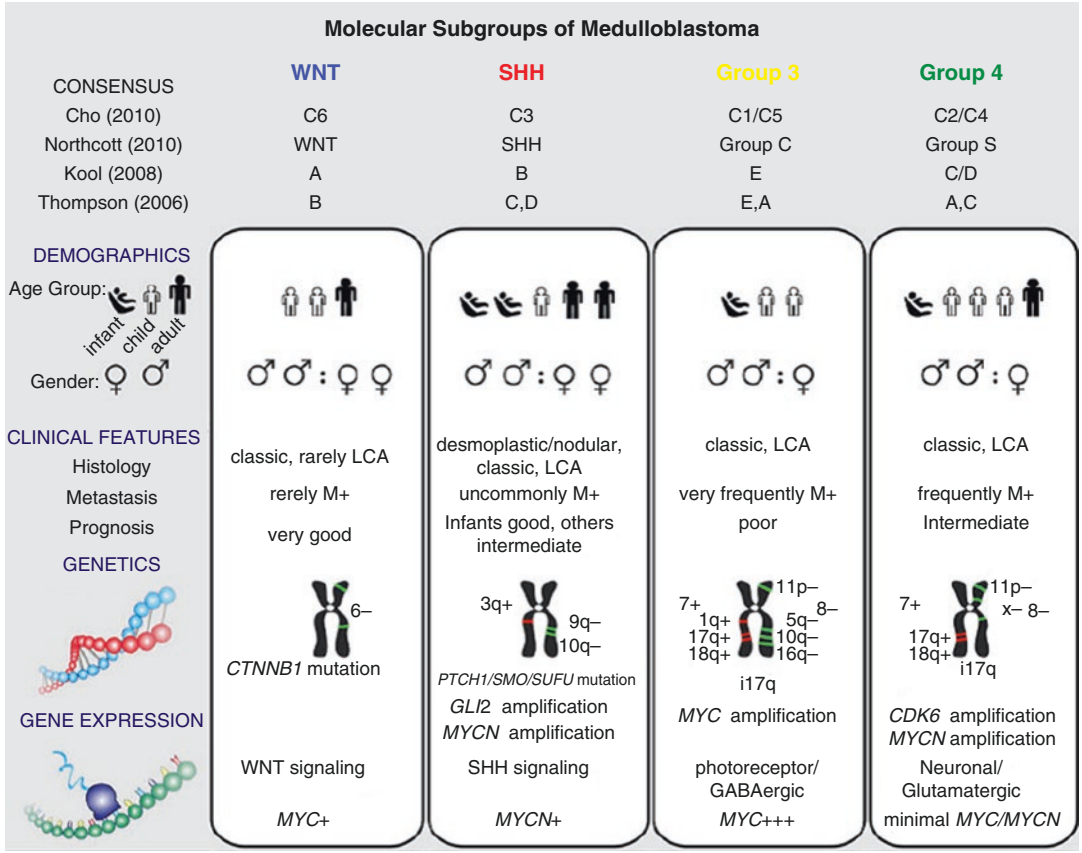

Fig. 9.2 Representation of the four molecular medulloblastoma groups. Source: Taylor, M. D., Northcott, P. A., Korshunov, A., *et al.* 2012. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol,* 123, 465–72

children desmoplastic histology is less likely to be associated with the SHH subgroup. Both WNT and SHH are equally represented between male and female patients, while there is near 2:1 male to female ration in the remaining two subgroups.

Group 3 subtype is seen with equal frequency as SHH but these patients experience the worst overall survival. Histologically, these tumors most often are classical medulloblastomas or possess large cell/anaplastic features. *MYC* amplication is common in this subgroup and is rarely seen in the other subgroups. Group 3 subtype is rarely if ever seen in adults and often present with metastatic disease. While the outcome for Group 3 is poor, patients without *MYC* amplification in this group fare better leading to the possible need to further subtype patients in the group (Cho et al. 2011). Group 4 is the most common subtype and appears to have intermediate prognosis. Isochrome 17q is frequently present in this subtype although not exclusively.

While medulloblastoma is the most common CNS embryonal tumor, there are several other tumor types in this category. This includes atypical teratoid/rhabdoid tumors (AT/RT) which will be discussed in a separate chapter. Historically, other CNS embryonal tumors were categorized as CNS primitive neuroectodermal tumors (PNET). However, central pathological review of PNET patients on recent Children's Oncology Group (COG) studies have highlighted the challenge of categorizing these tumors with a large portion of the patients ultimately diagnosed with high grade gliomas (Jakacki et al. 2015; Albright et al. 1995). In recent years, our understanding of

a

Embryonal tumours	
Medulloblastoma	9470/3
Desmoplastic/nodular medulloblastoma	9471/3
Medulloblastoma with extensive nodularity	*9471/3**
Anaplastic medulloblastoma	*9474/3**
Large cell medulloblastoma	9474/3
CNS primitive neuroectodermal tumour	9473/3
CNS Neuroblastoma	9500/3
CNS Ganglioneuroblastoma	9490/3
Medulloepithelioma	9501/3
Ependymoblastoma	9392/3
Atypical teratoid / rhabdoid tumour	9508/3

b

Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3*
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*

Fig. 9.3 Sagittal view (**a**) of matched cranial and spinal Fields, custom blocking of brain field (**b**) and custom blocking of PA spine field (**c**)

PNET has increased due to international collaboration and the application of advanced genomic techniques. Three distinct molecular subtypes, initially termed groups 1, 2 and 3 have been discovered. Group 1 tumors show frequent C19MC (chromosome 19q13.42 microRNA cluster) amplification and high LIN28 protein expression. This group, also called embryonal tumor with multilayered rosettes (ETMR), is a unifying group for medulloepithelioma, ependymoblastoma and embryonal tumor with abundant neutrophil and true rosettes (ETANTR). These tumors arise in younger children, more often females, and are associated with poor prognosis. Group 2 tumors have high OLIG2 expression, arise in older children and are frequently localized. Group 3 tumors, have limited expression of LIN28 or OLIG2 protein are associated with a high incidence of metastasis and arise across ages (Picard et al. 2012).

In the current WHO 2016 classification, the entity of PNET has been removed entirely (Fig. 9.3). In this chapter we have elected to refer to these tumors as non-medulloblastoma embryonal tumors (NMBET), excluding AT/RT (although these tumors technically reside in the embryonal tumor group). NMBET in the WHO 2016 classification include embryonal tumors with multilayered rosettes (ETMR) C19MC-altered, ETMR not-otherwise specified (NOS), medulloepithelioma, CNS neuroblastoma, CNS ganlgioneuroblastoma, and CNS embryonal tumor NOS. Tumors with C19MC amplification are now classified as ETMR, C19MC-altered although previously these tumors often were known as embryonal tumors with abundant neuropil and true rosettes (ETANTR), ETMR, ependymoblastoma or medulloepithelioma. C19MC amplification can be identified by FISH. Additionally, LIN28A expression, which is often present in ETMR tumors, can be detected by immunohistochemistry and can be a useful screening test. This can alert to the need for C19MC testing as LIN28A expression is not specific to ETMR tumors. The diagnosis of the other CNS embryonal tumors occurs after the

exclusion of more specific entities such as AT/RT and ETMR (Pickles et al. 2017). It is likely that in the future further molecular markers will help define tumors that currently will be called CNS embryonal tumor, NOS.

9.5 Staging and Work-Up

At presentation, MRI of the brain and spine with and without gadolinium contrast is indicated. Neuro-axis imaging is required for both medulloblastoma and NMBET due to the risk of spinal dissemination which is present in 25–30% of patients. Spinal imaging can be performed pre-operatively, but if done in the post-operative setting it must be delayed 10–14 days due to the risk of false positive results secondary to post-surgical blood products. Lumbar puncture is required for all patients in order to evaluate the cerebrospinal fluid (CSF) cytology. As most patients present with increased intracranial pressure, this procedure is typically performed post-operatively and also must be delayed 10–14 days after surgery. Following surgical resection, a post-operative MRI of the brain with and without gadolinium contrast should be performed within 48 h to determine extent of resection. Metastatic disease to the bone or bone marrow is exceedingly rare. Bone scan and bone marrow biopsy are only indicated if patients have symptomatic bone pain or abnormal blood counts.

The staging system for medulloblastoma includes T and M stages as devised by Chang in 1969 (Chang et al. 1969) (Table 9.1). Although T stage as defined by Chang is not used to stratify treatment for patients, M stage remains an important prognostic factor which changes clinical management. More often, patients are managed based on their risk group (average versus high risk). Average risk patients are defined as those patients ≥3 years of age, no evidence of metastatic disease and <1.5 cm^2 residual disease after surgical resection. Children under the age of 3 years are categorized as high risk and managed uniquely given the severe side effects of high dose craniospinal radiation in these young children.

Table 9.1 Chang staging system for medulloblastoma

Tumor stage	
T1	≤3 cm
T2	>3 cm
T3a	>3 cm with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka
T3b	>3 cm with invasion of the brainstem
T4	>3 cm with extension to third ventricle, midbrain or upper cervical cord
M stage	
M0	No evidence of metastatic disease
M1	Microscopic tumor cells found in the cerebrospinal fluid
M2	Gross nodular seeding in the cerebellar, cerebral subarachnoid space or in the third or lateral ventricles
M3	Gross nodular seeding in the spinal subarachnoid space
M4	Extraneuroaxial metastases

Chang, C. H., Housepian, E. M. & Herbert, C., JR. 1969. An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. *Radiology,* 93, 1351–9

9.6 Surgery

For both medulloblastoma and NMBET, maximal safe resection is recommended for all patients. The extent of surgical resection, especially in patients with non-metastatic disease, is predictive of outcome (Albright et al. 1996; Lannering et al. 2012). Post-operative MRI within 48–72 h after surgery is the standard in assessing extent of resection. For children presenting with hydrocephalus, resection of the primary tumor often obviates the need for a ventriculoperitoneal shunt. At many institutions, surgeons will place an external ventricular drain (EVD) at that time of surgery which can then be removed if reestablishment of CSF flow is demonstrated after resection of the tumor. In general, the literature indicates that approximately 30% of medulloblastoma patients undergo a CSF diversion surgery (Lin and Riva-Cambrin 2015).

Post-operative complications following surgery resection can include pseudomeningocele, meningitis and persistent hydrocephalus. Posterior fossa syndrome, also known as cerebellar mutism, is a significant post-operative

finding in 10–30% of medulloblastoma patients and is correlated with brainstem invasion by the tumor (Avula et al. 2015; De Smet et al. 2007; Robertson et al. 2006). Posterior fossa syndrome is characterized by mutism, truncal ataxia, emotional lability and cranial nerve palsies. Symptoms typically appear within days of surgery and improve in the weeks following surgery. However, for some patients the deficits can persist permanently.

9.7 Chemotherapy

9.7.1 Average Risk Disease

One of the initial clinical trials of chemotherapy allowed for medulloblastoma randomized patients to receive radiation therapy (35–40 Gy craniospinal irradiation (CSI) and 50–55 Gy to the posterior fossa) with or without adjuvant chemotherapy. Adjuvant chemotherapy consisted of 1- (2-chloroethyl)-3-cyclohexyl-nitrosourea (CCNU), vincristine, and prednisone (Evans et al. 1990). Although overall survival (OS) was the same between both arms, there was evidence of improved event-free survival (EFS) in patients with metastatic disease and large primary tumors. After a study in North America in which reduced dose CSI was delivered with no concurrent or adjuvant chemotherapy resulted in a decrease in EFS (Thomas et al. 2000), a small pilot study was performed through the Children's Cancer Group (CCG) evaluating the use of chemotherapy with reduced dose CSI (Packer et al. 1999). This study enrolled 65 patients with non-disseminated medulloblastoma who then receive 23.4 Gy CSI and 55.8 Gy to the posterior fossa. Vincristine was administered during radiation and following radiation patients received lomustine, vincristine and cisplatin chemotherapy. Progression-free survival (PFS) at 5 years was 79% ± 7% and this compared favorably with full-dose CSI alone.

A large phase III randomized controlled trial of 421 patients compared two different chemotherapy regimens in the setting of reduced dose CSI (23.4 Gy). All patients received concurrent vincristine with radiation therapy and were then randomized to either (1) CCNU, cisplatin, vincristine or (2) cisplatin, vincristine, cyclophosphamide (Packer et al. 2006). Five-year EFS and OS were 81% and 86%, respectively, with no difference between the chemotherapy arms. However, the results of this study were encouraging that non-disseminated medulloblastoma could be treated with reduced dose CSI and chemotherapy. This approach remains the current standard for the management of standard risk medulloblastoma in North America. The recently completed COG study ACNS0331 utilized alternating regimens cisplatin/CCNU/vincristine and cyclophosphamide/vincristine/MESNA for all patients.

9.7.2 High Risk Disease

For patients with high risk disease, the optimal chemotherapy regimen is still unknown as these patients continue to have significantly inferior survival to that of standard risk patients. A study by the German Society of Pediatric Hematology and Oncology (GPOH) compared a regimen of post-operative/pre-radiotherapy chemotherapy consisting of ifosfamide, cisplatin, methotrexate, etoposide and cytarabine to concurrent vincristine/radiotherapy after surgery followed by adjuvant CCNU, cisplatin and vincristine (Kortmann et al. 2000). Relapse-free survival of patients with M2/3 disease was 30% at 3 years with no difference between the two chemotherapy arms. High risk patients treated on St. Jude Medulloblastoma-96 (SJMB96) received 36–39.6 Gy CSI followed by tumor bed boost to 55.8 Gy followed by four cycles of high-dose chemotherapy (cisplatin, vincristine, cyclophosphamide, mesna) each followed by stem-cell rescue (Gajjar et al. 2006). Five-year EFS and OS were both 70% for high risk patients.

The COG high risk medulloblastoma/sPNET study ACNS0332 aimed to evaluate four chemotherapy treatment arms. All patients received 36–39.6 Gy CSI followed by posterior fossa boost to 55.8 Gy. The chemotherapy regimens all involved concurrent vincristine during radiation followed by maintenance chemotherapy consisting

of cisplatin, vincristine and cyclophosphamide. Arm A received no additional therapy than this, while arm B administered concurrent carboplatin with radiotherapy, arm C administered isotertinoin with maintenance chemotherapy and arm D administered both concurrent carboplatin with radiation and isotertinoin with maintenance chemotherapy. A futility analysis during this study demonstrated very low likelihood of benefit from the administration of isotertinoin and the two study arms containing this drug were closed.

9.7.3 Infants and Young Children

The treatment of children less than 3 years of age remains very challenging due to the significant effects of craniospinal radiation for these young children. Overall survival for infant medulloblastoma is worse than that of children and thus infant medulloblastoma is categorized as high risk disease. The approach for infant medulloblastoma has involved upfront surgery followed by chemotherapy leading to either delayed radiation or omission of radiation. In 1997, Duffner et al. reported outcome of children less than 3 years with malignant brain tumors treated with surgery and two 28-day cycles of cyclophosphamide/vincristine followed by one 28-day cycle of cisplatin/etoposide. The children received chemotherapy until age 3 or 4 or until progression, at which time they received CSI and posterior fossa boost. OS at 2 years was 46 ± 7% for the children with medulloblastoma (Duffner et al. 1993). The German HIT-SKK'92 study enrolled 43 children under the age of 3 years with medulloblastoma treated with maximal surgical resection followed by chemotherapy consisting of cyclophosphamide, vincristine and intraventricular and intravenous methotrexate (Rutkowski et al. 2005). Children in complete remission after chemotherapy received no further therapy. Twelve children (28%) had macroscopic metastatic disease at diagnosis (M2/M3). Five-year PFS and OS were 58 ± 9% and 66 ± 7%, respectively. Five-year OS for those children with complete resection and those with M2/M3 disease was 93 ± 6% and 38 ± 15%, respectively. For patients with M0/M1 disease, 21/31 patients remained in remission without the use of radiotherapy. Notably, moderate to severe leukoencephalopathy was noted in 15/23 children evaluated and was significantly correlated to the cumulative dose of intraventricular methotrexate. Additionally, compared to healthy control patients, neurocognitive outcome was significantly worse in the children receiving intraventricular methotrexate.

Another approach to young children with medulloblastoma evaluated the use of postoperative induction chemotherapy (cyclophosphamide/etoposide/cisplatin/vincristine) followed by myeloablative consolidation chemotherapy (thiotepa/etoposide/carboplatin) with autologous bone marrow rescue. The Head Start regimens have utilized this approach and reported 2-year OS of 62% for medulloblastoma patients (Mason et al. 1998). For infants with non-disseminated medulloblastoma treated on Head Start I and II, 5-year OS was 70 ± 10%. Radiation was utilized for 48% of the patients treated and notably, 4/21 patients died secondary to chemotherapy toxicity (Dhall et al. 2008). Throughout the studies on infant medulloblastoma, children with desmoplastic histology have experienced significantly better OS. Therefore, the COG is evaluating surgery and chemotherapy alone for children ≤4 years old with M0 nodular desmoplastic/MBEN medulloblastoma. This protocol is following the HIT SKK 2000 protocol without the administration of intraventricular methotrexate.

9.7.4 Non-Medulloblastoma Embryonal Tumors (NMBET) (Excluding Atypical Teratoid/Rhabdoid Tumors)

Recent revision of the WHO Brain Tumor Classification has removed the classification of supratentorial PNET; however, review of chemotherapeutic approaches historically applied to this previously-described entity are useful in discussion of modern treatment paradigms. To this end, descriptions of available published data evaluating treatment for sPNET are presented in Table 9.2. The rarity of these tumors and hetero-

Table 9.2 Clinical trials evaluating treatment for sPNET

Accrual time	Prospective trials	Age of patients (median)	No. of PBL patients	No of patients	No of M+	No of GTR	Treatment	HDCHT	EFS and OS		RT	Volume of RT	Dose of CSI	Positive prognostic factors
2001–2005	HIT 2000	Age < 4 (2.08)	8	17	6	5	S → CHT → ±RT	M+ only	24% 40%	Friedrich et al. (2013)	If Mo all, if M+ only if no CR post HDCHT	CSI + boost	24 Gy	
1998–2004	COG 99701	Age 3–21 (11.3)	23	60	12	25	s → RT + carbo + vinc → CHT	No	48% 58%	Jakacki et al. (2015)	All	CSI + boost	36 Gy with concurrent CHT	GTR (Mo patients), PBL
	Head Start I and II	Age < 10 (3.1)	13)	43	8	21	s → CHT → HDCHT ± RT	ALL	39% 49%	Fangusaro et al. (2008)	Age > 6 or non-surgical at end of induction	CSI + boost	23.4 Gy	
1993	CCG 9921	Age < 3	10	46	9		s → CHT → CHT ± RT	No	17% 31%	Geyer et al. (2005)	m+ at diagnosis or residual	Mo and younger than 18 months-focal RT, if older or m+ at diagnosis CSI + boost	18–30.6 Gy	None
1986–1990	POG I	Age < 3	?	36	Around 12	8	s → CHT → RT	No	2 year 19% 21%	Duffner et al. (1993)	All patients post CHT	CSI + boost	If Mo and no residual: 24 Gy. If one of the above: 35.2 Gy. Infants 90% dose	
1990–1997	SFOP	Age < 5 (2.2)	5	25	4	9	s → CHT	No	5 year OS 14%	Marec-Berared et al. (2002)	No			GTR, hemispheric location

(continued)

Table 9.2 (continued)

Accrual time	Prospective trials	Age of patients (median)	No. of PBL patients	No of patients	No of M+	No of GTR	Treatment	HDCHT	EFS and OS		RT	Volume of RT	Dose of CSI	Positive prognostic factors
1992-	POG 9233	Age < 3 years		38	9	10	S → CHT → ±RT	No	2 year OS for all: 46.7% 10 year OS for all: 29.3%	Strother et al. (2013)	Patients with m+ at diagnosis or who had residual non PD at completion of CHT	CSI + boost	If Mo: 27 Gy at age <18 months or 30 Gy if 18–30 months or 34.5 Gy if >30 months if M+ 3–4 Gy higher for each age group	GTR
1996–2003		(7.9) age 3–21	7	16	5	6	s → CHT for HR → RT all → HDCHT all	Yes all	68% 73%	Chintagumpala et al. (2009)	All	CSI + boost	If AR 23.4 if HR 36–39.6 Gy	None specified
1990-	PNET-3	Age 3–16	14	68	11	31	s → ±CHT → RT		48.3% 47%	Pizer et al. (2006)	All	CSI + boost	35 Gy	PBL

geneity of the group, the qualities that prompted removal of the term PNET from the WHO classification, also precluded the ability to undertake large studies specific to sPNET when it existed as an entity. These factors render optimal therapeutic recommendation for non-medulloblastoma embryonal tumors (NMBET) very difficult to describe. Notably, atypical teratoid/rhabdoid tumors are included in the category of NMBET; however, the discussion of AT/RT management will be presented in a separate chapter. Until recently, most patients were treated with high-risk medulloblastoma therapy, even after complete resection with no metastatic disease. However, data showing good outcomes treating with average risk therapy also exist (Chintagumpala et al. 2009). As for the younger group of patients, it is evident that NMBET respond to chemotherapy and some patients have been cured with chemotherapy and surgery alone; however, the general outcome for patients NMBET is worse than that for medulloblastoma patients. Five-year OS and EFS are around 30–50% and 40–60%, respectively (Jakacki et al. 2015; Fangusaro et al. 2008). OS is less for younger patients (Duffner et al. 1993; Geyer et al. 2005). It is difficult to say if the poorer results for the younger patients reflect diminished use of radiation or a different biology. In the majority of trials in patients with localized disease, gross total resection of the tumor was a positive prognostic factor. In some trials, pineoblastoma patients did better but this is not a universal finding. This patient group remains a very heterogenous group, and new classifications will hopefully drive future research into systemic treatment options that are driven by biological subclassifications of NMBET.

9.8 Radiotherapy

9.8.1 Volume

Craniospinal radiation (CSI) remains the standard treatment volume for children with medulloblastoma. This technique is designed to encompass the entire central nervous system including the brain and thecal sac. Attention of coverage of the entire craniospinal axis is important given the risk of relapse in the setting of coverage deviations (Carrie et al. 1999). Coverage of the cribiform plate should be evaluated as attempts to spare the lens can lead to underdose of this area which may have deleterious effects on local control (Miralbell et al. 1997). Following CSI, a boost to the posterior fossa or tumor bed is indicated for all patients. The contents of the posterior fossa are anatomically defined by the tentorium superiorly and the C1 vertebral canal inferiorly. The volume is defined by the boney confines of the occiput laterally and extends anteriorly the anterior surface of the brainstem. Registration of MRI imaging is highly suggested to aid in accurate contouring of the posterior fossa volume. Whether the boost coverage should include the entire posterior fossa or a more conformal boost of the tumor bed is controversial. For patients with standard risk disease, the treatment of a reduced volume in the posterior fossa to encompass the tumor bed plus a 1.5 cm margin is being prospectively analyzed in a randomized fashion on the COG protocol ACNS0331. In a study of 86 patients from St. Jude Children's Research Hospital, standard risk patients were treated with 23.5 Gy of CSI, 36 Gy to the entire posterior fossa and 55.8 Gy to the tumor bed +2 cm margin. The cumulative incidence of posterior fossa failure was 4.9 ± 2.4% (Merchant et al. 2008). Sethi et al. reported no failures in the posterior fossa outside of the tumor bed in 70 patients treated with conformal boost using proton therapy (Sethi et al. 2014). The planning target volume (PTV) is designed to account for daily treatment set-up inaccuracies. A margin of 3–5 mm around the clinical target volume (CTV) is recommended.

Treatment paradigms may evolve rapidly for patients with non-AT/RT NMBET; for the time being, CSI remains standard for this group of patients, with a volume the same as that described for treatment of medulloblastoma. Boost to the primary site is indicated for all patients. Recommended volumes for the boost treatment include an expansion of the tumor bed by 1 cm to form the CTV followed by further expansion by 3–5 mm to form the PTV.

9.8.2 Dose

In conjunction with chemotherapy, dose to the craniospinal axis of 23.4 Gy in 180 cGy per fraction remains the standard of care for patients with non-disseminated medulloblastoma. In the absence of chemotherapy, CSI to 23.4 Gy is inadequate. A randomized study of 126 standard risk medulloblastoma patients compared 23.4 Gy CSI to 36 Gy with all patients received a boost to the posterior fossa for a total dose of 54 Gy. The study was closed after planned interim analysis showed inferior 5-year EFS in the reduced dose CSI arm (67% versus 52%, p = 0.08) (Thomas et al. 2000). With the use of concurrent and adjuvant chemotherapy, CSI of 23.4 Gy followed by boost is associated with excellent EFS (Packer et al. 2006). However, there is interest in further reducing the dose of CSI for patients.

The recently completed COG study ACNS0331 randomized patients ages 3–7 years to 23.4 Gy CSI or 18 Gy CSI. No results are yet available. The current data for the use of 18 Gy is very limited and utilization of this lower dose is not recommended outside of a clinical trial (Jakacki et al. 2004). For patients with high risk disease, CSI doses of 36 Gy are recommended, and this is also the recommendation for patients with NMBET. Diffuse macroscopic spinal disease can be treated with a spinal dose of 39.6 Gy and focal sites of metastatic disease can be treated to a dose of 45 Gy (above the terminus of the spinal cord) or 50.4 Gy (below the terminus of the spinal cord). Focal sites of supratentorial metastatic disease can be treated with boost radiation to a total dose of 54–55.8 Gy, if feasible. Whole posterior fossa boost is indicated for patients with M2 disease involving the cerebellum. The posterior fossa boost in high risk disease is typically 55.8 Gy, with some groups utilizing 54 Gy. The use of hyperfractionated radiation therapy (HFRT) has been evaluated in a randomized study of 340 children in Europe (Lannering et al. 2012). HFRT consisted of 36 Gy CSI in 1.0 Gy fractions delivered twice daily. There was no difference in OS or EFS with the use of HFRT and standard daily fractions of 180-cGy remain the standard of care.

9.8.3 Technique

CSI requires a unique beam arrangement of matched fields in order to treat the entire craniospinal axis. Simulation for CSI requires straight alignment of the spine with arms at the side of the patient. For photon therapy, extending the head (i.e., raising the chin) and keeping the shoulders low aids in the placement of a lower brain/spine field junction which can decrease exit of the posterior spine field through the mouth. Patient positioning can be either prone or supine depending on institutional preference. Immobilization with a customized mask is utilized in both the prone and supine position.

Radiation to the brain is delivered with opposed lateral X-ray beams. The junction of the brain and spine fields must be above the shoulders to avoid entrance of the lateral brain field through the arms. The lateral brain fields require a collimator rotation that matches the divergence of the posterior spine field. The superior, posterior and anterior edge of the collimator flashes off of the skull and a customized block is drawn to block the face while providing adequate coverage of the temporal lobes and cribiform plate (Fig. 9.4). A couch kick is also commonly utilized with the lateral brain fields to align the divergence of the brain fields with the upper border of the PA spine field. Alternatively, the brain can be treated with a half-beam block technique which obviates the need for the couch kick.

The upper border of the PA spine field is matched to the lower border of the brain field. The inferior border of the spine field should provide a 2 cm margin on the inferior border of the thecal sac and thus is usually placed at the level of the S2–S3 interspace or lower. The lateral border of the spine field should encompass the vertebral body with a 1 cm margin on each side (Fig. 9.4). For older children, the length of the spine field may not be completely encompassed in a single field. An extended SSD technique can be used to increase the spine field, but some patients will require two spine fields. The match of the upper and lower spine field is recommended to occur below the termination of the spinal cord. In cases with significant curvature of the spine, field-in-field techniques utilizing

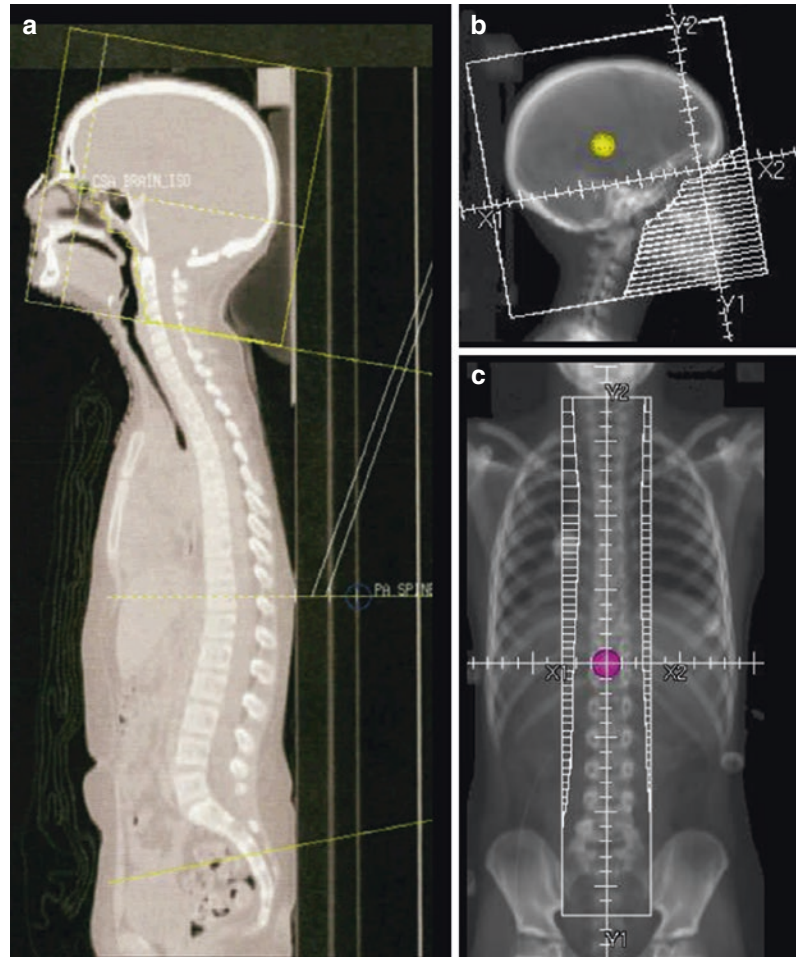

Fig. 9.4 Sagittal view (**a**) of matched cranial and spinal Fields, custom blocking of brain field (**b**) and custom blocking of PA spine field (**c**)

multi-leaf collimators (MLCs) can be employed to decrease heterogeneity in the spine dose.

There is some uncertainty in the daily set-up of the craniospinal junctions. To further decrease the risk of any significant dose overlap or gap at the site of the junction, the junctions are shifted 0.5–1 cm every 5 fractions.

Alternative techniques for the delivery of CSI include electron therapy, intensity modulated radiation therapy (IMRT) and proton therapy. Electron therapy is a viable technique but is rarely utilized. Delivery of CSI with IMRT delivers conformal high doses to the spine and brain, but low dose radiation is delivered to a large volume due to the multiple beam angles (Fig. 9.5) (Brodin et al. 2011). Proton therapy is able to deliver significantly less radiation to the parotid, thyroid, heart, lungs and bowel due to the sharp distal edge of the beam with no exit dose. This is most pronounced in the delivery of the PA spine field (Fig. 9.5). This decrease in exit dose may lead to a decrease in long-term risk of heart disease, lung toxicity and secondary malignancy, especially in neck, thorax and abdomen, although data on long-term follow-up of proton therapy patients are limited (Chung et al. 2013).

The posterior-fossa or conformal tumor bed boost is commonly treated with IMRT. Historically, the posterior fossa bed boost was delivered with an opposed lateral technique which treated a large volume of the temporal lobes and did not allow for cochlear sparing. With the use of IMRT, plan optimization can lead to significant decreases in the dose to the cochlea, temporal lobes and bilaterally hippocampus. The use of intensity modulated arc therapy can also deliver conformal treatments to the posterior fossa (Beltran et al. 2012). Further sparing of

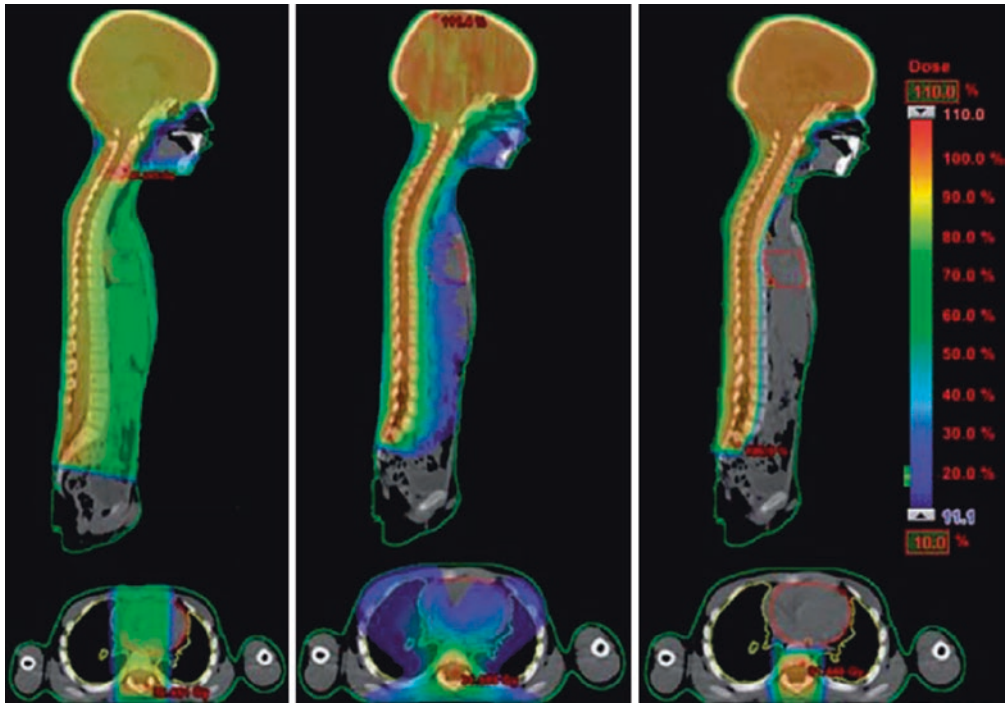

Fig. 9.5 Comparison of craniospinal dose delivered with (from left to right) 3D-conformal photon therapy, intensity modulated radiation therapy or proton therapy. Adapted from Brodin, N. P., Munck AF Rosenschold, P., Aznar, M. C., Kiil-Berthelsen, A., Vogelius, I. R., Nilsson, P., Lannering, B. & Bjork-Eriksson, T. 2011. Radiobiological risk estimates of adverse events and secondary cancer for proton and photon radiation therapy of pediatric medulloblastoma. *Acta Oncol,* 50, 806–16

critical structures near the posterior fossa can be achieved with the use of proton therapy (Fig. 9.6) (Macdonald et al. 2008). The lack of exit dose with proton therapy aids in decreasing dose to the pituitary, cochlea and temporal lobes. Plan comparisons with intensity modulated proton therapy (IMPT) show further reduction in some critical structures and increased conformality, especially for irregularly shaped targets.

9.9 Follow-Up

Survivors of medulloblastoma and NMBET are at risk for myriad late effects and are generally best followed in a dedicated survivorship clinic when possible. The multidisciplinary nature of necessary treatment, including craniospinal irradiation, puts several organ systems at risk for late effects. Many of these are modifiable with appropriate screening and intervention, making this a population for whom survivorship resources are well-directed.

As is true for any survivor of a childhood brain tumor, survivors are at risk for cognitive deficits and delays that result from, in all likelihood, combinations of the presence of tumor, surgical resection, and radiation. Whole brain radiotherapy, in particular, imposes significant intellectual risk. Radiotherapy appears to have its greatest negative effect on the youngest children, with intellectual deficits being inversely related to age at the time of radiation (Lassaletta et al. 2015). Most centers recommend comprehensive neuropsychologic evaluation yearly, if possible, with very important time points for testing being at the times of school transitions and/or if parents and teachers observe declines or changes.

Yearly survivorship visits should also include audiology, with risk to the cochlea being incurred from both platinum-based chemotherapies and whole brain radiation (Walker et al. 1989) as well as screening for cataracts. Newer techniques, including proton therapy and radiation boost volume reduction, have potential to mitigate risk of

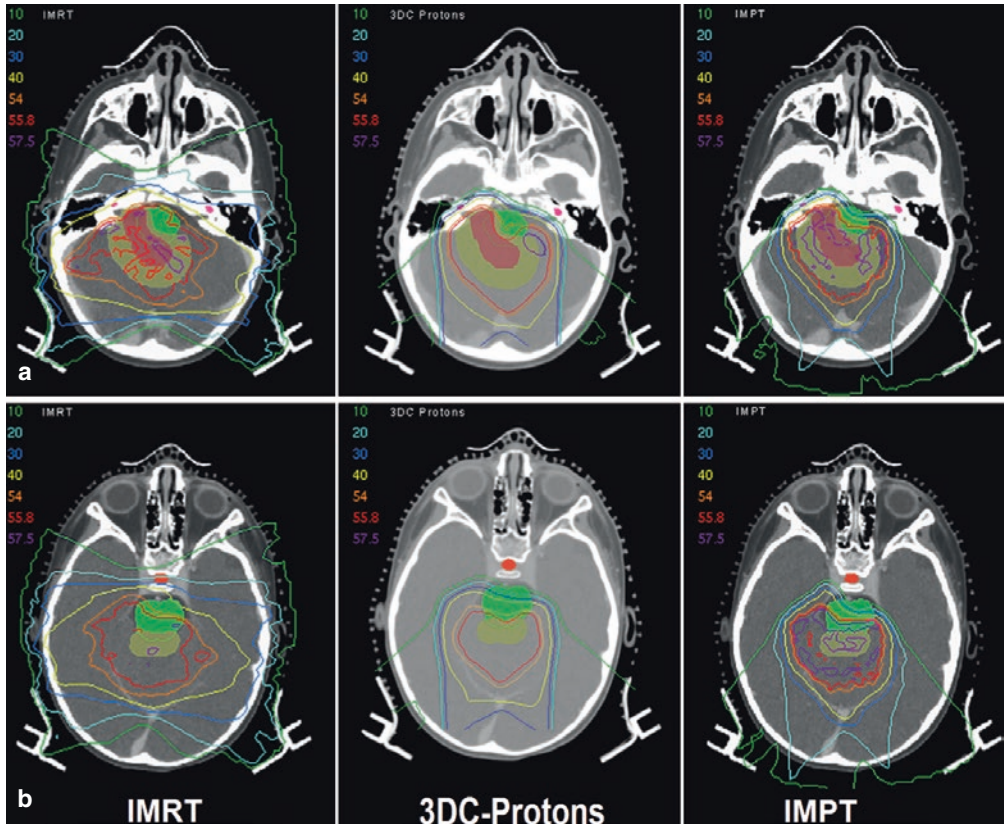

Fig. 9.6 Axial images of a conformal posterior fossa treatment using (from left to right) IMRT, 3D conformal protons, intensity modulated proton therapy (IMPT) with images at the level of cochlea (**a**) and at the level of temporal lobes (**b**). Adapted from Macdonald, S. M., Safai, S., Trofimov, A., Wolfgang, J., Fullerton, B., Yeap, B. Y., Bortfeld, T., Tarbell, N. J. & Yock, T. 2008. Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. *Int J Radiat Oncol Biol Phys,* 71, 979–86

both sensory neural hearing loss and cataract development (Moeller et al. 2011; Dinh et al. 2013). Whole brain radiation may threaten the pituitary axis and yearly endocrine evaluation is also warranted; the risk of endocrine abnormalities may also be reduced by techniques that limit pituitary exposure. Recent data regarding parotid dose during whole brain radiation support semi-annual dental evaluation and maintenance of dental insurance whenever possible (King et al. 2015).

The spinal portion of radiotherapy, when performed with X-rays in the most standard way, results in exit dose through anterior mediastinum, heart, breast tissue, stomach, pancreas, bowel, and ovaries. Patients should undergo early echocardiogram for monitoring of cardiac function as well as yearly thyroid function testing (Paulino 2002). Those who received 3600 cGy spinal radiation may have received dose to breast tissue approaching guidelines for early breast cancer screening with yearly MRI scans beginning 8 years after treatment, or at age 24 (Kumar et al. 2013). This can probably be avoided for patients having received more modest dose to the spine, or those for whom the spine was treated with particle therapy that eliminates exit dose. Patients should be counseled regarding risk of bowel obstruction, and diabetes screening is prudent. Finally, girls and young women having undergone CSI may benefit from reproductive endocrinology consultation prior to desiring pregnancy (Lester-Coll et al. 2014; Perez-Andujar et al. 2013).

Potential risks to cardiac, pulmonary, and endocrine systems, as well as second malignancy risk (most notably breast) all warrant avoidance of obesity and smoking in this survivor population.

Both of these modifiable risk factors should be addressed at each follow-up visit after active cancer therapy.

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Atypical Teratoid/Rhabdoid Tumor (AT/RT)

10

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10.1 Introduction

Atypical Teratoid/Rhabdoid Tumor (AT/RT) is a rare and aggressive tumor of the Pediatric Central Nervous System (CNS) that was first described in 1987 (Biggs et al. 1987). Its aggressive behavior and predilection for infants who are less than 2 years of age enticed further study and pathological characterization over the 1990s (Burger et al. 1998; Rorke et al. 1996b). AT/RT histopathology is characterized by complex rhabdoid, epithelial, and mesenchymal cellular morphology and is genetically defined by loss of SMARCB1 tumor suppressor gene. AT/RT remains a challenging disease, with high mortality rates despite aggressive multimodality therapy including surgery, various chemotherapy regimens with or without stem cell transplant, intrathecal chemotherapy, and radiotherapy. The challenge is due in part to the very young age of presentation for most patients which can limit aggressive treatment particularly radiotherapy, as well as the relatively high rate of disseminated disease at diagnosis. Retrospective series, reported across multiple institutions, helped guide the development of a Children Oncology Group (COG) study designed for AT/RT (ACNS0333) that closed for accrual in February 2014. This was the first cooperative group prospective study dedicated for AT/RT patients in an attempt to standardize the approach to treat AT/RT based on best available data from previous published experiences. This chapter discusses the epidemiology of AT/RT, clinical features and evaluation, pathology and genetic abnormalities, and current treatment approaches. In addition, experimental therapies under investigation, as well as salvage treatment options, are reviewed.

10.2 Epidemiology

A recent report on the incidence of AT/RT utilized data from the Central Brain Tumor Registry of the United States (CBTRUS) from 2001 to 2010 and showed an overall age-adjusted incidence of 0.07 per 100,000 (Ostrom et al. 2014). AT/RT patients represented 1.6% of the entire cohort of patients aged 19 years or less and 10% of patients aged 1 year or less.

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Incidence showed some increase depending on year of diagnosis from 2001–2004 compared to 2005–2010. The earlier period showed incidence of 0.05 per 100,000 compared to 0.08 per 100,000 at later period. This was consistent and more prominent for patients age 1 year or less, with incidence of 0.36 per 100,000 compared to 0.62 per 100,000.

In a population-based study of the Austrian Brain Tumor Registry on malignant CNS tumors for patients aged 0–14 from 1996 to 2006, AT/RT represented 6.1% of the entire cohort (Woehrer et al. 2010). Almost half of AT/RT cases were found to be misdiagnosed after performing a central pathology review. Misdiagnosis was more common in the period from 1996 to 2000 compared to after 2000. In contrast, none of the initially diagnosed AT/RT tumors was reclassified after central pathology review. A report from Canada also showed a similar pattern with a slight increase in the distribution of AT/RT during the 1990s reaching 1.1% compared to 2000s reaching 1.6% (Kaderali et al. 2009). The study reviewed all pediatric brain tumors at Sick Kids Hospital in Toronto from 1980 to 2008. This is likely due to improved awareness and recognition of pathologists to AT/RT, reflecting an expected learning curve since around 2000 when AT/RT was introduced to WHO classification system and incorporation of molecular diagnostic of SMARCB1 loss. Most studies showed male gender to represent slightly more than half ranging from 54 to 62% (Lafay-Cousin et al. 2012; Woehrer et al. 2010; Athale et al. 2009). However, recent data from the CBTRUS, representing one of the largest cohorts to date, showed no significant gender predilection (Ostrom et al. 2014).

10.3 Pathology

Malignant rhabdoid tumors (MRT) comprise a group of histologically diverse tumors, first characterized in the kidney, and now include tumors within various soft tissues and the CNS (Beckwith and Palmer 1978; Tsuneyoshi et al. 1985; Bonnin et al. 1984). MRT within the CNS were initially described as embryonal tumors, predominately as primitive neuroectodermal tumor or medulloblastoma, often in association with renal tumors (Bonnin et al. 1984; Chou and Anderson 1991; Biggs et al. 1987). These tumors were subsequently histologically defined by Rorke and colleagues as atypical teratoid/rhabdoid tumors (AT/RT) (Rorke 1987; Rorke et al. 1996a), and recognized as a separate entity with publication of the WHO classification of tumors of the nervous system in 2000 (Kleihues et al. 1993, 2002). Collectively, primary CNS AT/RT represents one of the most common extrarenal MRT (Parham et al. 1994) (Fig. 10.1; Table 10.1).

In gross tissue specimens, AT/RT appears as a soft pink to grey mass, often fairly well demarcated from the brain parenchyma, yet frequently with foci of necrosis, hemorrhage, dystrophic calcifications and cysts. Histologically, as is the case with other MRT, hallmarks of AT/RT include a highly malignant phenotype (WHO grade IV) with abundant proliferation, and a striking range of histopathologic diversity including sheets of cells with rhabdoid, primitive neuroectodermal, mesenchymal, and epitheliod features (Kleihues et al. 2002; Louis et al. 2007; Margol and Judkins 2014; Rorke et al. 1996a). Classic rhabdoid cells appear as large, discohesive, ovoid-to-polygonal cells with eosinophilic intracytoplasmic inclusions of whorled intermediate filaments (Margol and Judkins 2014; Rorke et al. 1996a; Weeks et al. 1989). However, these components are often found to variable degrees both within different tumors and regions of the same tumor, indicative of divergent differentiation along distinct histologic lines.

Immunohistochemical (IHC) analysis has revealed protein localization of vimentin, epithelial membrane antigen (EMA), and smooth muscle actin (SMA) in the majority of AT/RT (Burger et al. 1998). Yet immunoreactivity to additional markers of neuroepithelial differentiation, including glial fibrillary acidic protein (GFAP), and neuronal differentiation, including neurofilament protein (NFP), synaptophysin, and neuron specific enolase (NSE) is also commonly observed. Finally, cytokeratin and CD99 protein localization

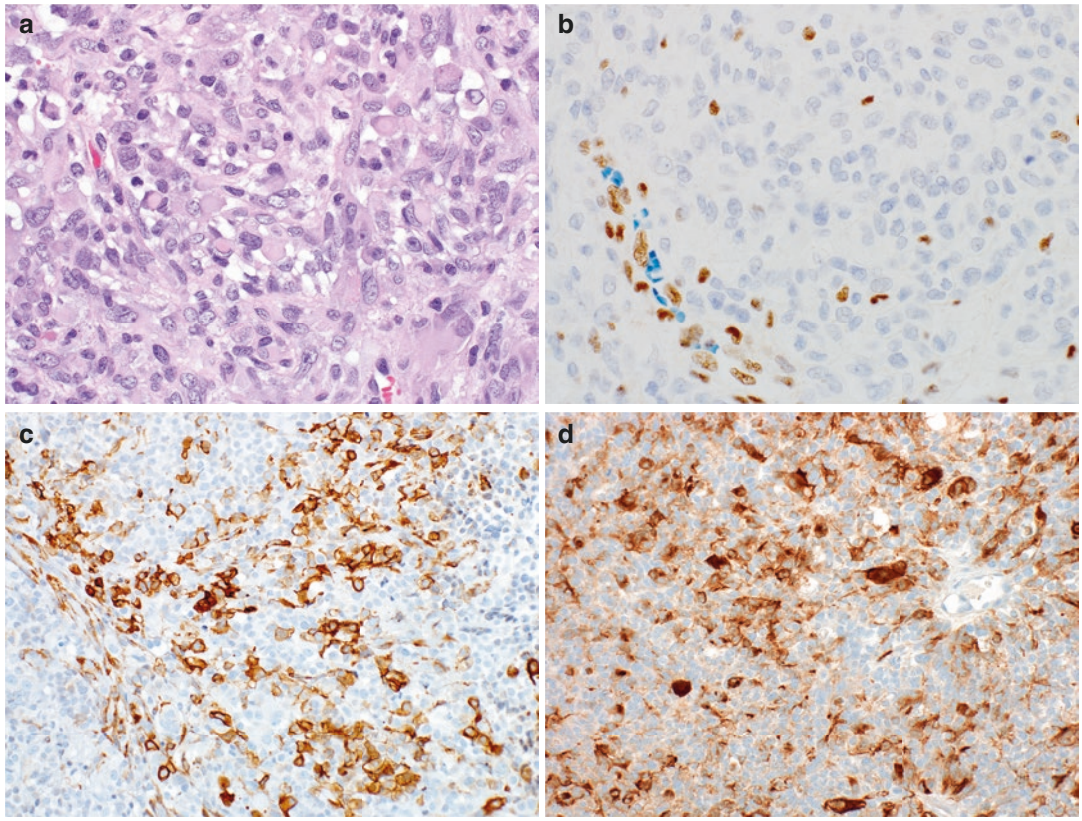

Fig. 10.1 Histologic characterization of atypical teratoid/rhabdoid tumor (AT/RT). (**a**) Hematoxilin and eosin staining of AT/RT. (**b**) Immunohistochemical analysis of INI/BAF47 loss in AT/RT tumor cells. Note the internal positive control of retained INI1 staining of cells in vessel walls. (**c**, **d**) Tumor cells immunoreactive with antibodies to smooth muscle actin (SMA) (**c**) and epithelial membrane antigen (EMA) (**d**), respectively (Courtesy of Brent Orr, M.D., Ph.D.; St. Jude Children's Research Hospital)

has been observed in many AT/RT (Louis et al. 2014). Importantly, germ cell tumor markers, including placental alkaline phosphatase protein (PLAP) and beta-human chorionic gonadotropin (β-HCG), are usually negative (Burger et al. 1998; Packer et al. 2002). Given the phenotypic diversity and resultant varied IHC profile found within AT/RT, conventional histopathologic diagnosis can be challenging.

Early cytogenetic studies revealed monosomy of chromosome 22 or partial deletion of 22q11.2 in the majority of AT/RT and non-CNS MRT (Biegel et al. 1989; Douglass et al. 1990). Subsequent investigations into this non-random chromosomal aberration revealed homozygous deletions or mutations of the hSNF5/INI1/BAF47/SMARCB1 gene (referred to as SMARCB1 from hereon), which maps to chromosome 22q11.22 (Versteege et al. 1998; Biegel et al. 1999). Furthermore, germline mutations of the SMARCB1 gene detected in a subset of pediatric patients can rarely be transmitted in an autosomal dominant fashion with incomplete penetrance resulting in early onset synchronous CNS and extra-CNS MRT (Biegel et al. 1999; Taylor et al. 2000). Rhabdoid tumor predisposition syndrome (RTPS), type 1 and type 2, have now been defined and as a result germline analysis is suggested for individuals of all ages with MRT (Eaton et al. 2011; Hasselblatt et al. 2011; Schneppenheim et al. 2010).

It is now thought that loss of SMARCB1 function, through alterations in DNA, RNA, and/or protein structure and function represents the defining molecular feature of MRT, including

Table 10.1 Select completed studies and ongoing investigations of atypical teratoid/rhabdoid tumor (AT/RT)

Study (institution)	Study period	Study type	Number of patients	Chemotherapy	Radiotherapy	Outcomes
Tekautz et al. (St. Jude) (Tekautz et al. 2005)	1984–2003	Retrospective	31	Various regimens	<3 yrs old: 2 focal, 1 CSI + boost ≥3 yrs old: CSI + boost	<3 yrs old: 2 yr EFS 11 ± 6% 2 yr OS 17 ± 8% ≥3 yrs old: 2 yr EFS 78 ± 14% 2 yr OS 89 ± 11%
Geyer et al. (CCG9921) (Geyer et al. 2005)	1993–1997	Phase II/III	28	Induction A: VCR/CDDP/CTX/VP Induction B: VCR/CDDP/IFOS/VP Maintenance: VCR/CDDP/CTX/VP	2 patients prior to progression (1 focal, 1 CSI)	5 yr EFS 14 ± 7% 5 yr OS 29 ± 9%
Strother et al. (POG 9233/34) (Strother et al. 2004)	1992–1998	Phase III	33	Standard vs. dose-intensified: VCR/CDDP/CTX/VP	None	Median OS 6.7 months 5 yr OS 0%
Lafay-Cousin et al. (Canadian PBTC) (Lafay-Cousin et al. 2012)	1995–2007	Retrospective	50	Various regimens	21 patients at some point during therapy	2 yr OS 36 ± 8%
Chi et al. (DFCI) (Chi et al. 2009)	2004–2006	Phase II	20	Modified IRS-III regimen	<3 yrs: focal ≥3 yrs: CSI + boost	2 yr PFS 53 ± 13% 2 yr OS 70 ± 10%
Zaky et al. (Head Start III) (Zaky et al. 2014)	2003–2009	Phase II	19	Regimen D: Induction: VCR/CDDP/CTX/VP/MTX Consolidation: Thio/VP/Carbo with ASCT Regimen D2: Dose reductions of HDMTX and CTX	None on protocol (2 protocol violations); 5 patients at progression	3 yr EFS 21 ± 9% 3 yr OS 26±10%
COG ACNS0333 (NCT00653068)	2008–2014	Phase III	–	Induction: VCR/CDDP/CTX/VP16/MTX Consolidation: Thio/Carbo/ASCT	Focal: infratentorial, M0, age ≥ 6 months; supratentorial, M0, age ≥ 12 months CSI + boost: encouraged for M+ patients	Pending
SJATRT (NCT02114229)	2014-present	Phase II	–	Newly diagnosed: alisertib + chemotherapy without ACST Recurrent: single agent alisertib	Focal: M0, age ≥ 12 months CSI + boost: M+ or residual, age ≥ 3 yrs	Pending

VCR vincristine, *CDDP* cisplatin, *CTX* cyclophosphamide, *VP* etoposide, *MTX* methotrexate, *Thio* thiotepa, *Carbo* carboplatin, *ASCT* autologous stem cell transplant, *IRS* intergroup rhabdomyosarcoma study, *yrs* years, *CSI* craniospinal radiotherapy, *EFS* event-free survival, *OS* overall survival, *PFS* progression-free survival

AT/RT. Thus, with the development of a specific monoclonal antibody and subsequent large scale tumor screening, it is now standard of care to screen all CNS embryonal tumors and tumors where non-CNS MRT is within the differential diagnosis for SMARCB1 protein localization loss through IHC (Judkins et al. 2004). Importantly, widespread application of SMARCB1 IHC and further molecular investigations have revealed that while the majority of AT/RT harbor alterations in SMARCB1, alterations in other genes and their gene products, most notably SMARCA4 (BRG1), may be altered in patients with AT/RT and intact SMARCB1 (Hasselblatt et al. 2011).

SMARCB1 is a core subunit of the SWI/SNF complex, one of at least five families of chromatin-remodeling complexes that plays a role in the regulation of diverse cellular processes including cell signaling, growth and differentiation (Lee and Roberts 2013). This complex consists of 10–15 core subunits, as well as a number of cell type specific subunits that may regulate cell lineage identity (Nie et al. 2000; Wilson and Roberts 2011). Alterations in several subunits other than SMARCB1 have also been implicated in a wide spectrum of cancers (Fujimoto et al. 2012; Stephens et al. 2012). While the precise function of SMARCB1 remains largely undefined, loss of function studies in the mouse clearly suggest a role as a tumor suppressor (Roberts et al. 2000). SMARCB1 and the SWI/SNF complex have been implicated in the DNA damage response pathway (Chai et al. 2005; Masliah-Planchon et al. 2015; Sinha et al. 2009), and while dispensable for the formation of the SWI/SNF complex, SMARCB1 does appear to contribute to targeting of the SWI/SNF complex to gene promoters (Doan et al. 2004; Kuwahara et al. 2013).

Initial genomic studies of human primary AT/RT have revealed that, despite the hypothesis that SMARCB1 inactivation may lead to enhanced DNA mutation, these tumors demonstrate a remarkably quiet genome with low rates of mutation with the exception of recurrent alterations in SMARCB (Hasselblatt et al. 2013; Lee et al. 2012). A subsequent large scale genomic study has suggested tumor subtyping into at least two distinct molecular subgroups on the basis of gene expression and copy number profiling (Torchia et al. 2015). While prospective validation awaits, based on the integration of the genetic analysis and clinicopathologic characteristics, the authors have suggested three separate patient risk categories related to overall survival that may, with likely subsequent refinement, allow for eventual employment of molecularly-driven risk-adapted therapy. Finally, while there are limited number of studies involving limited numbers of patients, comparative genomics of primary and recurrent tumors suggests as high as an eightfold mutation rate in recurrent tumors following multimodality therapy (Lee et al. 2012).

10.4 Clinical Features and Evaluation

AT/RT has consistently shown to be a disease of infants and young children. Median age in most reported studies ranges between 12–26 months (Ostrom et al. 2014; Lafay-Cousin et al. 2012; Woehrer et al. 2010; Athale et al. 2009; Rorke et al. 1996b). Around two-thirds to three-quarters of AT/RT patients are 2 to 3 years old and less at diagnosis (Woehrer et al. 2010; Rorke et al. 1996b; Lafay-Cousin et al. 2012; Ostrom et al. 2014). Moreover, Austrian Brain Registry data showed that for patients aged 0–3 years with malignant CNS tumors, AT/RT was almost as common as PNET and more common than medulloblastoma, glioblastoma and ependymoma. Around 20–40% of patients present with metastatic disease at diagnosis (Lafay-Cousin et al. 2012; Hilden et al. 2004; Packer et al. 2002; Athale et al. 2009) Sites of metastasis include leptomeningeal spread and less commonly metachronous rhabdoid tumor in the kidney.

AT/RT can arise almost equally in the supratentorial or infratentorial brain. Suprasellar and pineal region involvement are also reported within supratentorial brain locations. Infratentorial AT/RT is more common in younger patients who are less than 3 years, whereas supratentorial AT/RT is

more common in older patients. Recent data showed that 78% of infants presented with infratentorial ATRT. In contrast, 70% of children who are 6–18 years old presented with supratentorial disease (Ostrom et al. 2014). Less commonly, isolated spinal cord involvement was reported in around 5–7% of patients between multiple studies.

Presenting symptoms and signs are most commonly due to increased intracranial pressure including vomiting and headache. Lethargy and irritability may follow, in addition to neurological symptoms including cranial nerve palsies, hemiplegia, head tilt, and ataxia (Rorke et al. 1996b; Lafay-Cousin et al. 2012). Clinical evaluation and staging should include a careful history and physical examination, brain and spine imaging with magnetic resonance (MRI), and craniospinal fluid cytology assessment.

MRI features include intra-axial tumor with heterogenous T1 signal intensity due to cystic, necrotic, and hemorrhagic components (Fig. 10.2) (Meyers et al. 2006). There is a degree of variation in T2 intensity among different cases that could be hyperintense, isointense, or hypointense. Post-gadolinum contrast enhancement is present in most cases, although it can vary between mild to marked enhancement (Warmuth-Metz et al. 2008). A typical enhancement pattern is described as a strong wavy band enhancement surrounding a central cystic or necrotic area (Au Young et al. 2013). Peritumoral edema is often present to a varying degree. Computed Tomography scan features include hyperdense tumor and less often microcalcifications.

10.5 Role of Surgery

Several retrospective reviews showed superior outcome for patients who undergo Gross Total Resection or Near Total Resection (GTR or NTR) compared to patients who receive Subtotal Resection (STR) or biopsy (Woehrer et al. 2010; Athale et al. 2009; Hilden et al. 2004). Hilden et al. showed that patients who receive GTR achieve median survival of 20 months and EFS of 14 months compared to those who receive STR and achieve median survival of 15 months and EFS of 9 months (Hilden et al. 2004). Athale et al. also showed a statistically significant improvement in median survival for patients who undergo GTR of 21.3 months compared to partial resection of 12.3 months and even worse for those who receive biopsy only of 10.2 months ($p = 0.042$) (Athale et al. 2009). The recently closed COG ACNS0333 trial encouraged a second look surgery after induction chemotherapy in cases of residual gross tumor on reassessment imaging.

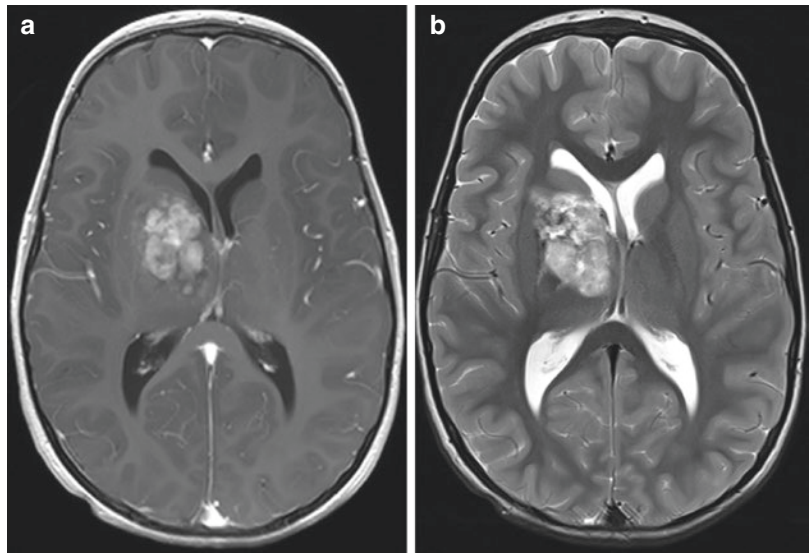

Fig. 10.2 Radiographic findings of a 6 year old child with atypical teratoid/rhabdoid tumor (AT/RT). Contrast enhanced axial T1 (**a**) and axial T2-weighted (**b**) images reveal a fairly well circumscribed mass centered in the right thalamus demonstrating heterogeneous enhancement on post-contrast T1–weighted image (**a**) and intermediate to high heterogeneous signal on T2-weighted image (**b**)

10.6 Role of Chemotherapy

10.6.1 Early Experience

Various chemotherapy regimens were developed since the early 1990s in an attempt to delay radiotherapy for infants and young children with malignant CNS tumors (Duffner et al. 1993). As AT/RT became more recognized as a malignant CNS tumor with aggressive behavior, and since around 75% of patients are 3 years old or younger at diagnosis, chemotherapy became an integral component of AT/RT treatment (Packer et al. 2002; Rorke et al. 1996b; Burger et al. 1998). Early reports on AT/RT treatment used various conventional chemotherapy regimens, however, outcomes were extremely poor (Athale et al. 2009). An abstract reviewed the outcome of 36 AT/RT patients, <3 years old, on the POG 9233/34 trial. Patients were randomized after surgery to receive standard dose (six 12-week cycles) versus intensive dose (eight 9-week cycles) of Cyclophosphamide, Vincristine, Cisplatin, and Etoposide. None of the patients survived, with a median event-free survival of 4.6 months and median survival of 6 months (Strother et al. 2004). The St. Jude Children's Research Hospital (SJCRH) experience showed poor results with chemotherapy alone, and improved outcomes with the addition of radiotherapy. Also, patients who were older than 3 years fared better when treated to protocols similar to those of medulloblastoma and PNET (Tekautz et al. 2005).

The Children Cancer Group (CCG) 9921 study, which was designed for young children with CNS tumors, showed a 5-year survival of 29% for the AT/RT subset of patients (Geyer et al. 2005). This study involved randomization of two induction chemotherapy regimens (Vincristine, Cisplatin, Cyclophosphamide and Etoposide vs. Vincristine, Carboplatin, Ifosfamide, and Etoposide). After 5 cycles of induction chemotherapy, maintenance chemotherapy was administered to both arms with 8 cycles of Vincristine, Etoposide, Carboplatin, and Cyclophosphamide. Both induction chemotherapy regimens were similar in efficacy but the second regimen had increased toxicity. Therefore, the better tolerated induction chemotherapy regimen became the backbone of studies that incorporated high dose chemotherapy (HDCT) and stem cell transplant.

10.6.2 High Dose Chemotherapy and Stem Cell Transplant

Several retrospective reports suggested that durable complete remission can be achieved with HDCT followed by stem cell rescue and avoidance of radiotherapy. The Canadian experience showed superior 2-year survival of 48% for patients treated with HDCT compared to 27.3% with conventional chemotherapy ($p = 0.036$) (Lafay-Cousin et al. 2012). Six out of eleven survivors treated with HDCT did not receive radiotherapy at a median follow up of 38 months. Also, Hilden et al. reported that 6 out of 13 patients treated with HDCT were alive with no evidence of disease at the time of the report (Hilden et al. 2004). The Austrian experience in the treatment of AT/RT combined both HDCT with stem cell transplant and Intrathecal (IT) Chemotherapy and showed excellent results with this strategy. All patients in this cohort received focal radiotherapy after transplant. Five-year EFS was 89% and 5-year OS was 100%. Cox-regression analysis of different variables showed HDCT to be a significant positive predictive factor for EFS ($p = 0.018$) and OS ($p = 0.039$) (Slavc et al. 2014).

Head Start I/II study was an early trial that adopted HDCT and stem cell rescue treatment strategy for AT/RT patients in 1992, with 13 patients enrolled (6 on Head Start I and 7 on Head Start II) (Gardner et al. 2008). The treatment scheme involved surgery followed by 5 cycles of induction chemotherapy: Cisplatin, Etoposide, Cyclophosphamide, and Vincristine. Methotrexate was added to induction chemotherapy in Head Start II. For patients who remained without progressive disease at reassessment after induction, they received 1 cycle of consolidation chemotherapy with Carboplatin, Etoposide and Thiotepa followed by stem cell rescue. Only one patient received radiotherapy after stem cell transplant and three at relapse. All six patients on Head Start I succumbed to their disease, whereas 3-year PFS

for Head Start II was 43%. Better results of Head Start II were attributed to the addition on Methotrexate to the chemotherapy regimen. Most toxicity events were hematopoietic, with also one toxic death due to infectious meningitis.

Head Start III used a similar study design that is illustrated in Fig. 10.3 (Zaky et al. 2014). Radiotherapy was only assigned for patients older than 6 years or with residual disease after induction chemotherapy. Unfortunately, only 4 patients out of 19 enrolled were able to complete induction chemotherapy. There were five toxic deaths during induction chemotherapy. Most toxicity occurred during induction phase and was hematopoietic in nature.

The lessons learned from Head Start were taken into account when CCG 99703 trial was designed for patients <36 months of age diagnosed with malignant CNS tumors (Cohen et al. 2015). Its purpose was to test the feasibility and tolerability to a novel-dose intensive chemotherapy regimen. The treatment scheme involved surgery followed by 3 cycles of induction of chemotherapy adopted from CCG 9221 (Cisplatin, Vincristin, Cyclophosphamide, Etoposide) followed by 3 "mini" marrow-ablative consolidation chemotherapy with Thiotepa and Carboplatin, followed by stem cell rescue. The administration of radiotherapy was left to the discretion of the radiation oncologist. Overall, this regimen was well tolerated with major toxicity related to bone marrow suppression and resulting infections. Toxic mortality rate was 2.5%. There were 8 patients diagnosed with AT/RT enrolled in the study out of 92 patients and their outcome showed 5-year EFS of 37.5% and 5-year OS of 62.5%.

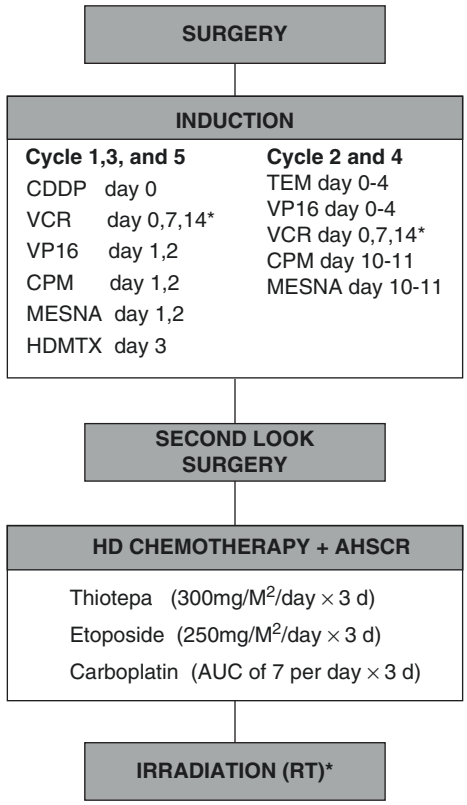

Fig. 10.3 Head Start III treatment scheme, with RT given for patients older than 6 years or with residual disease after induction. *CDDP* cisplain, *VCR* cincristine, *VP16* etoposide, *CPM* cyclophosphamide, *HDMTX* high-dose methotrexate, *TEM* temozolomide, *AHSCR* autologous stem cell rescue

The recently closed COG ACNS0333 trial built on those previous experiences. Treatment involved surgery followed by 2 cycles of induction chemotherapy that used the same CCG 9921 regimen but added Methotrexate based on the Head Start experience. Consolidation chemotherapy was identical to CCG 99703 with 3 cycles of Carboplatin and Thiotepa. Timing of radiotherapy was after induction chemotherapy, however, radiation was restricted to patients at least 12 months of age (for supratentorial tumors) or 6 months of age (for infratentorial tumors). If the patient did not meet these age criteria, radiotherapy would be delayed until after consolidation. Results from this recently closed trial are awaited.

10.6.3 Intergroup Rhabdomyosarcoma Study (IRS III) Chemotherapy Regimen

Oslen et al. published a case series of successful treatment of AT/RT with surgery, radiotherapy, chemotherapy and triple intrathecal (IT) chemotherapy. Three children were reported to be in remission. The treatment regimen was based on IRS III protocol designed to treat patients with parameningeal rhabdomyosarcoma with intracranial extension (Olson et al. 1995). An earlier case

report also showed sustained clinical remission for AT/RT patient treated with the same IRS-III protocol (Weinblatt and Kochen 1992). The results were encouraging to be further tested in a prospective phase II trial design. A multi-institutional trial enrolled 20 patients newly diagnosed with AT/RT with centrally reviewed pathology (Chi et al. 2009). Patients' median age at diagnosis was 26 months. Treatment involved maximal possible resection followed by 5-phase chemotherapy scheme over 51 weeks. Induction involved 3 phases over 18 weeks (pre-radiotherapy induction, chemoradiotherapy induction, post radiotherapy induction), followed by maintenance phase and finally continuation therapy phase. Chemotherapy drugs included Vincristine, Dactinomycin, Cyclophosphamide, Cisplatin, Doxorubicin and Temozolamide (Fig. 10.4). Triple IT chemotherapy included Cytarabine, Methotrexate, and Hydrocortisone. For patients with positive CSF, IT chemotherapy was administered weekly until CSF was negative on two consecutive assessments.

Overall, 12 out of 20 patients completed the treatment and 4 patients came off protocol due

Pre RT Induction

W 1	W 2	W 3	W 4	W 5	W 6	REEVAL
VCR	VCR	VCR	VCR	VCR	VCR	
CDDP			CDDP			
DOX			DOX			
CPM			VP16			
IT CT	IT CT		IT CT			

Chemo-RT Induction

W 7	W 8	W 9	W 10	W 11	W 12
VCR	VCR	VCR	VCR	VCR	VCR
CDDP			CDDP		
CPM			CPM		
VP16			VP16		
IT CT					
Radiotherapy					

Post RT Induction

W 13	W 16	REEVAL
VCR	VCR	
CDDP	CDDP	
CPM	CPM	
VP16	VP16	
IT CT		

Maintenance Chemotherapy

W 19	W 23	W 27	W 30	REEVAL	W 33	W 36	W 39	W 42	REEVAL
TMZ	TMZ	VCR	VCR		VCR	VCR	VCR	VCR	
ACD	ACD	DOX	CPM		DOX	CPM	DOX	CPM	
		CPM	ACD		CPM	ACD	CPM	ACD	
							Dexrazoxane		
IT CT		IT CT			IT CT		IT CT		

Continuation Chemotherapy

W 45	W 48	W 51	REEVAL
VCR	VCR	VCR	
DOX	CPM	DOX	
CPM	ACD	CPM	
Dexrazoxane		Dexrazoxane	
IT CT		IT CT	

Fig. 10.4 Chemotherapy scheme for Chi et al.: *VCR* vincristine, *CDDP* cisplatin, *DOX* doxorubicin, *CPM* cyclophosphamide, *VP16* etoposide, *ADC* dactinomycin, *TMZ* temozolamide, *IT CT* intrathecal chemotherapy (methotrexate, cytarabine, hydrocortisone), *REEVAL* revaluation imaging

to progressive disease. There was a single event of toxic death due to pneumococcal sepsis on week 2. The time required for protocol completion was 52–78 weeks. Chemotherapy dose adjustments were frequent due to grade III and IV bone marrow suppression. Nine patients were alive with no evidence of disease, with a 2-year PFS of 53% and 2-year OS of 70%. Although the results are promising, long term side effects associated with IT chemotherapy in addition to radiotherapy for infants may be significant and yet to unfold.

10.6.4 Intrathecal (IT) Chemotherapy

The rationale to use IT chemotherapy for AT/RT patients is the high rate of disseminated disease at diagnosis and toxicity associated with craniospinal irradiation (CSI) for very young children. IT chemotherapy was also added to some conventional chemotherapy regimens to enhance the therapeutic effect (Lafay-Cousin et al. 2012; Tekautz et al. 2005). A meta-analysis of observational studies showed a survival advantage with the addition of IT chemotherapy, with a 2-year survival of 64% in patients who received IT chemotherapy compared to 17% without IT chemotherapy ($p < 0.0001$) (Athale et al. 2009). Patients' characteristics in both groups were fairly comparable including mean age, metastatic disease at diagnosis, rate of GTR, and radiotherapy receipt. The result still favored IT chemotherapy for patients who received radiotherapy, with 2-year survival probability of 67% (95% CI 45–89) for patients who received both compared to 18.7% (95% CI 4.6–28) for those who received radiotherapy alone. Patients older than 3 years had no OS advantage with IT therapy and almost all of them received radiotherapy. In addition, both the Canadian and Austrian experiences showed no survival advantage associated with IT chemotherapy (Lafay-Cousin et al. 2012; Slavc et al. 2014). At present, IT chemotherapy is not considered an alternative to CSI for patients with metastatic disease.

10.7 Role of Radiotherapy

10.7.1 Radiotherapy Outcomes

AT/RT is associated with a very high risk of local recurrence as well as leptomeningeal spread. In one of the first retrospective series describing 52 patients at the Children's Hospital of Pennsylvania, the rate of leptomeningeal dissemination at diagnosis was 34% (Rorke et al. 1996a). Following initial treatment that most commonly included biopsy/partial resection (69%) and chemotherapy (83%), death from progressive disease occurred in 43 patients (83%). Rates of first relapse were local only in 27%, leptomeningeal alone in 10%, and combined local and leptomeningeal in 50%. Upfront radiotherapy was utilized in only 19% of cases, likely attributed to patients' young age (median 16.5 months). RT efficacy was discouraging, with objective responses observed in only 2 of 10 patients.

A SJCRH institutional series of 31 evaluable patients with AT/RT demonstrated significantly improved outcomes with the use of RT (Tekautz et al. 2005). Treatment included more extensive surgical resection (GTR/NTR in 69%) and increased use of RT in older patients (77%) as compared to the Children's Hospital of Pennsylvania series. Chemotherapy was administered in 31 patients (97%). For children >3 years old, RT consisted of risk-based craniospinal radiation (CSI) to 2340 cGy (GTR and M0) or 3600 cGy (all others) with subsequent focal boost to 5580 cGy. Patients who received RT had a 2-year OS of 90% in comparison to 10% with chemotherapy alone ($p = 0.007$). Important considerations include that age < 3 years was also associated with a dismal outcome (2-year OS of 17% compared to 89% in older patients, $p = 0.001$), and only 3 patients (13%) younger than 3 years received RT. Of the 3 younger patients who received RT (2 local only, 1 CSI), 2 were alive with no evidence of disease (NED). Similarly 6 of the 7 older patients who received RT (CSI plus boost) were alive and NED.

An updated analysis of the St Jude cohort demonstrated that delay of RT (≥1 month postoperatively) was associated with increased risk

of local failure (Pai Panandiker et al. 2012). The authors challenge the therapeutic strategy of immediate post-operative chemotherapy to delay RT in younger patients, as 14 of 23 patients (61%) receiving pre-irradiation chemotherapy experienced progression during chemotherapy. A worrisome finding was the high rate (52%) of developing disease progression in the potentially favorable subset of patients with localized disease who underwent GTR, where the risk progression of increased proportionally with increasing RT delay.

The benefit of RT in AT/RT is controversial (Squire et al. 2007) but has been demonstrated in additional retrospective studies (Chen et al. 2005; Chrzanowska et al. 2009). Of the 42 patients included on an AT/RT registry, 14 patients were alive and NED and 8 (57%) of these received radiation (Hilden et al. 2004). In the overall cohort only 13 patients (31%) received RT; of which 9 received focal RT and 4 craniospinal. A meta-analysis (Athale et al. 2009) demonstrated improved OS in patients younger than 3 years of age with the addition of RT to chemotherapy (median 15.8 months) in comparison to chemotherapy alone (median 7.9 months, P = 0.005). No conclusions could be made for patients older than 3 since all but one received RT. In a SEER analysis of AT/RT patients from 1973–2008, use of RT was an independent predictor of OS on multivariate analysis (Buscariollo et al. 2012). Interestingly, the benefit of RT was more pronounced in younger patients. An analysis of The Central Brain Tumor Registry of the United States likewise demonstrated significantly improved long-term survival in patients who received surgery plus RT (Ostrom et al. 2014). In contrast, a combined retrospective experience from the institutions of the Canadian Paediatric Brain Tumour Consortium did not show a survival benefit with the use of RT (Lafay-Cousin et al. 2012). Patient selection is major limitation in data interpretation which could both positively and negatively affect the apparent impact of RT.

A 2002 National Cancer Institute (NCI) workshop recommended that young patients with AT/RT be treated with surgery, aggressive chemotherapy, and focal RT. Because data was largely limited to institutional series, enrollment on a prospective study was encouraged (Packer et al. 2002). A multi-institutional prospective trial open from 2004 to 2006 treated 26 patients with surgery, intensive chemotherapy, and 15 of 20 (75%) evaluable patients received RT (Fig. 10.4) (Chi et al. 2009). Gross total resection was encouraged. Chemotherapy was administered pre-irradiation, concurrently with RT, post-irradiation, and also included intrathecal administration. RT was focal to the primary site for M0 patients (n = 11, 73%) whereas M+ children older than 3 years received craniospinal RT followed by boost. Focal RT of 5400 cGy was prescribed to predefined margins of 1.5 cm for infratentorial and 1.0 cm for supratentorial tumors, using intensity-modulated radiation therapy (IMRT) or 3-dimensional radiation therapy (3DCRT). The craniospinal dose was 3600 cGy with boost to 5400 cGy. While treatment was intensive (60% of successfully completed all therapy), favorable outcomes were reported with 2-year PFS of 53% and 2-year OS of 70%. All 9 patients who remained NED had a CR following induction chemotherapy, and 7 of these had a GTR. Progression occurred in 3 of 4 patients who received craniospinal RT, however, each had M3 disease. Long-term outcomes were not yet available to assess the neurocognitive outcomes of intensive therapy (including focal RT, intrathecal chemotherapy) given to very young children (3 patients less than 12 months).

Results are awaited from the recently completed COG ACNS0333, a trial of involving surgery followed by induction chemotherapy consisting of 2 cycles of methotrexate, vincristine, etoposide, cyclophosphamide, cisplatin (NCT00653068). Second look surgery is encouraged following chemotherapy for any initially unresectable disease. For consolidation chemotherapy, 3 cycles of thiotepa and carboplatin are administered followed by stem cell rescue. RT doses are age dependent (<3 years or ≥3 years). Focal RT is given for all M0 patients (5040 or 5400 cGy) and for patients with M+ disease craniospinal RT (2340 or 3600 cGy) is encouraged but not mandatory (with a boost to 5040 or 5400 cGy).

10.7.2 Radiotherapy Treatment Planning

With the overall treatment strategy of maximal safe surgery, intensive chemotherapy, and increasing inclusion of RT, survival outcomes for AT/RT are improving (Tekautz et al. 2005; Chi et al. 2009; De Amorim Bernstein et al. 2013; Mcgovern et al. 2014). In a series where 81% of patients did not receive upfront RT, half of all relapses involved both the primary site and neural axis (Rorke et al. 1996a). However, given the potential for significant toxicity with CSI, the determination of RT dose and volume should be made according to patient age and disease extent.

Patients older than 3 years of age with M0 disease have shown favorable outcomes with use of considered for craniospinal irradiation (CSI) followed by primary boost. For these patients, reduced dose craniospinal radiation (2340 cGy) followed by focal boost (5400–5580 cGy) is an acceptable radiotherapeutic approach, although there is considerable variation (Tekautz et al. 2005; De Amorim Bernstein et al. 2013; Mcgovern et al. 2014). In contrast to medulloblastoma, where multiple prospective trials have been feasible and are ongoing (ACNS0331, NCT00085735) to investigate the efficacy of CSI dose reductions (Bailey et al. 1995; Packer et al. 1999; Thomas et al. 2000), there is unlikely to be randomized data to assess the optimal dose as well as inclusion of CSI for AT/RT.

The strategy of chemotherapy intensification as rationale to give focal RT alone to M0 patients, particularly in patients older than 3 years of age, remains under investigation in the ACNS0333 trial. This is given in context of aggressive multimodality treatment including evaluation for second look surgery after induction chemotherapy, and intensive chemotherapy including stem cell rescue. In a prospective trial of 20 patients where all M0 patients were given focal RT, systemic treatment included 51 weeks of chemotherapy along with intrathecal chemotherapy was also given. This regimen was associated with significant toxicity, and 40% of patients were unable to complete planned therapy (Chi et al. 2009).

A commonly used definition for young age in pediatric brain tumors is less than 3 years old. In these patients, CSI is associated with potentially devastating neurocognitive effects (Radcliffe et al. 1994). For this reason focal RT to the tumor bed, with omission of CSI, should be considered for young M0 patients also receiving chemotherapy (Tekautz et al. 2005, Chi et al. 2009, De Amorim Bernstein et al. 2013, Mcgovern et al. 2014). The optimal focal boost dose is unknown. For young patients less than 3 years old, a focal boost of 5040 cGy has been reported in retrospective series as well as being studied prospectively in the closed ACNS0333 trial. In other studies focal boost to 5400 or 5580 cGy has been employed (Tekautz et al. 2005; Chi et al. 2009).

Older patients with evidence of leptomeningeal spread (M+) generally receive standard dose CSI (3600 cGy) followed by boost, although there is variation (Tekautz et al. 2005). Younger patients with M+ disease are particularly challenging, as RT to primary site alone has mixed results. In a prospective trial where focal RT was given to patients younger than 3 years, the 2 young patients with M+ disease both relapsed (Chi et al. 2009). In contrast there were 6 patients younger than 3 years old with M+ disease in an Austrian retrospective series, and 3 (50%) were long-term survivors following intensive chemotherapy and focal RT (Slavc et al. 2014). Reduced dose CSI to 2340 cGy followed by boost is a reasonable consideration, as was given in the recently closed COG trial.

For primary site RT, given as focal RT alone or boost following CSI, a typical gross tumor volume (GTV) to clinical tumor volume (CTV) margin is 1.0 cm; although a small margin of 0.5 cm is used in ongoing SJYC07 and SJATRT protocols at SJCRH (NCT00602667, NCT02114229). The GTV, determined upon careful review of preoperative and postoperative MRI studies, should include the resection cavity and any residual tumor (Fig. 10.5a, b). The CTV includes potential subclinical microscopic disease. A planning tumor volume (PTV) margin of 0.3–0.5 cm is added for setup uncertainty. Craniospinal RT techniques include conventional photon arrangement, intensity modulated radiation therapy (IMRT), and proton beam. Following CSI, supplemental boost radiation of 4500–5400 cGy can be given to residual metastatic sites while respecting spinal cord

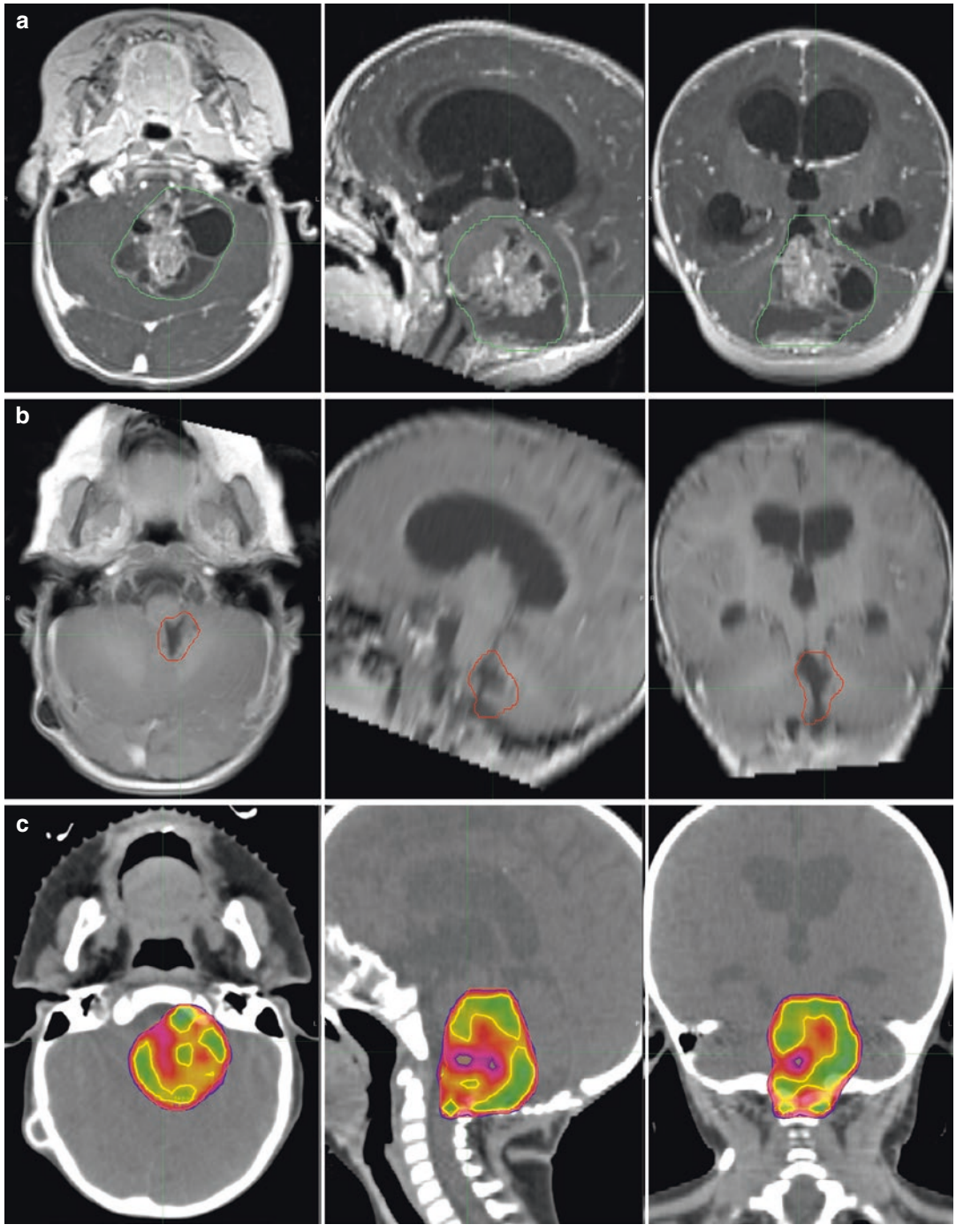

Fig. 10.5 Radiation treatment planning for atypical teratoid/rhabdoid tumor (AT/RT). Nine month old child who underwent subtotal resection (STR) with subsequent re-resection with gross total resection (GTR), followed by four cycles of induction chemotherapy, focal intensity modulated radiotherapy (IMRT) to 54 Gy over 30 fractions and maintenance chemotherapy per SJYCO7 clinical trial. (**a**) Pre-operative gross tumor volume (GTV) in green defined on axial T1 post-contrast MRI. (**b**) Post-operative GTV in red defined on axial T1 post-contrast MRI and informed by pre- and post-surgical and MRI findings. (**c**) Three dimensional dose distribution: planning target volume (*orange*); 95% isodose line (51.3 Gy; *purple*); 100% isodose line (54 Gy, *yellow*). (**d**) Dose volume histogram of target and organs at risk

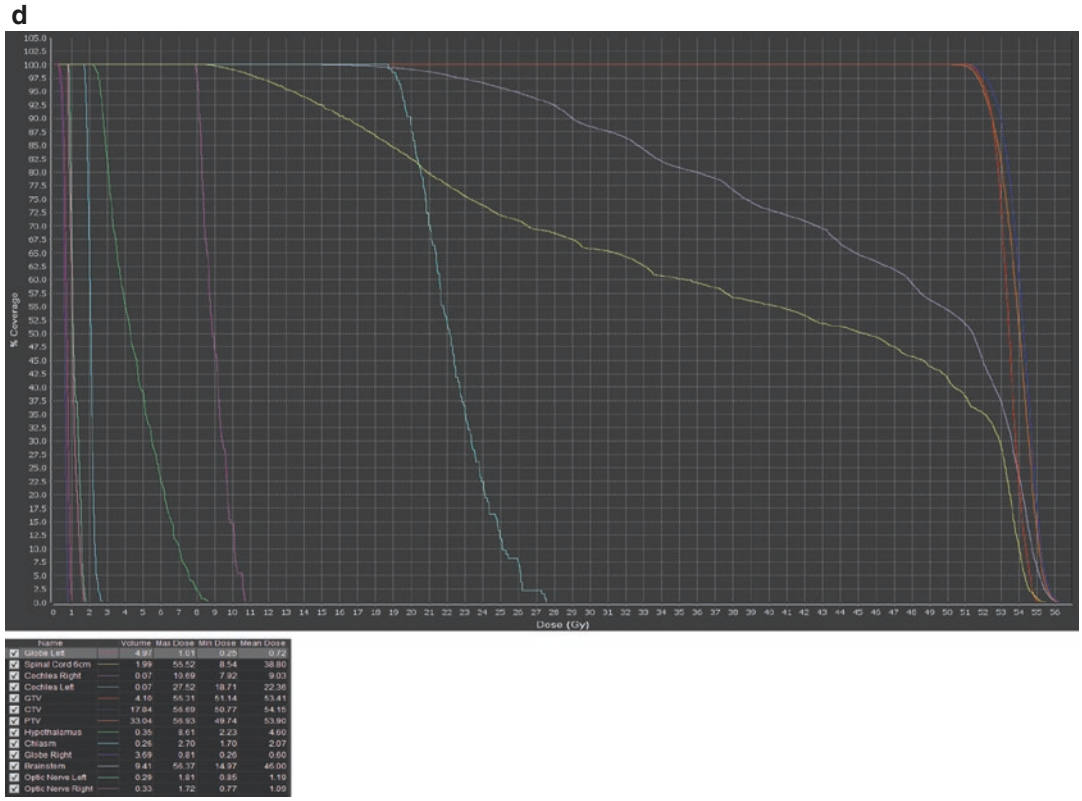

Fig. 10.5 (continued)

tolerance. Dosimetric considerations for focal RT, in addition to tumor coverage, include careful regard to cochlea dose as well as standard constraints for the brainstem and optic structures (Fig. 10.5c, d).

10.7.3 Proton Beam Radiation

Proton beam radiation (PBT) for pediatric brain tumors allows for improved sparing of normal tissues when compared to photon irradiation. When applied to longitudinal models of radiation-dose effects, a gain in Intelligence Quotient (IQ) for medulloblastoma and craniopharyngioma was predicted for proton beam (Merchant et al. 2008). As studies continue to show a subgroup of long term survivors with AT/RT, there are potential advantages with proton therapy for both infratentorial and supratentorial tumor locations.

Investigators from Massachusetts General Hospital reported on the use for 3-dimensional Proton Beam Therapy (3DPBT) for 10 consecutive patients with AT/RT treated from 2004 to 2011 (De Amorim Bernstein et al. 2013). Treatment included maximal safe resection, chemotherapy, and RT with either focal (age < 3) or craniospinal plus boost (age > 3) fields. All patients were M0 and in 8 of 10 a GTR/NTR was achieved. With a median follow-up of 27.3 months, 9 patients are alive and NED including the successful salvage of 1 patient. In the representative supratentorial case there was decreased dose to the surrounding cerebrum with PBT, and for the infratentorial location there was improved cochlear and pharyngeal sparing.

In a series of 31 patients from the M.D. Anderson Cancer Center treated with PBT and intensive chemotherapy, very favorable survival outcomes (median 31 months) were demonstrated (Mcgovern et al. 2014). All patients 3 years of age or older received craniospinal radiation to 2340–3600 cGy relative biological effectiveness (RBE) followed by boost (4320–5580 cGy RBE). Only two young patients that were 14 and 16 months old received CSI. Focal boost dose (ages 4–25 months) ranged from 900 to 5400 Gy RBE (median 5040 cGy RBE). Five patients (16%) exhibited clinical and radiographic signs of brainstem toxicity that resolved with medical management. Transient changes identified on brain imaging following proton beam radiation in very young children with brain tumors have been reported (Sabin et al. 2013). These include signal abnormalities as well as enhancement in brain tissue receiving high dose that occurred at a median time of 3.9 months after completion of PBT with a median resolution period of 2.3 months.

These early experiences support the use of PBT for AT/RT in settings where this technology is available. While survival outcomes are encouraging, they are retrospective in nature and may reflect consistent use of RT as well as patient selection. A significant proportion of patients will unfortunately expire from disease prior to developing late effects of therapy. Additionally, neurocognitive deficits are also evident in AT/RT survivors treated on regimens where RT was largely omitted (Lafay-Cousin et al. 2015). Therefore, the decision to refer a patient for travel to a proton beam facility is challenging (Patel et al. 2014). With the rapid development of PBT centers in the United States and worldwide, an increasing number of children will have access to this important treatment modality (Kerstiens and Johnstone 2014).

10.7.4 Radiosurgery

Radiosurgery entails the delivery of highly conformal RT in 1–5 treatments, which aims to overcome radioresistance by increasing the fractional dose and delivering higher RBE to precisely targeted tumors. Case reports describing the use of radiosurgery as part of initial therapy for AT/RT are rare. Authors from Haukeland University Hospital in Norway describe long-term survival (6 years) following surgery, chemotherapy and Gamma Knife Radiosurgery (GKS) in a 12 month old boy with supratentorial AT/RT (Hirth et al. 2003). In this patient 1800 cGy prescribed to the tumor margin, given for persistent disease following chemotherapy, resulted in complete tumor regression. GKS was used for 2 patients who also received chemotherapy following STR (Bambakidis et al. 2002). While both patients experienced leptomeningeal progression, GKS was noted to provide local control.

In a multi-institutional prospective trial, stereotactic surgery boost was allowed for patients with residual disease ≤2.5 cm on post RT imaging (Chi et al. 2009). Radiosurgery details were not reported. However, by recollection, 1 older patient did receive SRS for small residual tumor (personal communication 10/23/2015, K.M.). This patient unfortunately experienced rapid dissemination of disease. Radiosurgery boost is not included in radiotherapy guidelines for the recently closed ACNS 0333. However, radiosurgery is rarely a component of pediatric prospective trials. While radiosurgery boost remains investigational, further reports will hopefully add to these limited experiences.

Radiosurgery has been shown to be effective for recurrent brain tumors in select pediatric patients (Lo et al. 2008). There were three patients with Rhabdoid Tumor included in a Baylor University series reporting the use of Cyberknife radiosurgery for pediatric brain tumors. Doses were either single treatment (16–18 Gy) or hypofractionated (2400 cGy in 4 fractions). Two of these patients were alive 16 and 35 months from radiosurgery without evidence of tumor progression. Radionecrosis was observed in both long-term survivors, which for one patient was symptomatic but resolving. For several patients treated at Boston Children's Hospital, radiosurgery for salvage has been successful and well-tolerated (personal communication 10/23/2015,

K.M.). Given that options for recurrent AT/RT are limited, salvage radiosurgery is a reasonable consideration in appropriately in selected patients.

10.8 Treatment of Recurrent AT/RT

As is the case for primary AT/RT, management of recurrent disease is without standardization and outcomes are dismal. As failure of primary non-metastatic disease frequently involves a component of local failure, surgical and radiotherapeutic options may be considered depending on extent and location of recurrent disease as well as patient-related factors. In patients without prior receipt of focal radiation upfront, craniospinal radiotherapy is most commonly employed. Salvage chemotherapy is often given for recurrent disease and consists of a variety of regimens, determined by prior chemotherapy administration and treatment response, as well as patient and tumor characteristics. Enrollment in early-phase therapeutic trials, available through the Children's Oncology Group phase I institutions, the Pediatric Brain Tumor Consortium, or other collaborative groups is strongly encouraged in appropriately selected patients. Select ongoing studies for recurrent/refractory disease include the use of alisertib, as discussed within the Experimental Therapeutics section, reovirus in combination with sargramostim (NCT02444546), pomalidomide (NCT02415153), simvastatin, topotecan, and cyclophosphamide (NCT0239084), natural killer cell infusion (NCT02271711), melphalan, carboplatin, mannitol, and sodium thiosulfate (NCT00983398), and vorinostat and etoposide (NCT01294670).

10.9 Experimental Therapeutics

Identification of SMARCB1 mutation has led to extensive efforts to decipher the mechanisms that drive AT/RT oncogenesis, and from this several potential therapeutic targets have surfaced. Work initially based on tumor derived cell lines and subsequently on primary rhabdoid tumors as well as human cell line derived mouse xenograft has revealed upregulation of Aurora kinase A, a regulator of mitotic spindle formation and stability, in the absence of SMARCB1 function (Lee et al. 2011). Significant tumor response was seen with a specific Aurora kinase A inhibitor (MLN8237) in later experiments in rhabdoid mouse xenograft models through the Pediatric Preclinical Testing Program (PPTP) (Maris et al. 2010). Based on this preclinical data and the completion of a non-CNS recurrent/refractory solid tumor phase I COG study of MLN8237 (Mosse et al. 2012), researchers at SJCRH reported on a compassionate use single patient treatment plan for 4 patients with recurrent/refractory AT/RT treated with the Aurora kinase A inhibitor alisertib (MLN8237). This showed impressive response with disease stabilization and/or regression after 3 cycles in all 4 patients, with 2 patients with long term disease regression of 1 and 2 years, respectively (Wetmore et al. 2015). Building on the promising preclinical data, the recently opened phase II multi-institutional clinical trial SJATRT (NCT02114229) has begun to examine the role of alisertib alone or in combination with chemotherapy and radiotherapy in patients with recurrent/progressive or newly diagnosed CNS AT/RT or extra-CNS MRT. Patients are stratified into three primary strata: recurrent/progressive tumors, newly diagnosed AT/RT and <36 months of age, and newly diagnosed AT/RT and age $\geq$ 36 months. Those with recurrent/progressive disease receive single agent alisertib, while those with newly diagnosed disease receive alisertib in conjunction with age- and risk-adapted chemoradiotherapy.

Similar lines of investigation have revealed a role in the regulation of cyclin D1/cyclin dependent kinase (CDK) 4/6 activation in AT/RT tumorigenesis. Through re-introduction of SMARCB1 in a human rhabdoid cell line, it was initially shown that cells arrest in the G0-G1 phase, with an associated transcriptional repression of cyclin D1 (Betz et al. 2002; Versteege et al. 2002). Further work suggested direct recruitment of histone deacetylase activity to the cyclin D1 promoter was required for SMARCB1-dependent repression (Zhang et al. 2002). Work

from the same group that investigated the role of Aurora kinase A also demonstrated derepression of the cyclin D1 transcription with the loss of SMARCB1 in genetically engineered mouse model (GEMM), and abrogation of tumor formation with the subsequent genetic ablation of cyclin D1 (Tsikitis et al. 2005). Analysis of human primary tumors has revealed overexpression in the majority of CNS AT/RT and non-CNS MRT with confirmed SMARCB1 loss (Venneti et al. 2011). Subsequent pharmacologic inhibition of cyclin D1 in vitro and in vivo models has demonstrated sensitivity of rhabdoid tumors (Alarcon-Vargas et al. 2006). This and other data has led to the opening of an industry-led multi-center phase I study of LEE001, a small molecule inhibitor of cyclin dependent kinase 4/6 in pediatric patients with MRT and neuroblastoma (NCT001747876).

Other promising lines of investigation include SMARCB1-dependent regulation of the sonic hedgehog pathway (Shh), the Wnt/β-catenin pathway, insulin-like growth factor receptor (IGFR) signaling, and epigenetic regulation through antagonism of the polycomb repressive complex 2 (PRC2) (Ginn and Gajjar 2012; Kim and Roberts 2014). Transcriptional analysis of SMARCB1 deficient cells has revealed profiles similar to hedgehog mutant medulloblastoma, while re-introduction of SMARCB1 into rhabdoid cells leads to reductions in Shh downstream gene targets (Jagani et al. 2010). Interestingly and clinically relevant, this regulation appears to be downstream of cell surface receptors as inhibition of Smoothened had no effect on the expression of Shh targets in the absence of SMARCB1. Altered activation of the Wnt pathway resulting in expression of downstream β-catenin/TCF target genes has been shown following SMARCB1 loss, and in a similar fashion to that seen in relation to the Shh pathway, this appears to occur downstream of Wnt receptor-ligand signaling (Mora-Blanco et al. 2014). Expression analysis of IGF-1R and its ligand in both AT/RT cell lines and tumor samples has suggested an autocrine/paracrine loop (Ogino et al. 2001), and inhibition of IGF-1R through small molecule inhibitors has resulted in decreased cell proliferation and tumor formation in mice (Arcaro et al. 2007; Wohrle et al. 2013). Work initially done in flies and later in the mouse has revealed that chromatin remodeling by the SWI/SNF complex can be repressed by the polycomb group of proteins (Shao et al. 1999), and inactivation of PRC2 through loss of the catalytic subunit, enhancer of Zeste (EZH2), inhibits tumor formation following loss of SMARCB1 (Wilson et al. 2010). Subsequent studies with a small molecular inhibitor of EZH2, EPZ-6438, showed selective apoptosis of rhabdoid tumor cells in vitro and in vivo (Knutson et al. 2013). This inhibitor has moved to into human testing with ongoing early phase trials in adults with relapsed/refractory non-Hodgkin lymphoma and SMARCB1-deficient solid tumors, and a pediatric proof-of-concept phase I clinical study is planned for late 2015 (www.epizyme.com/programs/tazemetostat). As the genetic and epigenetic alterations continue to be elucidated in AT/RT, these and other targeted therapies are expected to ultimately drive a personalized treatment approach to this highly aggressive malignancy.

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CNS Germ Cell Tumors

11

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11.1 Introduction

11.1.1 Epidemiology

Malignant germ cell tumors represent approximately 3% of childhood according to cancer registries in North America and Europe (Kaatsch and Grabow 2012). In contrast, these tumors account for approximately 11% of childhood tumors in some Asian countries (Echevarria et al. 2008). The World Health Organization divides intracranial germ cell tumors into pure germinoma and nongerminomatous germ cell tumors (NGGCT). These classifications are prognostic and determine therapeutic interventions, with pure germinomas having a more favorable prognosis and requiring less therapy. Up to 65% of germ cell tumors are classified as pure germinoma and the remaining one-third included NGGCTs (Jennings et al. 1985). NGGCTs include embryonal carcinoma, endodermal sinus tumor (also known as yolk sac tumor), choriocarcinoma, teratoma (immature and mature), and mixed tumors with more than one element. Approximately 25% of NGGCTs are mixed.

Germinomas are more commonly found in males with a male to female ratio of approximately 2:1 and predominantly affect patients in their teens with approximately 75% of patients diagnosed with a primary CNS GCT being in the age range of 10–20.

Intracranial GCTs are commonly found in the pineal gland and the suprasellar regions, with pineal tumors occurring nearly twice as often as suprasellar GCTs. In 5–10% of cases both the suprasellar and pineal regions are involved; these tumors are referred to as multifocal, bifocal or multiple midline tumors and the disease is not considered metastatic if only these two regions are involved. These tumors can also arise in the basal ganglia, thalamus, cerebral hemisphere, and cerebellum (Kim et al. 1998). About 10% of the time these tumors can spread along the ventricular surfaces. Germ cell tumors may infiltrate the hypothalamus (11%), or disseminate to involve the third ventricle (22%) and spinal cord (10%) (Jennings et al. 1985).

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Germinomas have a tendency to spread through the subependymal lining and cerebrospinal fluid (CSF). Approximately 5–10% of patients present with either microscopic or macroscopic metastatic disease in the CSF at the time of diagnosis. Extraneural metastases at diagnosis are extremely uncommon.

11.1.2 Symptoms

Presenting symptoms for GCTs are dependent on the anatomical site of the primary tumor and its growth rate. The classical symptom of pineal primaries is Parinaud's syndrome (paralysis of upward gaze, headache and impaired pupillary constriction to light with preservation of accommodation). In addition tumors in this location frequently compress the Sylvian aqueduct leading to obstructive hydrocephalus, indicated by symptoms of raised intracranial pressure (diurnal headache, vomiting and lethargy). Some common presenting symptoms of suprasellar tumors include endocrine and visual field defects and/or reduced visual acuity. The frequent involvement of the pituitary stalk and the proximity of the tumor to the hypothalamic pituitary axis often lead to diabetes insipidus (DI). This symptom can sometimes precede the radiological diagnosis by up to a few years. Other presenting symptoms include growth delay, anorexia or weight gain, somnolence, mood swings, disrupted sleep pattern, electrolyte imbalances, temperature dysregulation, failure to thrive, precocious puberty, secondary amenorrhea, and panhypopituitarism. The diagnosis can be challenging given the broad spectrum of presenting symptoms and many patients exhibit symptoms for months before a diagnosis is made (Crawford et al. 2007).

11.1.3 Diagnostic Imaging

Magnetic resonance imaging (MRI) with and without contrast is the preferred method for imaging, but germ cell tumors can also be recognized on computed tomography (CT) imaging. On MRI, intracranial GCTs usually appear isointense or hypointense on T1 sequences and hyperintense on T2 sequences. These tumors typically show homogeneous enhancement with gadolinium or heterogeneous enhancement if cysts are present. NGGCTs commonly have high-signal components on T1-weighted images, representing hemorrhage, high-protein fluid or fat (Liang et al. 2002). MRI of the spine is necessary for complete staging as leptomeningeal spread of tumor can occur.

11.1.4 Histopathology

Classically, germinomas consist of large uniform cells with clear cytoplasm and a typical lymphocytic infiltration. OCT4 is a transcription factor encoded by the POU5F1 gene and is involved in the initiation, maintenance, and differentiation of pluripotent and germline cells during normal development. OCT4 is a highly specific and sensitive immunohistochemical marker for primary intracranial germinomas and may be superior to placental alkaline phosphatase (PLAP) (Hattab et al. 2005). Stains for AFP and HCG should be performed.

11.1.5 Tumor Markers

Any tumor with an elevated alpha-fetoprotein (AFP) (>10 μg/L or higher than the institutional normal range) can be assumed to contain elements of endodermal sinus (Yolk Sac) tumor, embryonal and/or immature teratoma. Pure endodermal sinus tumor or pure choriocarcinomas are often associated with dramatic elevations in AFP (>500 μg/L) or beta-hCG (>1000 IU/L), whereas immature teratomas have less dramatic elevations of AFP and/or beta-hCG. A serum AFP >1000 μg/L has recently been identified as a poor prognostic indicator (Matsutani 2008a), but since a significant proportion of these tumors have

mixed components, tumor markers alone cannot be used to risk stratify these patients. Syncytiotrophobastic cells can be present in pure germinomas and may secrete low levels of beta human chorionic gonadotropin (β-HCG). The current Children's Oncology Group Protocol allows for a level of 100, but the cut off is controversial. There is no evidence to suggest that a slight elevation of β-HCG levels is associated with a worse outcome.

Tumor markers should also be measured from the CSF. If a lumbar puncture can be safely performed, lumbar CSF is considered more accurate for tumor markers and cytology than ventricular CSF. However, if a lumbar puncture is contraindicated due to obstructive hydrocephalus and elevated risk of herniation or other reasons, then tumor markers from ventricular CSF can be used for diagnostic purpose.

11.1.6 Molecular Features

Little is currently known about the molecular features of this rare disease because of the limited tumor specimens available for research. Wang et al. (2014) reported an analysis of 62 cases by next-generation sequencing, single nucleotide polymorphism array and expression array. Although fewer therapeutic targets were found in NGGCTs, frequent AKT1 amplification and recurrent mTOR mutations were found and may be targetable with the use of AKT1/mTOR inhibitors.

11.1.7 Prognostic Factors

Older studies suggest that extent of resection is prognostic for NGGCTs (Schild et al. 1996). However, more recent series do not demonstrate a benefit to macroscopic complete resection (Matsutani 2001; Lai et al. 2015). The group from the University of Tokyo analyzed outcome data based on histology and proposed three prognostic groups: The good prognosis group includes pure germinoma and mature teratoma; the intermediate prognosis group consists of immature teratoma, teratoma with malignant transformation, and mixed tumors mainly composed of germinoma or teratoma; and the poor prognosis group consists of choriocarcinoma, yolk sac tumors, embryonal carcinoma, and mixed tumors mainly composed of malignant germ cell tumors (Matsutani et al. 1997). From a review of 32 patients with NGGCT treated in Korea using multimodality therapy, intermediate prognosis group ($p = 0.012$) and craniospinal irradiation (CSI) ($p = 0.008$) were significantly associated with increased recurrence free survival. CSI was the only significant prognostic factor ($p = 0.022$) for overall survival (OS) (Kim et al. 2012).

11.2 Management

11.2.1 Surgery

An elevated level of AFP in either the CSF or serum or high levels of beta-HCG are sufficient to classify a tumor as a NGGCT, although tumor tissue is useful for prognostic classification and biologic studies. Histologic examination is otherwise necessary to establish a definitive diagnosis of an intracranial germ cell tumor and to obtain the histologic subtype. A tissue sample should be obtained unless surgery cannot be performed safely. It is important to note that there may be sampling error in the event of a mixed tumor. When the tissue diagnosis is discordant from the CSF and/or serum markers, treatment should be based upon the result that is associated with the most malignant histology and worst prognosis so that the patient is not undertreated.

In an emergency situation, an endoscopic third ventriculostomy (ETV) or ventriculoperitoneal shunt with or without a prior external ventricular drainage (EVD) will alleviate raised intracranial pressure secondary to obstructive hydrocephalus. Otherwise a pathological diagnosis should be obtained via an elective procedure of an open or stereotactic biopsy.

In addition, an ETV enables relief of hydrocephalus without the need for an external shunt and also allows neurosurgeons to inspect the ventricles and can in some cases visualize plaques on the walls of the ventricles walls not visible on MRI imaging. When biopsied these plaques are often consistent with germinomatous ventricular spread. The prognostic significance of this remains unclear when treated with a radiation field that encompasses the whole ventricles and the current COG study does not recommend additional dose to regions of disease that cannot be visualized by MRI.

11.2.2 Extent of Resection and Germinoma

Historically (last century) the management of primary CNS germinomas was based on clinical and radiological features as well as a "radiosensitivity test". If a suspected germinoma demonstrated a marked reduction after a radiation dose of 20 Gy in 10 fractions over 2 weeks the diagnosis of germinoma was perceived as proven and no pathological verification was sought. Today, in the absence of pathologically elevated tumor markers a pathological verification is mandatory, given the rare but real presence of differential diagnoses. Given the high chemo- and radiosensitivity as well as cure rates of germinomas with conventional non-surgical oncological modalities no larger series are available to assess the benefit of an upfront attempt of a complete resection. However there is some evidence, given the location of most tumors in central, critical areas that a primary aggressive surgical approach can be associated with a high and thus avoidable morbidity rate (Nicholson et al. 2002). Primary surgery for germinomas is reserved for the very small group of patients who do not achieve a complete response at the end of first line therapy. If a significant residual mass remains and is removed this pathologically nearly always corresponds to a diagnosis of mature teratoma on histopathological assessment.

11.2.3 Extent of Resection and NGGCT

There are no definitive data that suggest that gross total resection (GTR) of NGGCT at the time of diagnosis improves either recurrence free or OS (Matsutani 2001; Lai et al. 2015). However, early results from two prospective series suggest that residual masses after chemotherapy and/or radiation in patients with intracranial NGGCTs have a poorer prognosis. In SIOP CNS GCT 96 (Calaminus et al. 2008b), 16 of 34 patients with residual masses after chemoradiotherapy experienced recurrent disease, leading to a progression-free survival (PFS) of 34%. From the Japanese GCT study group, patients with intermediate-prognosis NGGCTs, the tumor recurrence rate was 32% for those with residual mass after chemoradiation compared to 5% for those without (Matsutani 2008c). Therefore, resection of residual tumors after chemotherapy and/or RT may have a role, with a few small series suggesting that GTR may improve survival (Calaminus et al. 2005; Ogawa et al. 2003). At resection, the majority of residual masses in patients with intracranial NGGCTs after chemotherapy and/or RT are mature teratoma and/or necrotic/scar tissue (Souweidane et al. 2010), although viable tumor cells have also been observed (Calaminus et al. 2005, Ogawa et al. 2003).

Ongoing Children's Oncology Group Study, ACNS 1123 (Clinicaltrials.gov identifier: NCT01602666) suggests strong consideration for second-look surgery in patients who have residual tumors after chemoradiotherapy.

11.2.4 Role of Chemotherapy: Germinoma

Germinomas are inherently chemosensitive and it is recognized that the use of large volume and/or higher dose radiotherapy in very young children are associated with noticeable late morbidity (Calaminus et al. 2005). Thus focus in the pediatric oncology community has been for a

long time to develop primary chemotherapy strategies for germinomas albeit the proportion of germinomas diagnosed in children under the age of 10 is comparatively low. However, despite being highly chemosensitive, only a limited number of patients are chemocurable and most patients require salvage treatment including radiotherapy (Balmaceda et al. 1996). At present chemotherapy is successfully used in combined modality treatment approaches in patients with localized disease (Buckner et al. 1999; Takano et al. 2015). This aims to reduce the volume and/or the dose of radiotherapy with a reduction of late morbidity associated with radiotherapy particularly in very young children. The backbone of most reported multiagent chemotherapy protocols are platinum derivatives (particularly carboplatinum), epipodophyllotoxins (etoposide), alkylating agents (e.g., cyclophosfamide, ifosfamide) and/or antibiotics (bleomycin). The most common chemotherapy morbidities are short term but can be life threatening. These include haematological morbidities with the risk of bleeding and infection (particularly neutropenic sepsis), renal and hearing impairment, hemorrhagic cystitis, electrolyte disturbances (specifically in patients with DI) and infertility to name a few. Thus patients with known DI should not be treated in centers without easy access to a tertiary endocrinology service.

11.2.5 Role of Radiotherapy: Germinoma

Germinomas are extremely radiosensitive and 5-year survival rates of up to 95% have been reported with radiotherapy alone (Calaminus et al. 2013). Historically, the gold standard treatment for germinomas has been craniospinal radiotherapy followed by a boost to the primary site (Bamberg et al. 1999). It is generally accepted that the pattern of relapse in localized germinomas is dominated by ventricular recurrences and it is unusual to develop an isolated spinal cord relapse (Alapetite et al. 2010; Rogers et al. 2005). A review of the published literature is highly suggestive that in completely staged patients with localized germinomas irradiation of the ventricles followed by a boost to the primary tumor area gives equivalent long term control rates compared to wide field radiotherapy with craniospinal RT (Rogers et al. 2005). Historically the craniospinal axis was treated to a dose of 30–35 Gy followed by a boost of 10–20 Gy in 7–12 fractions to the primary tumor site. Over the last 2 decades consecutive studies performed in Europe have demonstrated that a reduction of the dose to the craniospinal axis to 24 Gy is equivalent to higher doses with respect to long term disease free survival. In addition, there was no loss of local control when reducing the primary tumor dose from 50–54 Gy to 40–45 Gy. In the United States (US), if radiotherapy alone is used for localized disease, the whole ventricular volume receives 24 Gy followed by boost for a total dose of 45–50 Gy to the primary and for disseminated disease, the craniospinal axis receives 24 Gy followed by a primary boost for a total dose of 45–50 Gy. Conventionally, in Europe the gross tumor volume (GTV) is defined as the whole extent of the ventricular system including the fourth ventricle with a margin of 0.5 cm to clinical target volume (CTV) and 0.3–0.5 cm from CTV to planning target volume (PTV) as defined in the current European CNS GCT 2 protocol. However in the US current protocols define the whole ventricle as a CTV and just add a 0.3–0.5 cm margin for PTV, thus using a generally a smaller final target volume for the WVRT component compared to their European counterparts. The primary tumor GTV should be defined as the visible tumor plus 0.5.–1.0 cm margin to CTV and 0.3–0.5 cm CTV to PTV margin. If clinically feasible a repeat planning scan should be performed after 1–2 weeks of the WVRT/CSA RT when defining the phase 2 volume when delivering RT alone given the potential significant and meaningful regression that can occur even after such low doses. Such an approach will further minimize the amount of normal

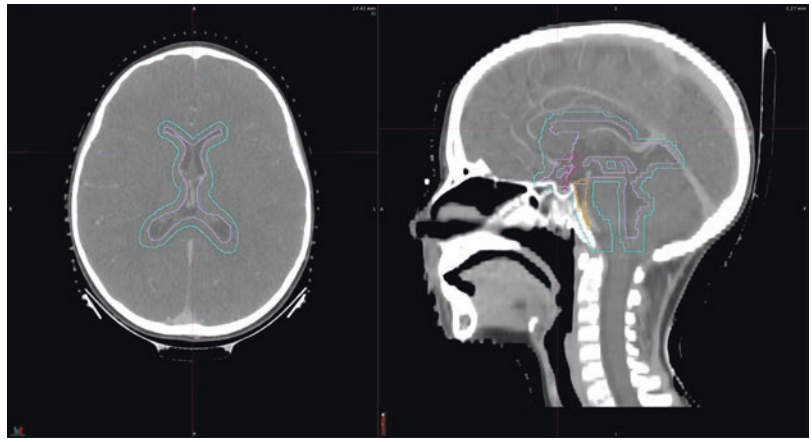

Fig. 11.1 Target volume illustration: WVRT CTV in *purple*, PTV primary+WVRT in *green*, prepontine cistern in *orange*

brain receiving higher doses of radiation. It is important to incorporate the boost volume in the upfront whole ventricular volume. Figure 11.1 demonstrates the incorporation of the prepontine cistern primary boost PTV within the WVRT PTV. If the primary radiotherapy approach in completely staged patients is the use of whole ventricular radiotherapy (WVI) dose prescription are identical with the dose prescription for craniospinal axis radiotherapy. The use of three-dimensional planning and conformal radiotherapy in conjunction with reduced volumes is likely to minimize the amount of normal tissue irradiated to high doses of radiotherapy and thus will possibly reduce late sequelae. However, using a primary complex treatment approach to cover the (WVI) volume with e.g., IMRT/VMAT or proton therapy may only lead to minimal sparing of the mean brain dose compared to more conventional approaches and particularly in teenage or older patient not translate into measurable differences in late sequelae (Raggi et al. 2008). Preliminary disease control with proton therapy compares favorably to the literature, with local control, PFS, and OS rates were 100%, 95%, and 100%, respectively after median follow up 28 months (Macdonald et al. 2011). Dosimetric comparisons demonstrate the advantage of proton radiation over IMRT for whole-ventricle radiation. Intensity-modulated proton therapy with pencil beam scanning may provide additional sparing of the brain and temporal lobes as compared with 3D-CPT for this treatment. See Fig. 11.2 for IMRT versus proton therapy WVRT. While it is unlikely that a benefit to these advanced techniques will ever be proven, minimizing radiation in children and young adults should be a priority and advanced techniques when available should be utilized for this highly curable disease.

There is currently no controversy over the volume that should be treated in patients with evidence of metastatic disease. In germinoma CSF positive disease is a risk factor for spinal seeding but does not predict for recurrence when treated with craniospinal radiotherapy. Patients with disease outside of the suprasellar and pineal gland that is noncontiguous with primary tumor should be considered to have metastatic disease. Long-term control in excess of 85–90% at 5 years is achieved even in the presence of widespread macroscopic metastatic disease if craniospinal irradiation to dose levels of 24–30 Gy and boosts to all sites of macroscopic disease up to a dose of 40–45 Gy is given (Calaminus et al. 2013).

Craniospinal radiotherapy remains the gold standard for patients with disseminated M1 and M2/3 disease. In those whose disease is in a primary atypical location, e.g., basal ganglia, craniospinal radiation is also recommended. Of note, patients with disease outside of the suprasellar and pineal gland that is noncontiguous with primary tumor should be considered to have metastatic disease (Calaminus et al. 2013).

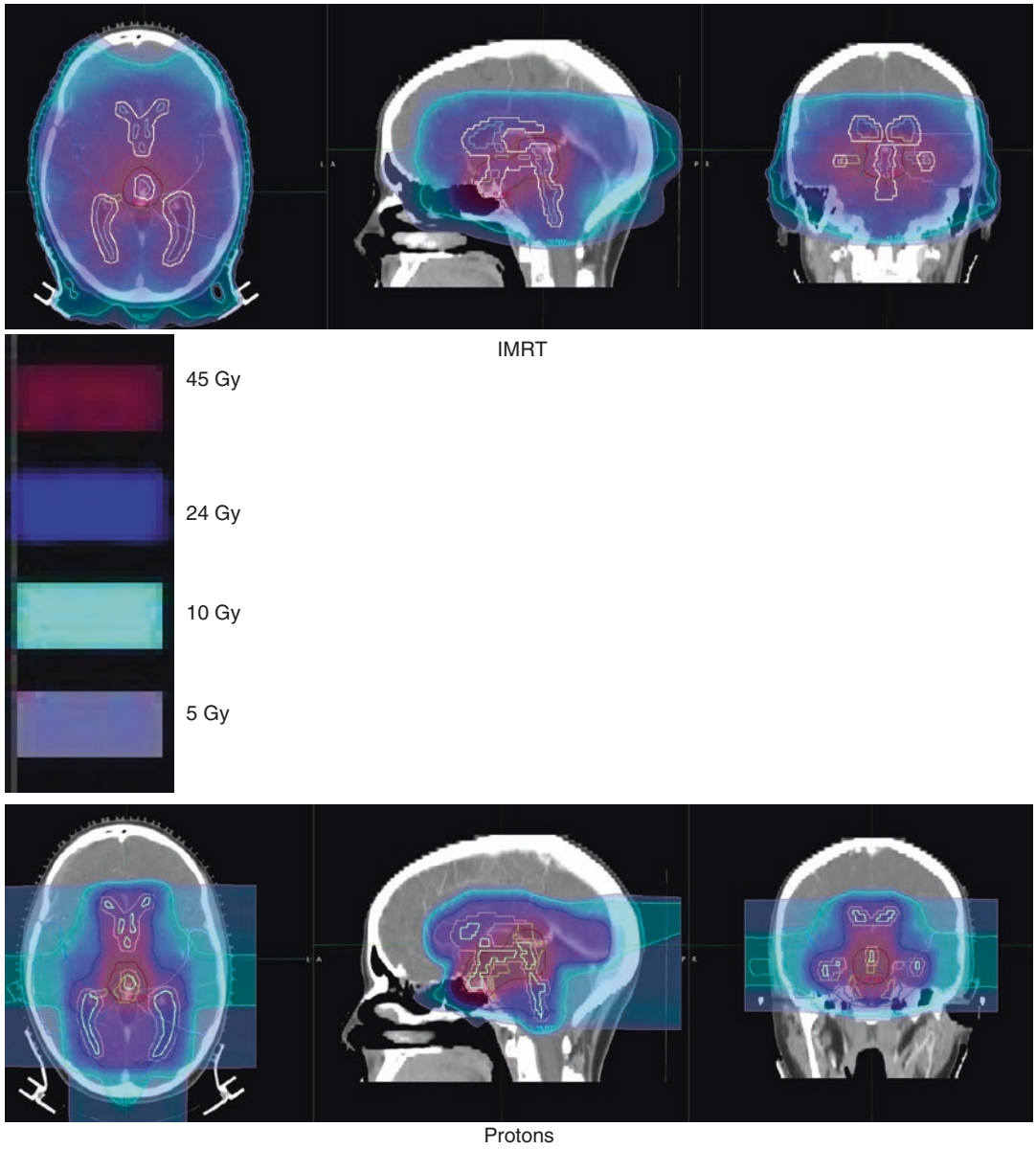

Fig. 11.2 IMRT dose distribution for WVRT and primary site boost along the top. Proton therapy dose distribution for WVRT and primary site boost along the bottom of the figure

11.2.6 Chemotherapy Followed by Reduced Radiotherapy-Localized Germinoma

The primary overall treatment approach in the US is to treat localized GCTs with chemotherapy followed by reduced dose/volume radiotherapy with the goal of reducing long-term radiotherapy-associate morbidity (Fouladi et al. 1998). There is evidence suggesting that the primary tumor dose can be lowered when combined multiagent chemotherapy has achieved a radiological complete response (Alapetite et al. 2002; Buckner et al. 1999; Matsutani et al. 1997). The SIOP CNS GCT 96 trial evaluated in a non-randomized fashion induction chemotherapy fol-

lowed by reduced radiation volume (focal radiotherapy) and compared this to the then standard of care craniospinal irradiation. The OS for the treatment groups was similar and exceeded 95% (Calaminus et al. 2013). However, there was an excess of ventricular relapses in patients treated with induction chemotherapy followed by focal radiotherapy making a case for at least WVI in localized germinoma treated with combined modality treatment a concept which is supported by other clinical study groups (Alapetite et al. 2002; Eom et al. 2008; Joo et al. 2014; Schoenfeld et al. 2014). Currently, Children's Oncology Group is investigating induction chemotherapy with 4 cycles of carboplatin/etoposide followed by response adapted radiotherapy for localized germinoma (ACNS 1123; Clinicaltrials.gov identifier: NCT01602666). Patients with a complete response will receive 18 Gy WVI followed by boost to the primary for a total dose of 30 Gy and those with a partial response receive 24 Gy WVI followed by boost to the primary for a total dose of 36 Gy. Off trial, common doses for those who receive a complete response to induction chemotherapy is 21–24 Gy WVI followed by a boost to 30–36 Gy. Patients with metastatic disease are not eligible for ACNS1123. When induction chemotherapy is used for these patients, similar radiation doses are used for those patients that achieve a complete response, but the wide field volume includes the entire craniospinal axis rather than the whole ventricle volume.

11.2.7 Role of Chemotherapy: NGGCT

Chemotherapy regimens utilizing cisplatin, etoposide and either ifosfamide or cyclophosphamide have greatly improved the outcomes of patients with non-CNS GCTs over the last few decades (Williams et al. 1987; Einhorn 1986; Einhorn and Williams 1980). There have been several trials utilizing chemotherapy alone with radiotherapy reserved for salvage for CNS GCTs. The first international germ cell study used a regimen of 4 cycles of carboplatin, etoposide, and bleomycin plus 2 additional cycles of the same or intensified with cyclophosphamide if less than a complete response. The 2-year survival rate for NGGCT was 62% on this study, and 5 patients out of 26 NGGCT patients died from causes other than disease (Balmaceda et al. 1996). Based on the fact that patients who received cyclophosphamide at the time of relapse all had a complete response, the Second International CNS GCT study group protocol looked to improved outcomes with intensification of the first two courses of therapy with the substitution of cisplatin for carboplatin and the addition of high-dose cyclophosphamide and secondly, the provision of a fifth and sixth course of therapy in patients achieving a complete response (CR) after four courses of therapy (Kellie et al. 2004). Sixteen of seventeen assessable patients achieved a CR or partial response (PR) to two courses of chemotherapy. There was one chemotherapy related death in this second study and the 5-year OS was 75% with an event-free survival (EFS) of 36%. Eleven patients relapsed. Of the relapsed patients with imaging data available, 7 (78%) of 9 had evidence of leptomeningeal or distant metastases, and 2 (22%) of 9 had recurrence localized to the primary site. Carboplatin regimens have shown similar efficacies as compared to cisplatin regimens with the added benefit of easier outpatient administration (Balmaceda et al. 1996; Baranzelli 1999; Calaminus et al. 1994; Robertson et al. 1997). Chemotherapy only strategies, however, despite resulting in high response rates, did not provide an acceptable PFS in NGGCT patients (Balmaceda and Finlay 2004; Balmaceda et al. 1996; Baranzelli 1999; Baranzelli et al. 1998; Chang et al. 1995; Kellie et al. 2004).

11.2.8 Role of Chemoradiotherapy: NGGCT

Radiation therapy plays an important role in the treatment of NGGCT; however, regimens that use radiotherapy alone have only achieved

5-year OS rates of 20–40%, and most patients relapse within 18 months of diagnosis (Dearnaley et al. 1990; Hoffman et al. 1991; Jennings et al. 1985; Matsutani et al. 1997). Similarly those who have received intensive chemotherapy alone upfront have 5-year EFS of 36% (Kellie et al. 2004). Combined modality therapy including chemotherapy and radiotherapy is considered the current standard of care (Table 11.1). Since CSI and whole brain irradiation (WBI) are associated with significant late effects, minimizing exposure to radiotherapy by stratifying patients according to risk of disease progression after combined modality therapy has been the hallmark of recent international clinical trial designs (Constine et al. 1993; Copeland et al. 1985; Mulhern et al. 1998). ACNS0122 utilized 36 Gy CSI with involved field radiation (IFR) to 54 Gy following 6 cycles of chemotherapy, and this resulted in a 2-year PFS and OS of 84.4 ± 4% and 93 ± 3%, respectively (Goldman 2008a, b, 2010; Goldman and Zhou 2009). The Japanese GCT study group treated "intermediate prognosis" patients with 5 cycles of carboplatin and etoposide followed by WVI to 30.6 Gy and IFR to 50 Gy and showed a 10-year PFS and OS rates of 81.5% and 89.3%, respectively (Matsutani 2008b, d). Patients with predominantly malignant germ cell tumor elements formed the Japanese "poor prognosis group" and were treated with 3 cycles of ifosfamide, cisplatin, etoposide and CSI. They received an additional 5 cycles of the same chemotherapy after CSI. The 10-year PFS and OS rates were 58.8% and 62.7%, respectively (Matsutani 2008b, d).

Results from the Société Internationale d'Oncologie Pédiatrique (SIOP) CNS GCT-96 supports the use of smaller field radiation for patients will all NGGCT histologies if disease is localized. NGGCT patients with localized disease (n = 102) received four courses of chemotherapy (cisplatin, ifosfamide and etoposide) followed by involved field radiotherapy (tumor bed plus margin) to 54 Gy. At a median

Table 11.1 NGGCT neoadjuvant chemotherapy and radiotherapy outcomes

Study	N	Chemotherapy regimen	Radiotherapy	5 year-PFS	5 year-OS
Robertson et al. (1997)	18	CDDP/VP-16 ×4 and post RT: VBL, Bl, VP-16, Carbo ×4	Total dose: 55 Gy, CSI for M+, field size varied	67 ± 9%	74 ± 10%
ACNS 0122 (Goldman et al. 2015)	102 localized	Cyc 1, 3, 5: Carbo/VP-16 Cyc 2, 4, 6: I/VP-16	36 Gy CSI → 18 Gy TB boost	84 ± 4%	93 ± 3%
Nakamura et al. (2011)	14[a] localized	CDDP/VP-16 ×3 or I/CDDP/VP-16 ×3	Total dose ≥ 44.5 Gy (R: 44.5–60 Gy) 24 Gy (R: 24–40 Gy) WBRT/WVRT → 15–30 Gy boost to tumor M+: 30 Gy spine	86%	93%
MAKEI 89 (Calaminus et al. 2005)	28 (M unknown)	Bl/VP-16/CDDP ×2 and VBL/I/CDDP ×2	Total dose: 50 Gy 30 Gy CSI → 20 Gy TB boost	57 ± 9%	
SIOP 96 (Calaminus 2005b; Calaminus et al. 2008a)		CDDP/VP-16/I ×4	54 Gy IFRT for M0 M+ 30 Gy CSI + 24 Gy TB boost	PFS: <CR: 37 ± 10% Cr: 86 ± 4%	

N number of patients, *CDDP* cisplatin, *VP-16* etoposide, *Carbo* Carboplatin, *I* ifosfamide, *VBL* vinblastine, *Bl* bleomycin

[a]Of note all patients except for 1 underwent GTR of tumor if residual disease was present after chemotherapy and radiotherapy

follow-up of 39 months, the reported PFS for the M0 patients was 67% (Calaminus 2003, 2005a). There were 25 relapses in this group including 17 local, 2 ventricular, 1 distant, and 5 combined.

The outcome data of patients enrolled on ACNS0122 are very promising for patients who achieved a CR (complete radiographic and tumor marker response) and PR (>65% reduction in measurable disease radiographically and normalization of tumor markers) after induction chemotherapy (Goldman et al. 2015). Overall, induction chemotherapy produced an objective response rate of 69% (CR or PR) in the evaluable patients. Of the 15 patients who underwent second-look surgery after induction therapy, only 2 (13%) had residual NGGCTs. Nine patients had teratomas, 6 of which were mature and 3 were malignant. Patients proceeded to 36 Gy CSI followed by a tumor bed boost for a total dose of 54 Gy. The median follow up time for the patients without an event was 5.1 years. Five-year EFS and OS were 84% and 93%, respectively. Patients who did not achieve CR or PR were recommended to undergo consolidation chemotherapy with thiotepa and etoposide followed by peripheral blood stem cell rescue and then craniospinal radiotherapy with tumor bed boost. The encouraging results of this study and efficacy of this chemotherapy regimen led to the use of the same chemotherapeutic regimen in the current COG ACNS 1123 (NCT01602666), in an attempt to maintain a relevant comparison group. This trial is a Phase II trial of response-based radiation therapy for patients with localized tumors. Patients need to achieve a CR either by chemotherapy alone or chemotherapy and second-look surgery confirming mature teratoma or scar/fibrosis to receive radiation to the whole ventricle plus a tumor boost, instead of CSI. The dose is 30.6 Gy to the whole ventricle followed by an involved field boost of 23.4 Gy for a total dose of 54 Gy. Results from this trial may influence practice patterns in the US for children with localized NGGCT who have an excellent response to chemotherapy.

11.3 Outcomes and Late Effects

Acharya et al. (2015) performed a Surveillance, Epidemiology, and End Results (SEER) database analysis of long term outcomes for patients with CNS germ cell tumors. This report included 405 patients with pure germinoma and 94 NGGCT patients. Interestingly, OS at 20 and 30 years for GGCTs was 84.1% and 61.9%, respectively, and was 86.7% for NGGCTs at both time points. Five-year survivors experienced a tenfold increase in mortality risk compared with their peers. Five-year survivors of pure germinoma experienced a nearly 59-fold increase in risk of death from stroke. At 25 years, the cumulative incidence of death due to cancer and subsequent malignancy was 16% and 6.0%, respectively. The group concluded that although CNS germinomas have favorable cure rates, late recurrences, subsequent malignancies, and stroke significantly affect long-term survival.

A Japanese group reviewed their neuroendocrine and height outcomes for patients treated with chemoradiotherapy. Median total radiotherapy dose was 36 Gy for pure germinoma and 45 Gy for NGGCTs.

Treatment outcomes, growth height, and neuroendocrine functions in patients with intracranial germ cell tumors treated with chemoradiation therapy (Odagiri et al. 2012). The standard deviation scores (SDSs) of final heights recorded at the last assessment tended to be lower than those at initial diagnosis. This was also seen in patients with primary tumors located away from the hypothalamic-pituitary axis (HPA). In 16 patients with tumors adjacent to the HPA, 8 showed metabolic changes suggestive of hypothalamic obesity and/or growth hormone deficiency, and 13 had other pituitary hormone deficiencies. In contrast, 4 of 5 patients with tumors away from the HPA did not show any neuroendocrine dysfunctions except for a tendency to short stature.

The group from the Hospital for Sick Children in Toronto performed a longitudinal neurocognitive study of CNS germ cell tumor patients (Mabbott et al. 2011). Results demonstrated that intelligence, academic functioning, and receptive

vocabulary were not significantly compromised in most patients. However, working memory, information processing speed, and visual memory declined significantly over time in all patients. Patients with pineal tumors showed early and stable deficits, whereas patients with suprasellar and bifocal tumors showed more protracted declines. Results were also impacted by radiotherapy treatment volume with patients treated with ventricular radiation having better outcomes than those who received craniospinal radiation.

11.4 Growing Teratoma Syndrome and Role of Second Look Surgery

Often times, residual masses post-therapy can be necrosis and fibrosis devoid of tumor or even mature growing teratoma, a phenomenon known as growing teratoma syndrome (O'Callaghan et al. 1997). It is important to distinguish this entity from residual active or progressive malignancy. On ACNS0122 study, there has been 21 second-look surgeries on 19 patients. The pathology on these surgeries included 13 teratomas (4 growing teratoma syndrome), 4 fibrosis devoid of tumor and 4 NGGCT (Goldman 2010).

Conclusions

Germ cell tumors represent a heterogeneous group of tumors that occur predominantly in older children or very young adults. Although these patients are more likely to be full grown, they still represent a young population of cancer patients that have a high likelihood of being long-term survivors. Current studies and treatment regimens aim to provide a high likelihood of cure while minimizing long-term adverse effects are treatment. The most widely utilized regimens for pure germinoma include chemotherapy followed by reduced dose RT (whole vent followed by boost for localized/bifocal and CSI followed by boost for disseminated disease). For NGGCT, cure is more difficult to achieve, but recent trials show excellent results for chemotherapy followed by CSI and a focal boost to at least 50 Gy. Current efforts aim to reduce the RT volume from CSI to WVRT while maintaining a dose of 50–54 Gy to primary disease, which seems critical to long-term disease control. Future investigations may allow for novel agents to help maximize our therapeutic ratio for these patients.

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Childhood Ependymoma

12

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12.1 Introduction

Childhood ependymoma (EP) is a complex and malignant tumor that often arises in difficult locations in young children who suffer from the effects of tumor and aggressive surgery prior to consideration of adjuvant therapy, which is high-dose irradiation. Radiation therapy for EP has evolved considerably during the past 25 years both in methods and indications. Highly-focused irradiation administered post-operatively with limited margins surrounding the residual tumor and/or tumor bed in children of all ages is the current standard. The past history of radiation therapy for EP includes larger treatment volumes, even craniospinal irradiation, restricted to older children and delay or omission of radiation therapy in young patients. Indeed, during an era when the use of radiation therapy has been removed as a standard primary or adjuvant therapy for many childhood tumors, the use of radiation therapy has increased in the treatment of childhood EP and the excellent results and improved functional outcomes have served as an example of the benefit of newer treatment methods and template for the use of radiation therapy in the treatment of other tumors that involved young children.

Ependymoma is a neuroepithelial tumor that typically arises from the ependymal lining of the ventricular system or central canal of the spinal cord (Smyth et al. 2000). Approximately 90% of pediatric EPs are intracranial, with most involving the ependymal lining of the fourth ventricle. The most common location for EP is the posterior fossa (PF) (Smyth et al. 2000; Vaidya et al. 2012). Up to 30% of intracranial EPs are located in the supratentorial (ST) compartment arising from the lateral or third ventricle or as intraparenchymal lesions remote from the ventricular system (Reni et al. 2007; Smyth et al. 2000). Spinal cord EPs (occurring in <10% of pediatric patients) (Reni et al. 2007) are common in the central canal of the cervical-thoracic spinal cord and appear rarely as myxopapillary tumors in the filum terminale, conus-medullaris, or cauda equina (Teo et al. 2003; Zacharoulis and Moreno 2009) (Fig. 12.1).

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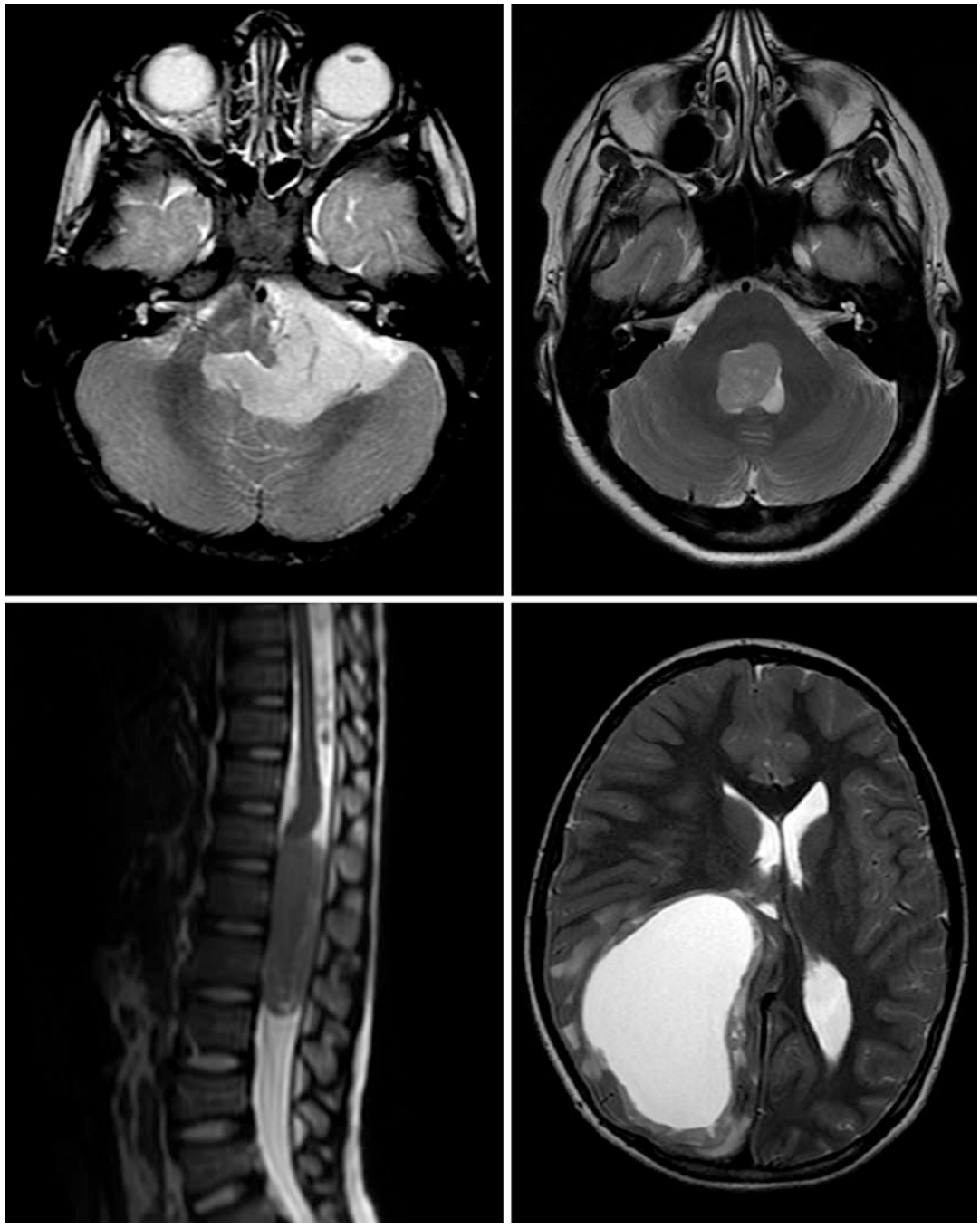

Fig. 12.1 Left cerebellopontine angle ependymoma (*upper left*), fourth ventricle ependymoma (*upper right*), spinal cord ependymoma (*lower left*), and right fronto-parietal ependymoma (*lower right*)

EP accounts for 6–10% of brain tumors in children. At presentation, current standard initial treatment for children with EP consists of maximally safe surgical resection, with the goal of gross total resection (GTR), and post-operative standard fractionated radiation therapy (RT) for microscopic residual tumor (Hoffman et al. 2014). By using this approach, 5-year overall

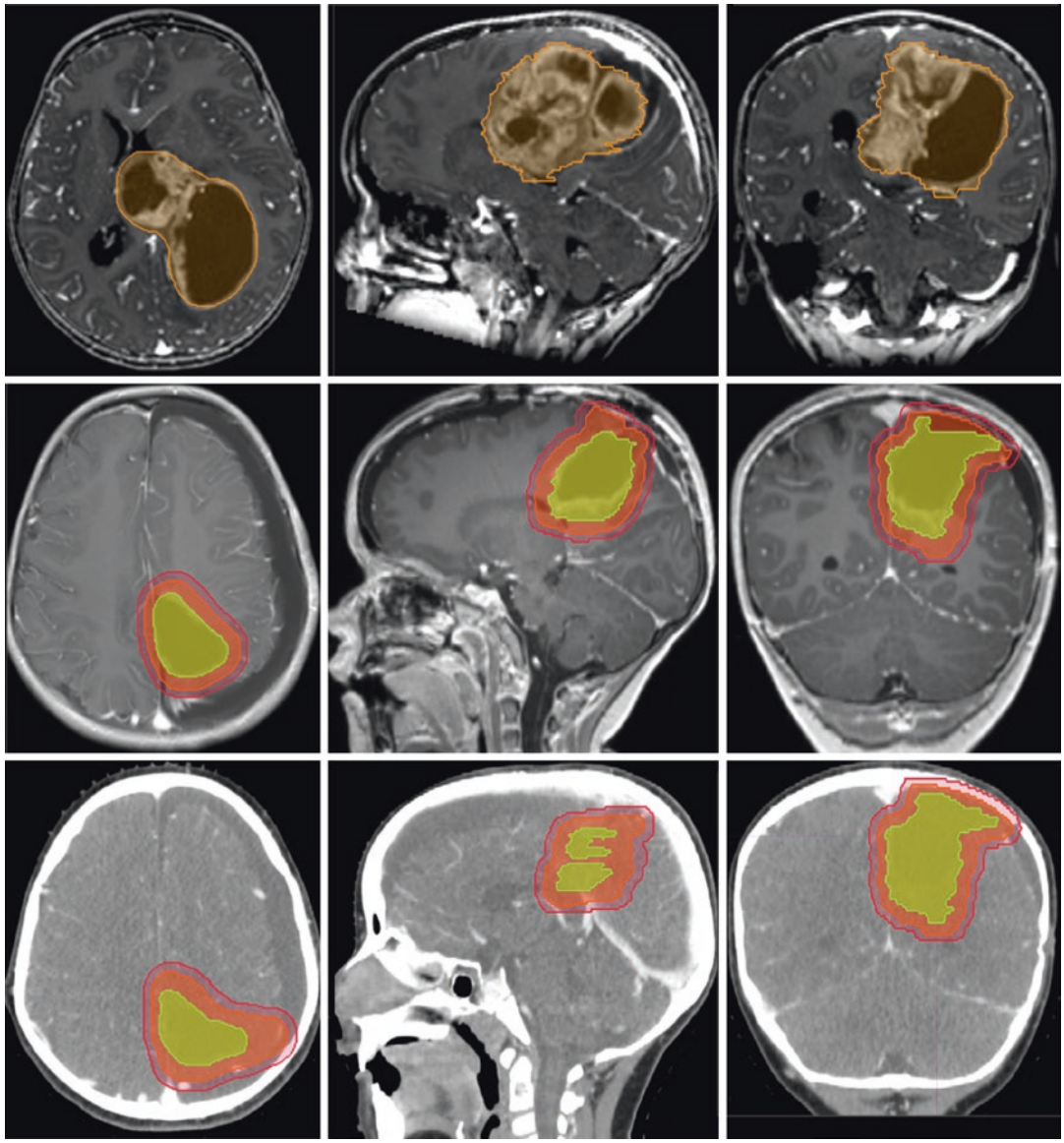

Fig. 12.2 Supratentorial ependymoma pre-operative (*upper row*) MR images; post-operative (*middle row*) MR images showing gross-tumor volume (*yellow*), clinical target volume (*orange*), and planning target volume (*red*); post-operative contrast-enhanced treatment planning CT (*lower row*) showing target volumes as outlined on MR

survival (OS) and event-free survival (EFS) of 86% and 55%, respectively, have been achieved (Gajjar et al. 2013). EP can spread locally into adjacent structures or via the cerebrospinal fluid (CSF) throughout the subarachnoid space (drop metastasis) (Paulino et al. 2002), especially in the case of high-grade tumors. "Sugar coating" of the meninges does not constitute metastatic disease and is likely an inflammatory process. EP metastases most often appear to be nodular (Fig. 12.2).

The clinical behavior of ependymal tumors is highly variable, and approximately 40% of patients might not be cured because of the paucity of effective and easily available treatment options (Merchant 2009). Surgical resection is the first line of treatment. Several studies have

shown the benefits of adjuvant radiotherapy, although the ideal volume of irradiation remains controversial. The role of chemotherapy, however, is uncertain, with little evidence supporting its use (Vaidya et al. 2012).

The prognosis for pediatric EP remains poorer than that for other brain tumors. Definitive prognostic factors include extent of tumor resection, presence of metastases at initial diagnosis, and age at presentation (Reni et al. 2007; Shim et al. 2009). The significance of factors such as tumor location and histopathologic grade and the role of adjuvant therapy remain unclear (Reni et al. 2007, Shim et al. 2009). Research is currently focused on the molecular subtyping of EP to define diverse subgroups and more accurately predict the expected behavior of each subgroup (Vaidya et al. 2012).

12.2 Prognostic Factors

12.2.1 Age at Presentation

Most studies on pediatric EP have reported younger age at presentation as an adverse prognostic factor. In three studies, the 5-year OS was 22–42% in children aged 3 years or younger compared with 69–75% for those older than 3 years (Paulino et al. 2002; Perilongo et al. 1997; Pollack et al. 1995). Delay in diagnosis due to non-specific signs or symptoms (Tamburrini et al. 2009), more aggressive tumor biology (Nazar et al. 1990), delay or avoidance of irradiation (Duffner et al. 1998), and lower radiation doses (Duffner et al. 1998) can affect results in younger children.

12.2.2 Extent of Surgical Resection

The extent of resection is the single most important prognostic factor for EP (Duffner et al. 1993; Massimino et al. 2004; Merchant et al. 2009; Paulino et al. 2002; Perilongo et al. 1997; Pollack et al. 1995; Robertson et al. 1998; Rousseau et al. 1994). Advances in surgical techniques, such as operating microscopes and image-guided resection, have led to improvement in patient outcomes. A study reported that the 5-year progression-free survival (PFS) was 51–79% for patients who underwent complete resection compared with 9–44% for those with underwent subtotal resection (STR) (Vaidya et al. 2012). The fact that more than 90% of tumor recurrence occurs locally highlights the importance of complete resection (Chiu et al. 1992; Nazar et al. 1990).

12.2.3 Site of Primary Tumor

The ability to resect a tumor is highly dependent on the tumor site within the central nervous system (CNS). In a review of 10 studies reporting 307 patients, complete resection was achieved in 53% of 128 patients with ST-EP (Bouffet et al. 1998). Complete resection was achieved in only 29% of the 179 children with infratentorial lesions. Spinal cord tumors, however, were excised without affecting function in only 27–45% of patients. This disparity arises because surgical resection is more difficult for PF-EPs because of frequent involvement of the brainstem and multiple cranial nerves (Tamburrini et al. 2009). Higher rates of complete resection for ST-EPs likely explain the better prognosis and disease-free survival rates for children with these tumors (Vaidya et al. 2012).

The current standard of care for EP includes maximal safe surgical resection, followed by focal radiotherapy (Merchant 2009; Merchant et al. 2009). Several reports indicate that there was no tumor recurrence in a subset of patients with completely resected ST tumors even in the absence of adjuvant therapy (Venkatramani et al. 2012), which underscores the need for better stratification of patients. Furthermore, although adjuvant chemotherapy continues to be a part of many trial protocols, especially in young children for avoiding or delaying RT, several clinical trials have found no survival benefit of adding chemotherapy at the time of primary diagnosis or at recurrence (Bouffet et al. 2009; Bouffet and Foreman 1999; Duffner et al. 1993).

12.2.4 Histopathologic Grade

Accurate histopathologic diagnosis according to the World Health Organization (WHO) classification for CNS tumors (Ellison et al. 2011; Louis et al. 2007; Pajtler et al. 2015) is challenging for ependymal tumors. Distinction between grade II EP and grade III anaplastic EP is often difficult, with poor inter-observer reproducibility, even if grading is performed by experienced neuropathologists (Ellison et al. 2011). Grade I EP, or myxopapillary (occurring in the spine) and subependymomas (SEs; occurring across all compartments), generally have more readily distinguishable histopathologic characteristics. However, the grading of EPs can be complicated because many tumors show isolated areas, each representing distinct grades, which presents a challenge to predict which tumor component will influence the overall biologic behavior (Pajtler et al. 2015).

The role of histopathologic grade as a prognostic factor remains contradictory. A review reported that the 5-year OS was 10–47% for patients with anaplastic EP and 55–87% for those with low-grade tumors (Reni et al. 2007). Contrary to this, some studies have reported no differences in survival—or even an opposite survival trend—for patients with anaplastic EP or low-grade tumors. Two studies reported a 5-year PFS of 78% and 46% for patients with anaplastic tumors and a 5-year PFS of 17% and 57% for those with low-grade tumors (Robertson et al. 1998; Rousseau et al. 1994). Classification of EP tumors by molecular subtype is likely to obviate the need for conventional histopathologic classification in the coming years.

12.2.5 Molecular Prognostic Factors

Despite the histopathologic similarities among variants of EP at different anatomic sites, the molecular biology of EP remains heterogeneous and is associated with distinct genetic and epigenetic alterations as well as diverse transcriptional programs (Carter et al. 2002; Dyer et al. 2002; Korshunov et al. 2010; Mack et al. 2014; Mendrzyk et al. 2006; Parker et al. 2014; Wani et al. 2012; Witt et al. 2011). Functional cross-species studies reveal that these molecular differences reflect regionally discrete cells of origin (Johnson et al. 2010; Parker et al. 2014; Taylor et al. 2005). An association between neurofibromatosis type 2 (i.e., germline mutations in the *NF2* gene) as well as sporadic mutations in *NF2* has long been known as a hallmark genetic aberration in spinal EP (Ebert et al. 1999; Rubio et al. 1994).

Other immunohistochemical markers have not adequately reflected the biologic heterogeneity of EP and cannot reliably distinguish between histologic grades and subgroups of EPs. The only molecular marker that has been consistently associated with unfavorable outcome is gain of chromosome arm 1q (Godfraind et al. 2012; Kilday et al. 2012; Korshunov et al. 2010; Mendrzyk et al. 2006; Modena et al. 2012), particularly in childhood PF-EP. Homozygous deletion of the CDKN2A/B locus is another marker associated with inferior prognosis, mainly in ST-EP (Korshunov et al. 2010).

Recent large-scale genomic and epigenomic studies have revealed the first driver genes in ST-EPs. Fusions between *RELA*, which encodes an NF-kB component, and the poorly characterized gene *C11orf95* resulting from chromothripsis (local chromosome shattering) on chromosome 11 occur in more than 70% of patients with ST-EPs (Parker et al. 2014). Strikingly, the *C11orf95–RELA* fusion alone can drive tumorigenesis when aberrantly expressed in neural stem cells (Parker et al. 2014).

For PF-EPs, two distinct molecular subgroups were consistently identified in two independent studies that used different methods and non-overlapping patient cohorts (Wani et al. 2012, Witt et al. 2011). These subgroups [provisionally termed PF Group A (PFA) and PF Group B (PFB)] are associated with distinct transcriptomic, genetic, epigenetic, and clinical features and are much more informative than WHO grading alone (Archer and Pomeroy 2011).

In 2015, Pajtler et al. used genome-wide DNA methylation patterns to identify nine distinct molecular subgroups of ependymal tumors across all age groups (three subtypes in each anatomic compartment of the CNS) (Pajtler et al. 2015):

- Spine (SP), with subtypes SE, MPE, and EP (with NF2 association), all associated with excellent OS and PFS
- PF, with subtypes SE, EP-A, and EP-B
- ST, with subtypes SE, EP-YAP1, and EP-*RELA*

These molecular subgroups are genetically, epigenetically, transcriptionally, demographically, and clinically distinct. Whether they also have different cells of origin, as suggested by Johnson et al., remains to be proven in further functional studies (Johnson et al. 2010). A biologic classification might help researchers and clinicians to better understand the heterogeneity of this disease as compared with the epigenetic subgroups of medulloblastoma (Kool et al. 2012). For example, Pajtler et al. showed that patients in the PF-EP-A and ST-EP-*RELA* (*C11orf95–RELA* fusion) subgroups had dismal outcomes with current treatment approaches. These patients were in the high-risk category, with a 10-year OS of approximately 50% and a 10-year PFS of approximately 20% (Pajtler et al. 2015).

12.3 Radiation Therapy

12.3.1 Radiation Dose

There is sufficient evidence to show that adjuvant post-operative RT, when compared to surgery alone, improves local control and is associated with a more favorable prognosis. Although data from prospective randomized trials are scarce largely due to rarity of the tumor, multiple retrospective studies have demonstrated that adjuvant RT improves local control as well as OS in patients with EP. Thus, RT is currently considered to be standard adjuvant therapy after the resection of intracranial EP (Chan and McMullen 2012; Stuben et al. 1997). The total dose varies from 45 to 54 Gy to the tumor bed in 1.5–1.8 Gy/fraction. Boost doses of approximately 10 Gy have been recommended for macroscopic disease in some studies (Reni et al. 2007; Stuben et al. 1997). Two studies showed that higher radiation doses can improve outcomes in intracranial EP: the 5-year OS for patients given a dose of >50 Gy was 58% and 51%, compared with 33% and 18% for those given a dose of ≤50 Gy (Chiu et al. 1992; Goldwein et al. 1990). Dose escalation to 66 Gy by using hyper-fractionated RT was safe but was not associated with an improvement in outcome (Conter et al. 2009).

A total dose of 54 Gy is widely considered as the minimum dose required for local tumor control with gross residual and tumor bed concentrations of microscopic disease. Higher doses are considered to be more efficacious based on the first principles of RT and our understanding that local failure is a dominant component of first failure. The standard RT dose for patients without residual disease is 54–59.4 Gy in 1.8 Gy/fraction, and a more recent series used 59.4 Gy at 1.8 Gy/day for all patients except those under the age of 18 months who underwent GTR and had been treated with a dose of 54 Gy.

Local failure is predominant mode of failure in children with treated with post-operative radiation therapy for ependymoma. Beginning with the POG-9132 study (1991–1994) the primary site dose was escalated to 69.6 Gy using a hyper-fractionated approach (1.2 Gy BID) and later to 59.4 Gy (1.8 Gy daily) consistent with the treatment of other aggressive or high-grade brain tumors. Based on our experience which includes a high-rate of gross-total resection (>80%) the cumulative incidence of local failure is approximately 16.3% (9.6–23.0, 95% CI) when measured at 5–7 years (Table 12.1).

12.3.2 Irradiation Volume

A controversial aspect in the RT management of pediatric EP is determining the appropriate field size and volume for irradiation [local field or craniospinal irradiation (CSI)]. CSI involves prophylactic irradiation of the entire craniospinal axis, with additional focal boost to tumor sites (Merchant and Fouladi 2005).

Previous studies showed that EP had a predilection for leptomeningeal failures with high rates of metastatic seeding (32%) (Merchant et al. 1997; Nazar et al. 1990; Salazar et al. 1975). Consequently, CSI was the standard RT

Table 12.1 Radiation guidelines reported in single institution and cooperative groups studies and reports

Source	Treatment dates	Age restriction	Target volume	CTV Margin	Dose cGy/CcGE	Total (IT/ST)	Modality
US Cooperative Group Studies							
POG-9132 (Kovnar et al. 1998)	1991–1994	>36 months	Pre-op	2.0 cm	69.6/1.2 BID	31 (31/0)	Photon
CCG-9942 (Garvin et al. 2012)	1995–1999	>36 months	Pre-op	1.5 cm	59.4/1.8 55.8/1.8	84 (49/35)	Photon
ACNS0121 (Merchant 2001 (ClinicalTrials.gov Identified: NCT00027846))	2003–2007	>12 months	Post-op	1.0 cm	59.4/1.8 54.0/1.8	378 (TBD)	Photon-Proton
ACNS0831 (Smith 2010 (ClinicalTrials.gov Identifier: NCT01096368))	2010-Present	>12 months	Post-op	0.5 cm	59.4/1.8 54.0/1.8	>300 (TBD)	Photon-Proton
Single or Multi-Institution Studies							
St. Jude (Merchant et al. 2009)	1997–2003	>12 months	Post-op	1.0 cm	59.4/1.8 54.0/1.8	153 (122/31)	Photon
PSI (Ares et al. 2016)	2004–2013	>12 months	Post-op	1.0–0.5 cm	59.4/1.8	50 (36/14)	Proton-PBS only
French Cohort (Ducassou et al. 2015)	2000–2013	>36 months	No details	No details	59.4/1.8 54.0/1.8	177 (136/41)	Photon-Proton
Italian Cohort (Gandola et al. 2015)	2003-	>36 months	No details	No details	59.4/1.8 67.8/1.8–2.0	143 (TBD)	Photon

approach used for EP for many years. These earlier studies had flaws and biases, including autopsy findings of seeding in patients who died because of local disease. Another problem was that these studies were largely conducted before the introduction of magnetic resonance imaging (MRI), when the extent of disease was not accurately known. The improvement in imaging techniques to adequately stage the craniospinal axis and modern patterns of failure studies have shown that isolated spinal failures for intracranial EP are rare even in the absence of CSI (Perilongo et al. 1997; Rezai et al. 1996; Taylor 2004). More recent studies have reported seeding rates of only 3–10% (Merchant et al. 1997; Pollack et al. 1995; Vanuytsel and Brada 1991; Wallner et al. 1986). Therefore, the majority of spinal failures will occur in patients with preexisting local failure (Rezai et al. 1996; Sutton et al. 1990). Reviews have confirmed that patients with localized disease do not require prophylactic CSI irradiation, because more than 90% of the recurrence occurs locally (Chiu et al. 1992; Nazar et al. 1990) and the additional morbidity associated with CSI cannot be justified. Even for anaplastic and infratentorial EP, which are associated with a poor prognosis, prophylactic CSI has not resulted in a survival benefit (Timmermann et al. 2005). Thus, local-field RT has become the standard treatment volume for intracranial EP (Chan and Mcmullen 2012).

Defining the clinical target volume (CTV) for local-field RT in EP has been the subject of intense debate. A large study by Merchant et al. established that a 1 cm CTV margin around the tumor cavity to account for the microscopic extent of disease is sufficient to achieve high levels of local control in the setting of GTR

Table 12.2 Clinical target volume margins by clinical trial

Clinical trial (sponsor)	CTV margin	Month/year of activation and identifier (clinicaltrials.gov)
ACNS0121 (COG)	Post-op tumor bed + 1.0 cm	August 2003 NCT00027846
SJYC07 (St. Jude)	Post-op tumor bed + 0.5 cm	November 2007 NCT00602667
ACNS0831 (COG)	Post-op tumor bed + 0.5 cm	March 2010 NCT01096368

Abbreviations: *CTV* clinical target volume, *COG* Children's Oncology Group, *post-op* post-operative, *St. Jude*, St. Jude Children's Research Hospital

(Merchant et al. 1999). This 1 cm margin was the established CTV margin used in the recent Children's Oncology Group (COG) trial ACNS0121. Interestingly, patterns of failure and treatment effects data from St. Jude Children's Research Hospital (St. Jude) indicate that a smaller CTV margin can likely allow adequate local control and possibly reduce neurocognitive late effects (Merchant et al. 2002b). The COG trial ACNS0831 is investigating a further reduction in treatment volume to a 5 mm CTV to 54 Gy and no CTV expansion for the final boost treatment to 59.4 Gy (Chan and Mcmullen 2012) (Table 12.2).

12.4 Radiation-Related Complications

12.4.1 Neurologic, Endocrine, and Cognitive Effects

The potential late effects of irradiation have led to past and present decisions about the indications for radiation therapy in the treatment of EP and the need to question its use in selected patients. Recovery of neurological impairment after aggressive neurosurgery is not impeded by radiation therapy although one might wonder whether the rate of improvement would be greater in the non-irradiated child (Merchant et al. 2010; Morris et al. 2009). Hearing loss is uncommon from radiation therapy alone and more easily avoided with the application of advanced radiation therapy methods and prioritizing avoidance of the hearing apparatus (Hua et al. 2008). Given the relatively common posterior fossa location and its distance from the hormone-producing regions of the brain, avoidance of the hypothalamic pituitary axis in treatment planning has become easier leading to the expectation of fewer cases of growth, thyroid, adrenal, and gonadotropin deficiency. Nevertheless, collateral irradiation of the hypothalamic-pituitary axis, even with very low doses, may result over many years in the development of hormone deficiency (Merchant et al. 2011).

Although 20 years has passed since the activation of the St. Jude RT1 trial that included very young children with EP and frontline post-operative irradiation has been adopted by the pediatric cooperative groups in successive trials because of published data and personal experiences, investigators remain curious about cognitive function in this group of children, especially those who were very young at the time of treatment. The data from the St. Jude series thoroughly cover the first 5 years after radiation therapy with assessment of global intelligence, memory, behavior, learning, adaptive function, and academic achievement (Conklin et al. 2008; Di Pinto et al. 2010; Netson et al. 2012); however, there is an opportunity to learn more by assessing this group that has now survived more than 10 years and beyond regarding their overall function and quality of life.

12.4.2 Necrosis, Vasculopathy, and Secondary Brain Tumors

The most concerning and rare complications of radiation therapy are necrosis, vasculopathy, and secondary brain tumors are challenging to understand. As expected necrosis after frontline treatment most often occurs 3–6 months after treatment and manifests itself by asymptomatic imaging changes including T2-prolongation and parenchymal enhancement. And while it's often possible to review a particular case of necrosis and identify factors attributing to the event such

as mass effect from tumor, tumor and surgery-related ischemia, site-specific neurological injury, increased intracranial pressure from hydrocephalus and/or CSF shunt failure, history of infectious or chemotherapy-related toxicity there are cases when necrosis clearly arises from the irradiation of normal tissues in a patient that otherwise may not have predisposing factors. The St. Jude series which assessed more than 100 children with posterior fossa EP reported the cumulative incidence of necrosis to be approximately 2.5% when measured at any time after 1 year (Merchant et al. 2009). All three cases of necrosis in that series occurred during the first year. No other comparable data exist. Vasculopathy is a rare complication of irradiation, in the same St. Jude series there was only one case reported. Clearly irradiation of the central vasculature is required for vasculopathy to develop and this may be avoided in the majority of cases. Finally, secondary brain tumor including malignant glioma is one of the most devastating complications of irradiation. The brainstem is most often involved and all cases are fatal. The St. Jude series reported the incidence of malignant brain tumor at 7 years to be approximately 2.3% (Merchant et al. 2009).

12.4.3 Imaging and Treatment Planning

EP can exhibit heterogeneous enhancement (i.e., portions of the gross tumor might not show enhancement). Both T1 and T2 MRI might be required to adequately establish the full extent of the target. Given the significant anatomic distortion after surgery for EPs, particularly those in the PF, proper definition of the resection cavity must include review of pre-operative and post-operative MRI to include the full extent of the initial disease within the gross target volume (Chan and Mcmullen 2012).

The combination of computed tomography planning and MRI has some limitations in the PF, and some common artifacts in that region can lead to misinterpretation of the target definition. Alignment of the spinal cord can be problematic when diagnostic images are acquired in a position different from that used for treatment. MRI to identify the target should be performed in the same simulation position to improve the quality of image fusion and target delineation.

Neuroimaging has been shown to be important beyond the determination of extent of resection. Sabin et al. (2016) reviewed children treated with post-operative irradiation to examine the association between tumor location in the posterior fossa and extent of resection, pattern of recurrence and survival status. There was no association between pattern of recurrence and survival status based on tumor location or difference in survival comparing patients with centered tumors to those with lateralized tumors; however, considering only patients who died of disease, there was a statistically significant difference in survival favoring centered tumors.

12.4.4 Very Young Children

The treatment of very young children with primary brain tumors is particularly challenging. For very young patients with medulloblastoma, standard management is chemotherapy to delay CSI until the patient reaches 3 years of age. The same approach has been applied to EP. However, a delay in RT, even in the presence of chemotherapy, tends to increase the risk of tumor recurrence. The St. Jude RT-1 trial showed that patients who received preradiation chemotherapy had a poorer 3-year PFS than those receiving immediate adjuvant irradiation (49% vs. 84%, respectively) (Merchant et al. 2002a). Patients with EP who are younger than 3 years can be treated with RT at an early age without severe toxicity (Merchant et al. 2005). EP has a more limited treatment volume and tends to occur in the PF, thus allowing the sparing of most structures involved in higher cognitive function. In the recently completed ACNS0121 trial, patients aged 1 year and older could receive upfront conformal RT (Chan and Mcmullen 2012).

Radiation dose and volume effects have been establised for children with EP. Merchant and colleagues showed that radiation dosimetry

predicts IQ after conformal radiation therapy in pediatric patients with localized EP. The key finding of this investigation which included 88 children who underwent 327 IQ tests during a 5 year interval that included baseline testing was that unique dose-volume intervals of the supratentorial brain could be used to estimate IQ after conformal radiation therapy provided age was included in the model (Merchant et al. 2005). Further, the same group showed the importance of the cerebellum. Mean posterior cerebellum dose was found to be associated with change in IQ and academic achievement in children with posterior fossa EP, thus, sparing portions of the cerebellum should also be considered in treatment planning for these patients (Merchant et al. 2014). Key to these modeling investigations was the sample size, baseline testing, and accounting for clinical factors and treatments and procedures other than irradiation that might impact outcome. The impact of hydrocephalus is a poignant example (Merchant et al. 2004a; Merchant et al. 2014).

The need for adjuvant RT in patients with completely resected ST-EP is also under investigation. Published series of spinal EPs show that complete resection alone is often sufficient to achieve long-term local control (Ferrante et al. 1992; Hanbali et al. 2002). GTR for EP of the fourth ventricle is challenging, with microscopic complete resection even more difficult because of the proximity of the fourth ventricle to lower cranial nerves and because adjuvant RT likely helps sterilize microscopic residual disease. For ST tumors, except for those that require resection of eloquent brain regions, the anatomic constraints of surgery are fewer and GTR rates are much higher than for PF tumors. A small series from the Beth Israel Medical Center, New York, suggested that long-term local control can be achieved by GTR alone (Hukin et al. 1998). In the ACNS0121 trial, patients with completely resected low-grade ST-EP were assigned to the observation arm (no RT). Preliminary results from 11 patients in the observation arm showed that two patients had relapses within the first 12 months, both of whom were salvaged with surgery and RT and remain disease free (Children's Oncology Group 2011). This strategy has been retained in the ACNS0831 trial.

12.4.5 Spinal Ependymoma

The epidemiology, pathologic characteristics, and behavior of spinal EP are distinct from those for cranial EP. Myxopapillary ependymoma (MPE) is the predominant histologic variant in spinal EP. These tumors appear to be rarer in children than in adults. In the pediatric population, MPE is usually seen in adolescents. MPE represents 13% of ependymal tumors (Chao et al. 2011).

MPE was first recognized as a distinct histologic variant of EP by Kernohan (1932). The designation "myxopapillary" is based on the histologic appearance of MPE. MPEs produce mucin and, because of their branching vasculature, form tumor cells arranged in papillae (Pica et al. 2009; Sonneland et al. 1985). MPEs are categorized as grade 1 tumors by the WHO and are considered benign tumors characterized by slow, indolent growth and a long disease course (Al-Halabi et al. 2010). In general, MPEs arise in the lumbosacral spine, specifically in association with the conus medullaris, cauda equina, or filum terminale (Bagley et al. 2007; Chao et al. 2011). MPEs rarely arise at other sites in the spinal cord or outside the neuroaxis (Akyurek et al. 2006). Most patients with MPE are male, and MPEs are diagnosed in the third or fourth decade of life (Bagley et al. 2007).

MPEs are also capable of distant spread. One third of treatment failures occur at distant sites with or without a primary site failure (Akyurek et al. 2006). MPEs are rare but more aggressive in children. They are associated with higher incidences of intracranial and spinal dissemination (Akyurek et al. 2006; Bagley et al. 2007; Merchant et al. 2000; Pica et al. 2009; Sonneland et al. 1985). A study from St. Jude reported a higher-than-expected rate of subarachnoid dissemination at presentation in patients with MPEs, which resulted in the use of craniospinal RT rather than involved-field radiation in three of four patients (Merchant et al. 2000).

Maximal safe resection is considered the standard of care for MPE. Currently, there is no clearly defined role for adjuvant RT, although it has been recommended after STR. Some studies recommend adjuvant RT for all patients after surgery, regardless of the extent of resection

(Akyurek et al. 2006; Al-Halabi et al. 2010). Other studies advocate adjuvant RT for patients receiving piecemeal GTR as opposed to en-bloc resections, based on the increased rates of local recurrence (Volpp et al. 2007). In general, it is very difficult to determine the extension of resection at this site. Because of the rarity of MPE in children, most studies have been limited to retrospective analysis. The primary treatment is GTR, with no clearly defined role for adjuvant RT. Sometimes, conservative management without the use of adjuvant RT in pediatric patients with a high risk of craniospinal dissemination can result in the need to give RT with a more extended field.

In a recent retrospective study by the Johns Hopkins Hospital, all children with spine EP received surgery that consisted of GTR or STR. The median dose of adjuvant RT was 50.4 Gy (range, 45–54 Gy). All patients receiving RT were treated at the involved site. After a median follow-up of 7.2 years, local control rates at 5 and 10 years were 62.5% and 30%, respectively, for the group undergoing surgery alone versus 100% at both time points for those undergoing surgery and adjuvant RT. Further, 50% of patients receiving surgery alone had local failure. Local failure occurred in all patients receiving STR compared with 33% of patients receiving GTR alone. One patient in the surgery and adjuvant RT group had recurrence at a distant site 1 year after diagnosis (Agbahiwe et al. 2013).

12.4.6 New Radiotherapy Modalities

In a phase II trial, 88 pediatric patients receiving three-dimensional conformal RT (77 receiving a dose of 59.4 Gy and 15 patients under the age of 18 months receiving a dose of 54 Gy) showed a higher 10-year PFS (69%) (Merchant et al. 2004b) than that reported in older studies for patients receiving conventional RT (31–46%). A potential bias in the phase II study, however, was the high (84%) rate of GTR. The study also reported better preservation of neurocognitive function in those receiving conformal RT than in those treated with conventional radiation therapy (Figs. 12.3 and 12.4).

A study evaluating adjuvant fractionated stereotactic RT in 80 patients (mean total dose 52.2 Gy, range 50.4–58 Gy) reported a high 5-year PFS of

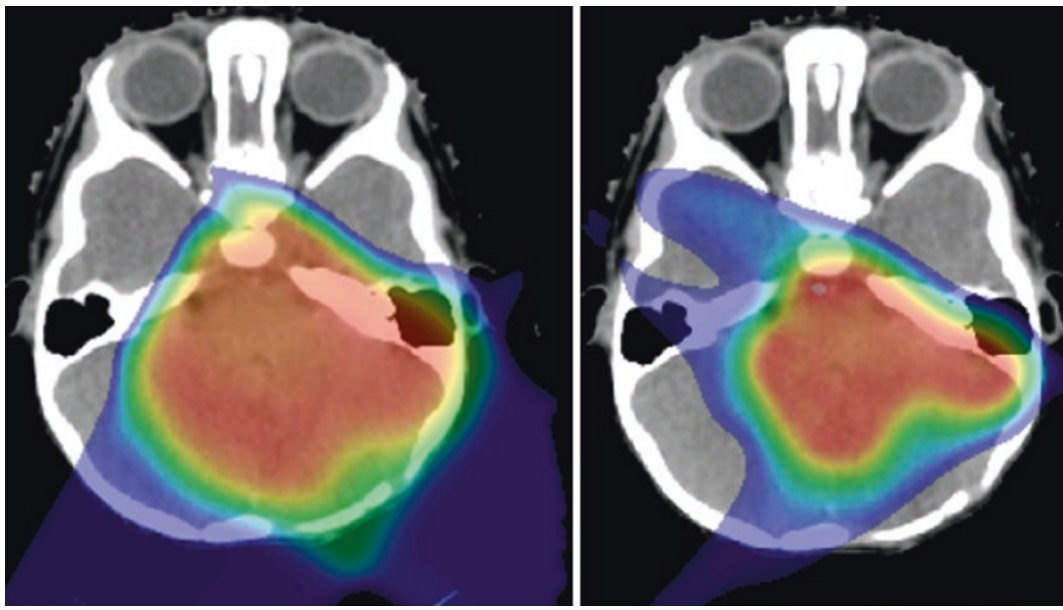

Fig. 12.3 Treatment planning CT with dose display (>10 Cobalt-Grey Equivalent) for proton therapy plans using passively-scattered (*left*) and pencil-beam scanning methods (*right*)

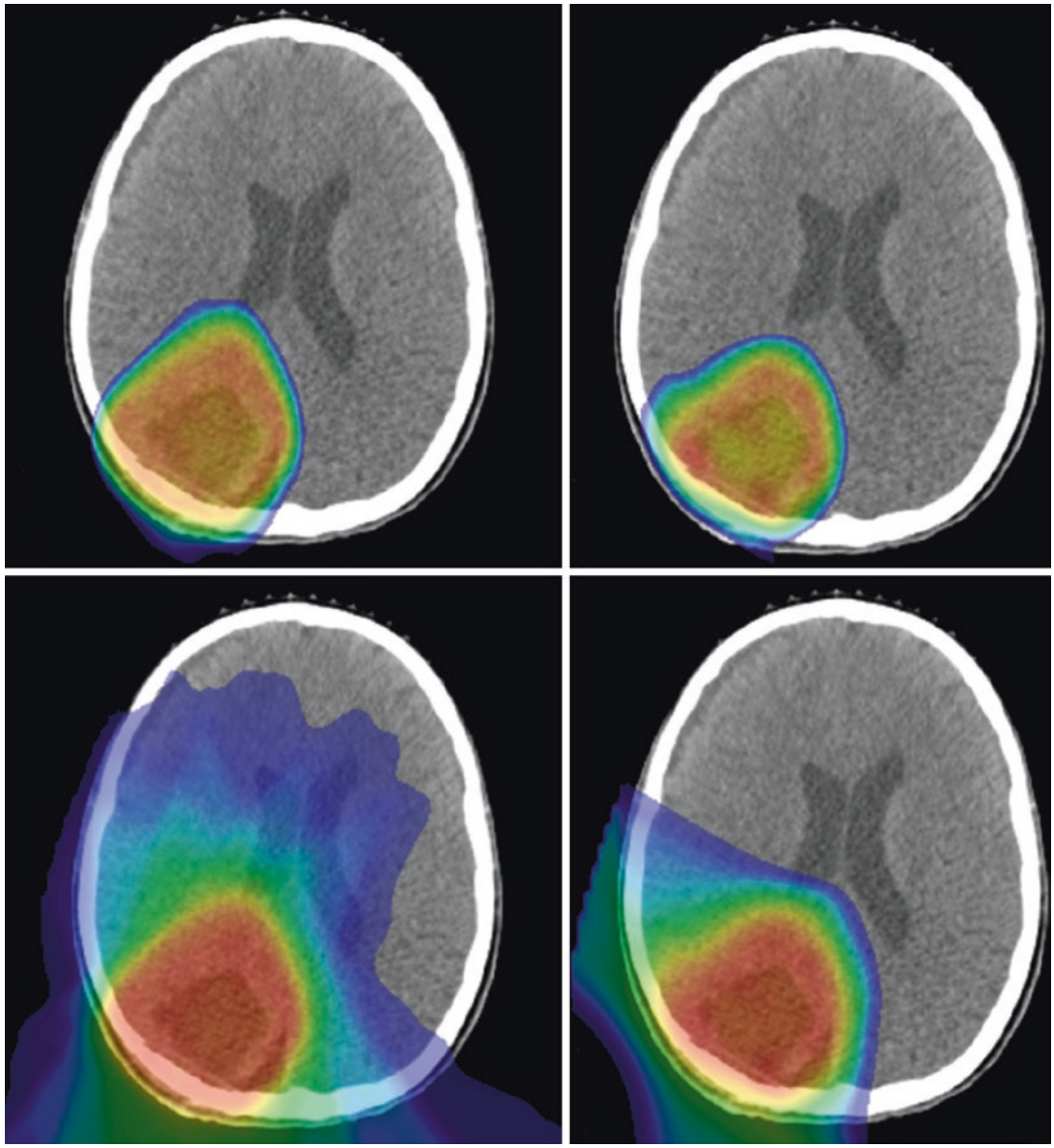

Fig. 12.4 Intensity-modulated photon (*left*, *top* and *bottom*) and proton (*right*, *top* and *bottom*) therapy plans displaying dose distributions greater than 40 (*top row*) or 10 (*bottom row*) *Grey* or *Cobalt-Grey* Equivalent, respectively

87% (Combs et al. 2006). However, radiosurgery has not yet been established as a standard adjuvant therapy for EP (Chan and McMullen 2012).

12.4.7 Intensity-Modulated Radiation Therapy

Recent studies show that treatment of a local field does not compromise local control and survival in patients with EP. Intensity-modulated radiation therapy (IMRT) has been used over the last 12 years to treat EP in an effort to spare surrounding normal tissues from high doses of radiation. Given that the volume adjacent to the target receives less radiation, there are concerns that IMRT might compromise local control. However, the local control and survival rates for patients receiving IMRT are comparable with those for patients who

received previous therapies that used larger treatment volumes (Schroeder et al. 2008). All failures have been reported within the high-dose region, suggesting that IMRT does not diminish local control (Merchant et al. 2002b; Schroeder et al. 2008).

12.4.8 Proton Therapy

Approximately 66% of intracranial childhood EPs occur in the PF, arising along the lining of the fourth ventricle (Smyth et al. 2000). These tumors often extend to the cerebellopontine angle through the foramina of Luschka or dorsally through the foramen of Magendie, thus placing the tumor in close proximity to critical structures such as the brainstem, cranial nerves, cochlea, and temporal lobes. Proton therapy appears to offer a better sparing of surrounding critical structures (e.g., chiasma optic, cochlea, hypothalamus, pituitary gland, and pharynx) than does IMRT (MacDonald and Yock 2010; Timmermann et al. 2007). For ST-EPs, proton therapy appears to spare the more eloquent and cognitive areas. Proton therapy offers the advantage of lower radiation doses to organs at risk (MacDonald and Yock 2010, Timmermann et al. 2007).

12.5 Chemotherapy

Chemotherapy has a limited role in the treatment of EP. Phase II trials of chemotherapy suggest that platinum agents have the highest efficacy against EP (Duffner et al. 1993). Objective response rates as high as 48% have been reported for patients receiving platinum-based chemotherapy (Bouffet and Foreman 1999). However, for patients with gross residual disease, complete responses are rare and are achieved in approximately 10% of patients receiving platinum-based regimens (Duffner et al. 1993). A higher response rate is achieved with combination therapy than with single-agent therapy.

Chemotherapy has been assessed in several clinical scenarios, including adjuvant treatment, as bridging therapy to postpone RT in infants, as neoadjuvant therapy before second-look surgery, and as high-dose aggressive therapy delivered with stem cell transplantation (Chan and McMullen 2012). However, there is no conclusive evidence of benefit to patients in any of these indications. A study reported that high-dose chemotherapy followed by stem cell transplantation was associated with toxicity-related death in 33% of patients with intracranial EP (Mason et al. 1998). Children's Cancer Group (CCG) 942, the only randomized trial comparing the use of adjuvant chemotherapy after conventional surgery and RT, found no improvement in outcomes when chemotherapy was used (Evans et al. 1996). The CCG 921 trial found no improvement with the eight-drugs-in-1-day regimen compared with the CCNU–vincristine–prednisone adjuvant therapy (Robertson et al. 1998). Both these CCG trials do not represent ideal conditions, because CCG 942 did not use cisplatin-based chemotherapy and CCG 921 was not randomized. The role of adjuvant chemotherapy will be assessed in the upcoming COG ACNS0831 trial, in which patients will be randomized to receive 4 cycles of maintenance chemotherapy or be observed after receiving standard therapy (Chan and McMullen 2012).

Baby POG-1 was a seminal study in which patients younger than 3 years with brain tumors of different histologies received chemotherapy to postpone RT until they were older (Duffner et al. 1993). As a result, the use of chemotherapy to postpone or even eliminate adjuvant radiotherapy has been evaluated for EP. The St. Jude RT-1 trial, which included 48 children under the age of 3 years, demonstrated that using chemotherapy to delay RT actually worsened the likelihood of disease recurrence. Furthermore, patients receiving upfront radiotherapy, even those younger than 3 years, had excellent functional outcomes (Merchant et al. 2002a).

Another indication for patients to receive chemotherapy is in case of tumors that are not completely resectable at the time of first surgery. In this situation, chemotherapy has been proposed as a means of inducing a response that can improve the resectability of the tumor, thereby allowing a second-look surgery. This approach was originally used by a group from the Bristol

Royal Hospital for Children, United Kingdom, who reported that three of four children with residual disease after initial surgery were able to undergo complete resection after chemotherapy, followed by a second-look surgery (Foreman et al. 1997). The efficacy of this approach was investigated in the ACNS0121 trial, with early data indicating acceptably low rates of surgical morbidity. As such, this strategy has remained a part of the ACNS0831 protocol, which is also investigating the role of adjuvant chemotherapy.

The role of chemotherapy in the management of EP remains uncertain. There is scant evidence that adjuvant chemotherapy improves outcome or gives a survival advantage (Vaidya et al. 2012). Thus, the efficacy of chemotherapy in EP warrants further study. Although there is evidence that chemotherapy can induce a partial or complete response in some patients, there are no convincing findings showing that it improves OS.

12.6 Tumor Recurrence

Many EPs can recur despite aggressive first management, often early during the disease course. The outcomes of patients with tumor recurrence are very poor (5-year OS 10–27%) (Bouffet et al. 1998). Despite a high rate of failure, there is no standard of care for recurrent EP. Given the prognostic significance of GTR in the primary setting and the efficacy of RT in some patients, a similar therapeutic approach, though with different radiation techniques, is often used for patients at relapse (Hoffman et al. 2014). Chemotherapy, though potentially effective, does not offer sustained response at relapse (Bouffet et al. 2009; Gajjar et al. 2013).

In older reported series, the majority of failures occured within the high-dose region. More recently, and with the increased rate of GTR and following high-dose conformal photon therapy, the 7-year cumulative incidence of local failure is only slightly greater than distant failure (12.6% vs. 8.6%) (Rousseau et al. 1994). The volume to irradiate in the second course is only the site of the recurrence with tight margins. Sometimes the recurrence is not at the primary local site but in the spine at which point it becomes necessary to irradiate the neuraxis. This situation is usually challenging because the patient may have already received high dose irradiation to a subsite involving the posterior fossa. Memphis (St. Jude) and Toronto (Sick Kids) series have the best overall survival with salvage therapy and they attribute their success to the good reception and the new course with effective dose of irradiation or a new course of at least 54 Gy (Bouffet et al. 2012; Merchant et al. 2008; Stafford et al. 2000). The current debate is whether to treat local recurrences with focal re-irradiation versus craniospinal. The latter might be appropriate for older patients and those harboring biomarkers predictive of metastatic progression.

The majority of failures are seen within the high-dose region. The volume to irradiate in the second course should include only the site of recurrence with tight margins. Sometimes, recurrence is not at the primary local site but at the spine. In such cases, it is necessary to irradiate the entire craniospinal space. This situation is usually challenging, because the patient has already received high-dose irradiation in the PF during the first treatment. Patients treated in the St. Jude (Memphis) and SickKids (Toronto) series have had the best OS with salvage therapy, which can be attributed to the acceptance of re-irradiation with an effective dose of irradiation or a new course of at least 54 Gy (Bouffet et al. 2012, Merchant et al. 2008, Stafford et al. 2000).

12.6.1 Re-irradiation

The technique used for re-irradiation depends on the site involved. Some studies support the efficacy of single-fraction radiosurgery (Hodgson et al. 2001; Kano et al. 2010; Merchant et al. 2008; Stafford et al. 2000; Stauder et al. 2012), whereas others report that it is associated with significant and unacceptable toxicity (Hodgson et al. 2001; Merchant et al. 2008). The St. Jude series reported radiation necrosis in all the six patients treated with radiosurgery, of whom one patient died due to radiation necrosis of the brainstem (Merchant et al. 2008). Merchant et al.

recommend fractionated RT to treat relapsed EP (Merchant et al. 2008). A study by Hoffman et al. in which fractionated stereotactic radiosurgery was administered in 3 fractions of 8 Gy to 12 patients reported a median EFS of 3.4 years (Hoffman et al. 2014). Although the treatment was fractionated in this series, radiation necrosis was seen in 6 of 12 patients. Of these 6 patients, 3 were asymptomatic and no patient died from the treatment.

The use of advanced technology is essential in salvage therapy to decrease the risk of major complications. IMRT is strongly recommended to spare the organs at risk. In some settings, proton therapy can offer a dosimetry advantage and preserve the brainstem, especially when there is recurrence in the PF when the target volume is adjacent to brainstem and/or spinal cord.

Conclusion

The search for the cure of EP remains a challenge in pediatric oncology. Many patients continue to die from their disease, especially those who do not have the access to skilled neurosurgeons and radiation oncologists. Newer RT methods have improved the survival and quality of life of patients and reduced complications associated with normal tissue irradiation. The identification of different subtypes of EP, each with a distinct behavior, necessitates the validation of these subtypes in the setting of existing and newer treatments in order to improve the outcomes of children diagnosed with this tumor.

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Childhood Craniopharyngioma

13

Thomas E. Merchant

13.1 Introduction

Craniopharyngioma is a unique brain tumor characterized by its consistent midline location and intimate association with the hypothalamic pituitary axis, visual pathways, and central cerebrovasculature. Children diagnosed with craniopharyngioma commonly present with endocrine deficiencies, visual deficits, headaches, and in more advanced cases neurological deficits affecting cranial nerves and long-tracts. The more advanced presentations include extensive tumor with mass effect or obstruction of CSF flow. The debilitating effects of this tumor prior to diagnosis are often noted in young children when signs of increased intracranial pressure are overlooked and vision loss occurs. The extent of tumor and its clinical impact affect treatment and prognosis both tumor control rates and functional outcomes. The tumor is comprised of solid and cystic components, the latter often responsible for the signs and symptoms observed at presentation.

Considering North America, the incidence of craniopharyngioma is stable amongst diverse geographic groups and races with an age adjusted incidence of 0.1 per 100,000 based on the 2000 United States (US) standard population with a slightly higher incidence 0.12 for those age 0–14 or 0–19 years and 0.13 for those 55–64 and 65–74 years. The total number of new pediatric cases annually within the US is estimated to be approximately 160 ages 0–19 years (Ostrom et al. 2015) (Fig. 13.1). The rarity of this tumor is an important consideration. Few centers have significant experience in the treatment of craniopharyngioma. This fact is made evidence by the small numbers in institutional series that describe experiences over many decades (Kiehna and Merchant 2010). By WHO criteria craniopharyn-

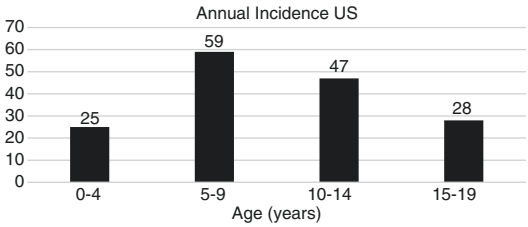

Fig. 13.1 Annual incidence of craniopharyngioma in the US based on SEER 2008–2012

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gioma is a grade I tumor including both adamantinomatous and papillary subtypes. The latter is most commonly seen in adults. Despite its designation as a catastrophic disease of childhood and associated morbidity and mortality, craniopharyngioma is usually not included among cancer center statistics.

13.2 Craniopharyngioma Biology

Craniopharyngioma arises in the sellar region as is thought to be derived from remnants of the primordium of the anterior pituitary. There are two subtypes of craniopharyngioma: adamantinomatous (ACP) and papillary (PCP). ACP occurs mainly in children under 15 years of age. PCP occurs in adults between the ages of 50 and 74 years. The cell of origin of human ACP remains unknown (Martinez-Barbera 2015).

The biology of ACP is understood in the context of the Wnt single transduction pathway. Wnt signaling is critical in embryonic development, differentiation of pluripotent stem cells, the proliferation of embryonic stem cells, and is known to be involved in carcinogenesis (Anastas and Moon 2013; van Amerongen and Nusse 2009). The pathway begins with the binding of the Wnt ligand to the membrane bound protein Frizzled (Fz). Binding leads to the stabilization of β-catenin. β-catenin is maintained in the cells at low levels in a complex of proteins. The absence of Wnt causes β-catenin to be degraded though ubiquitination. Stable β-catenin is translocated to the nucleus and induces the expression of target genes such as CMYC and CCND1 (Serman et al. 2014). The hallmark of ACP is clusters of cells with nuclear-cytoplasmic accumulation of β-catenin. Mutations of Ser/Thr residues in exon 3 of the CTNNB1 gene prevent ubiquitination. The result is overexpression of the Wnt/β-catenin pathway and uncontrolled cell proliferation.

13.3 Surgery

The treatment of craniopharyngioma has a number of controversies and challenges. Surgical resection is a valid approach and may be characterized as radical or limited. Radical surgery is defined as complete microscopic resection with no evidence of residual disease by surgical or neuroimaging report. Radical surgery maybe proposed when the chance of complete resection is high or morbidity acceptable and limited in its impact on long-term functional outcomes. Radical surgery may be proposed for very young children when the alternative, radiation therapy, may have age-related side effects. Surgery is characterized as limited when the goal is to decompress optic structures, reduce mass effect and neurological symptoms, restore CSF flow, and confirm the diagnosis when neuroimaging findings are equivocal. In some cases the choice of performing radical surgery and limited surgery is made at the time of the operation as exploration may be required to understand the association of the tumor with critical anatomy and to estimate the potential for surgical morbidity.

Surgery that does not involve tumor resection may play a central and important role in preparing the patient for radical surgery or limited surgery and radiation therapy. CSF shunting, temporary or permanent may be considered for selective cases where outflow is obstructed. And while surgery may be used to open CSF pathways, under certain conditions resection may not be possible or symptomatic hydrocephalus is observed after surgery and requires management when obstruction is not present.

Surgery for craniopharyngioma includes cyst drainage through open or closed procedures. Placement of a catheter into the cyst(s) that is permanently attached to an intracranial reservoir placed under the skin is often required. Indeed the use of an Ommaya reservoir is a common practice to manage cyst components of craniopharyngioma in unresectable patients and in preparation for radiation therapy or alternative therapies. There are many approaches to surgery and techniques available to limit morbidity and mortality. The approaches are driven by tumor extent, size, and shape. A variety of transcranial approaches have been used historically; however, more recently transnasal surgery is considered feasible even in younger patients. Endonasal endoscopic surgery has become increasingly popular and may result in

similar extent of resection compared to other approached. It may be preferred under certain circumstances (Dhandapani et al. 2016).

Radical surgery is appropriate for patients with tumors that may be completely removed without damaging the anterior hypothalamus and affecting the quality of life. For other patients, limited surgery followed by conformal, fractionated external beam irradiation should be considered. The side effects of surgery include operative and peri-operative morbidity and mortality: patients treated with surgery risk acute complications affecting neurological and endocrine function and late effects involving metabolism, achievement, personality and problem behavior.

Because radical resection and radiation therapy yield similar rates of disease control, more information is required about the morbidity and mortality of the primary surgery approach. Surgical series tend to lack functional outcomes data. Patients treated with radical surgery should be compared to irradiated patients using similar measures to improve patient selection for treatment. It is not considered feasible to randomize patients to these two very different treatment approaches.

13.4 Comparing Radical Surgery to Radiation Therapy With or Without Surgery

A comparison of disease control and functional outcomes for patients treated with primary surgery versus those treated with more limited or no surgery and radiation therapy has not been done prospectively because of the small number of patients with this disease and management controversies and concerns that generate selection bias. Despite limited data on morbidity and the factors that influence functional outcomes, radiotherapy avoidance remains a primary goal in the management of these patients at some centers. The literature demonstrates good disease control regardless of treatment approach and modality-specific side effects. Primary surgery patients are more likely to experience acute effects involving neurological function and long-term side effects on personality, depending on the extent of hypothalamic involvement and dissection. Long-term cognitive and vascular effects have been observed in patients treated with limited surgery and radiation therapy. Most patients present with pre-existing endocrinopathy, and both treatments have similar rates of anterior pituitary endocrinopathy; however, those who undergo primary surgery are more likely to experience hypothalamic damage, vision loss, or acute stroke (Huang et al. 1997; Lustig et al. 2003; MacDonald and Hoffman 1997). Collecting information about the acute, early, and late effects of both treatment approaches in a prospective protocol would be a rational alternative to randomization.

The rate of gross total resection (GTR) varies widely in the literature, and the rate of tumor recurrence in patients treated primarily with surgery is related to patient selection (Kiehna and Merchant 2010). Even though these patients may be salvaged with a high rate of success using radiation therapy, they tend to suffer the combined effects of both approaches (Merchant et al. 2002b).

It is important to consider the factors that influence patient selection, disease control, and acute, peri-operative effects. Consider one of the largest US series including patients treated with primary surgery. Clinical and treatment factors negatively affecting progression-free (PFS) and overall survival (OS) were subtotal resection (STR), tumor size >5 cm, and the presence of hydrocephalus or CSF shunting (Elliott et al. 2010). It is logical that STR would affect PFS but not OS, since patients who have disease progression after primary surgery may be successfully salvaged with radiation therapy. It may be that patients treated with STR are prone to progression and subsequently undergo a second surgery instead of irradiation and are at increased risk for peri-operative morbidity and mortality. The explanation for tumor size, hydrocephalus, and ventriculoperitoneal (VP) shunting impacting PFS suggests more extensive or unresectable disease and a probable association with STR. There is no logical explanation of the relationship between tumor size and OS. This finding may be attributed to the morbidity and mortality of salvage (*i.e.,* second) surgery. It has been noted that recurrent tumors are more likely to lose their tissue planes, making second surgery dangerous (Elliott et al. 2009). There were three deaths in the

reported series, two among the 57 primary patients and one among the 29 patients with recurrent tumors. The recurrence rate was 22% among 81 patients who were not among those who died perioperatively (n = 3) or were lost to follow-up (n = 2). The median time to recurrence was 20 months, and the 2-year PFS rate was 85%. Based on their findings, and because PFS in patients with recurrent tumors was low, it can be concluded that it is not in the best interest of the patient to undergo a second attempt at radical resection unless the patient is young and conditions for resection and complete removal are favorable. The death rate during the interval of their study was 15%. The follow-up median was 8.3 years, ranging from 3 months to 22.8 years. These data support the policy of one attempt at major resection and post-operative irradiation in patients who undergo STR. Although it may not be detrimental to delay irradiation for an amount of time measured in months, growth will ultimately occur, affecting the target volume and potentially increasing the morbidity arising from irradiation.

There is limited information on cognitive function and quality-of-life outcomes after primary surgery. Quality of life and behavioral follow-ups for 29 patients (Sands et al. 2005) were reported from a series that included a primary surgery approach. They found that social-emotional and behavioral functions were within the normal range for externalizing problems but borderline for internalizing problems. Tumor recurrence and additional surgery were associated with decreased physical functioning. Retrochiasmatic tumor location was associated with lower psychosocial quality of life and impaired social-emotional and behavioral function. There was no association between outcome and sex, age, tumor size, or hydrocephalus. These findings differed from the findings of other, much older surgical series and suggest that more patients are needed for such a study. Assessment of quality of life is important in this group, and there needs to be more information about outcomes after the primary surgery approach to better understand the effects of GTR.

Hypothalamic dysfunction may be characterized in patients treated with surgery using acquire variables similar to those used in the grading scale of DeVile (Devile et al. 1996), where mild, moderate, and severe dysfunction were scored according to postoperative obesity (BMI > 2SD) and a lack of behavioral or psychological symptoms (mild); obesity with hyperphagia or memory disturbances (moderate); and extreme obesity and hyperphagia with behavioral disturbances including rage, disturbances of thermoregulation, sleep-wake cycles, or memory (severe). Other classifications include the functional status of patients and acquire variables similar to those of Wen (Wen et al. 1989), whose four-part functional classification index has been used in many surgical series. The classifications are class I—grossly normal and independent, mild hormone disturbances, seizures well controlled with medication; class II—independent, panhypopituitarism, mild to moderate visual compromise, cranial nerve deficits, mild psychological dysfunction; class III—partially dependent, serious visual compromise, serious neurological deficits including hemiparesis or refractory seizures, learning disabilities, or poorly controlled psychological disorders; and class IV—entirely dependent on others for care. These scales were used by Elliott and Wisoff (2009) in their assessment of 19 very young children with craniopharyngioma. The median age at the time of surgery was 3 years, and very few patients had more than one surgery to achieve GTR, which was successful in 18/19 (94.7%) patients. Hypothalamic morbidity at any level occurred in 4/17 (23.5%) of patients for whom data were available. There was no statistical difference between pre- and post-operative functional scores among the group of evaluated patients. Recurrence was noted in 33% of patients after a median time of 16 months. It might be helpful to further the assessment of these patients considering presenting signs and symptoms based on presence of headache, vision loss, behavioral changes, diabetes insipidus, endocrine symptoms, or focal neurological deficits as clinical variables. The relationship of the tumor to the optic chiasm may be assessed in planning for surgery as prechiasmatic, retrochiasmatic, complex, lateral, or predominantly third ventricle.

One important caveat in reviewing surgical data is that radical resection denotes GTR. This is not achievable in all patients, and the rate of progression after GTR at experienced centers approaches 25% (Weiner et al. 1994). GTR is defined as no tumor by

visual (GTR-macro) or microscopic (GTR-micro) inspection. No residual disease by imaging and no evidence of enhancement or microscopic calcifications are considered by many to be GTR (Elliott and Wisoff 2009). If blood products obscure the post-operative cavity, imaging, including CT, should be repeated 1 month later as there should be no rush to initiate adjuvant therapy. In the series by Elliot (Elliott et al. 2009), the recurrence rate was 24% among a group of 49 patients with calcification on pre-operative CT scan. There was no significant difference in the rate of tumor recurrence based on post-operative calcification, and they found the Hoffman scale was not particularly useful in their study, probably because of small numbers. The Hoffman scale (Hoffman 1985) has five levels: grade 1—a normal CT scan; grade 2—tiny calcific fleck but no residual tumor; grade 3—a small calcific chunk without evidence of enhancement or mass effect; grade 4—a small contrast-enhancing lesion without mass effect; and grade 5—lesion with significant enhancement and mass effect.

The PFS after radical surgery versus limited surgery and radiation therapy should be similar, approximately 75%, when measured between 5 and 10 years after diagnosis and initial treatment. The caveat is that radical surgery means GTR and limited surgery means cyst drainage, decompression with limited dissection, and tumor removal or no surgical manipulation of the tumor. It should not be the goal of any study to compare local disease control for these two groups; rather, it is most relevant to compare acute and late effects of treatment. There is another cohort to consider: patients who undergo radical surgery who do not achieve GTR and require post-operative irradiation and those treated primarily with GTR who later have local tumor progression and require radiation therapy. The third cohort can be characterized by surgical extent, which adds value to the analysis of surgical factors by bridging the defined group of limited surgery patients and those treated with radical surgery. There is no difference in outcomes comparing patients treated with immediate post-operative radiation therapy to those treated initially with surgery and who experience progression prior to subsequent irradiation (Lo et al. 2014).

13.5 Surgery Planning

Neurosurgical input and intervention are integral to the treatment of children with craniopharyngioma before, during and after radiation therapy. Patients should be evaluated by neurosurgery experts for resection, decompression, biopsy, Ommaya reservoir placement, CSF shunting or similar procedures. As noted earlier, exploratory surgery may be required. Because craniopharyngioma may undergo spontaneous or radiation-induced cyst enlargement, unplanned neurosurgical intervention may be required after the patient has started treatment. Pre-operative evaluation should include, whenever possible, a detailed ophthalmologic examination, including visual field assessment and endocrinology consultation. Pre-operative imaging should include a CT scan and MRI of the brain.

The goal of surgical intervention should be to facilitate tumor control, keeping surgical morbidity to a minimum. Common indications for surgical intervention directed at the tumor include establishing a tissue diagnosis, tumor control by radical resection, relieving tumor mass effect to reduce symptoms, and decreasing the target volume for radiation therapy. Patients should always be selected for radical surgery based on the neurosurgeon's assessment that a GTR may be achieved with acceptable post-operative morbidity. The Wen classification system (I-II) may serve as a guide (Wen et al. 1989). This assessment should include patient and tumor characteristics and consider the treating neurosurgeon's experience. The decision should ultimately be made by the parents and with guidance of the multidisciplinary treatment following a discussion about the risks and benefits of surgery. To avoid operative hypothalamic damage, the degree of pre-operative hypothalamic involvement may be assessed clinically or by neuroimaging using systems similar to the grading system proposed by Puget et al. (2007). The Puget Scale: Grade 0—no hypothalamic involvement; Grade 1—tumor abutting or displacing the hypothalamus; Grade 2—hypothalamic involvement with hypothalamus no longer identifiable. Pre-operative hypothalamic involvement, clinical or

radiographic Puget Grade 2 (Devile et al. 1996; Puget et al. 2007), should be a contraindication to attempting GTR (Fig. 13.2). In addition, GTR is not recommended for patients who have already had a previous but unsuccessful attempt at a GTR. Patients with poor functional status (Wen et al. 1989), Wen Class III-IV, previous stroke, or arterial or hypothalamic injury are also not good candidates for GTR. It is recognized that in certain cases, the feasibility of radical surgery may initially require exploration (Fig. 13.3).

Patients may be selected for less than radical surgery and subsequent radiation therapy based

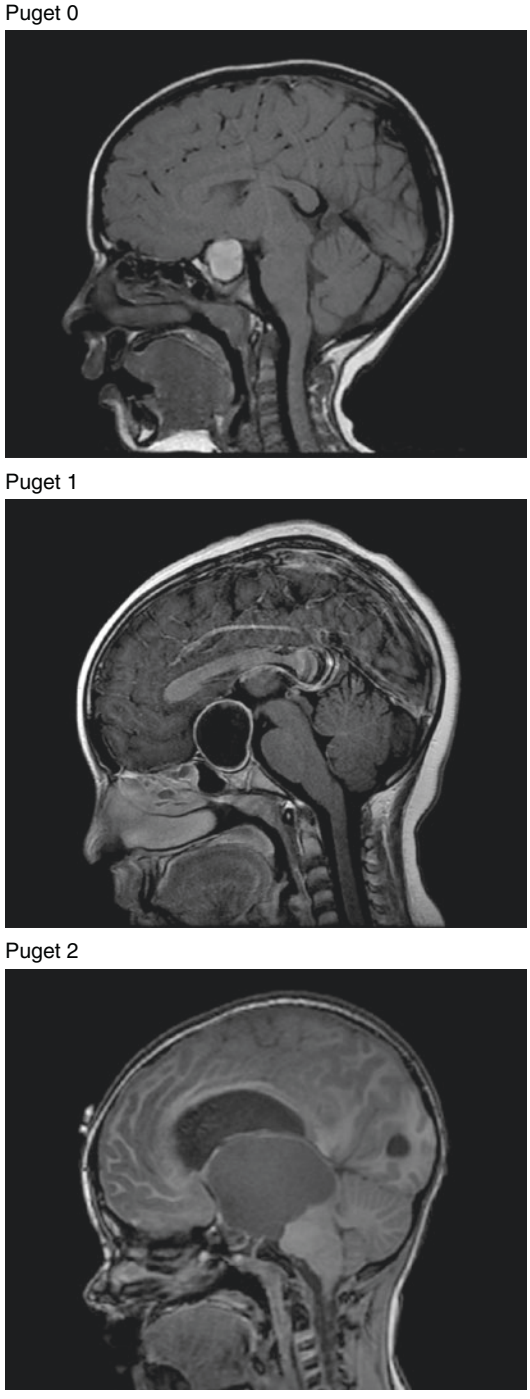


Fig. 13.2 Examples of Puget scale

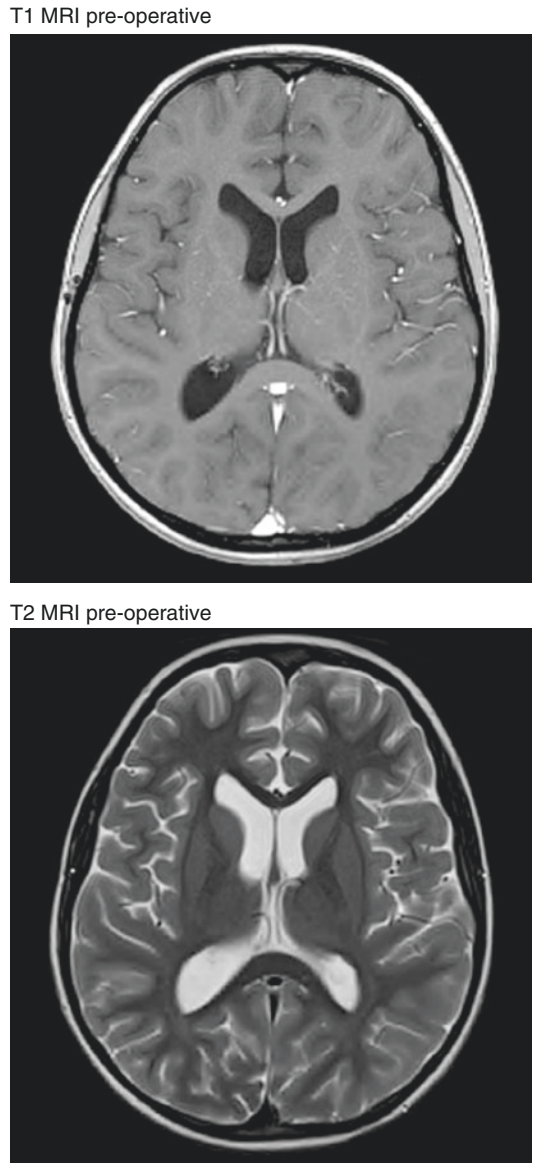
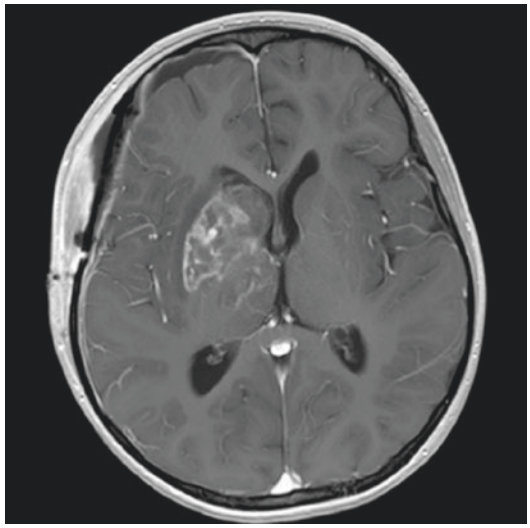


Fig. 13.3 Examples of subacute ischemia after surgery for craniopharyngioma

T1 MRI after stroke



T2 MRI after stroke

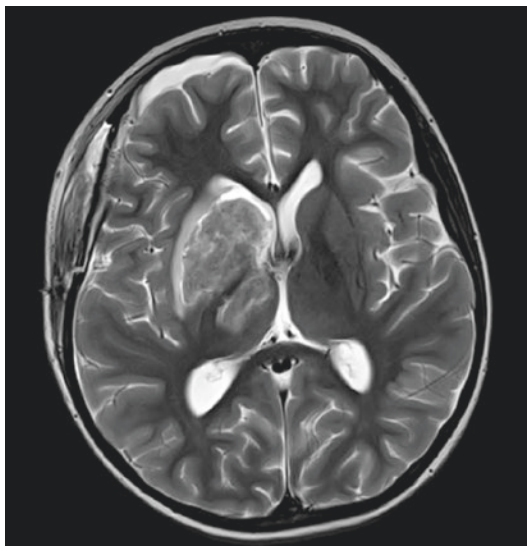
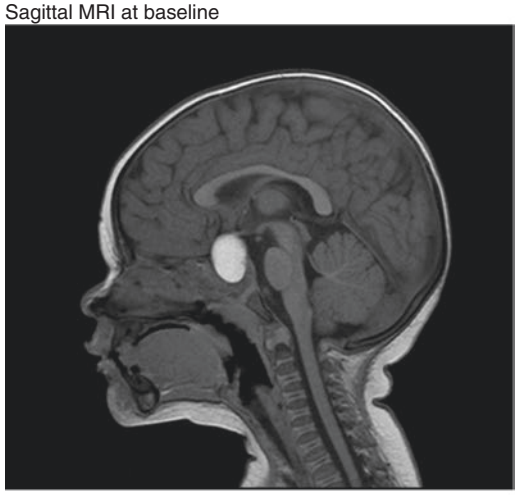


Fig. 13.3 (continued)

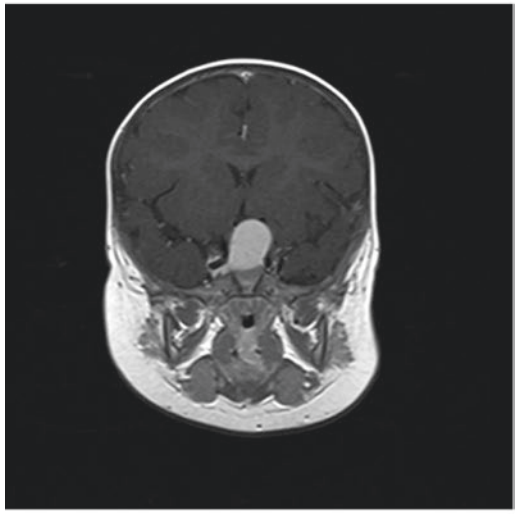
on the opinion of the neurosurgeon that a GTR cannot be achieved with acceptable morbidity. In some instances surgery, both radical and limited, may not be indicated. These patients, diagnosed based on imaging findings, may proceed directly to radiation therapy in the absence of any attempt to invasively establish a diagnosis; however, the patient and parents need to understand the unique nature of this situation.

Surgical evaluation, including the physical and neurologic examinations and detailed visual examination by ophthalmology, is critical since the surgical method to decompress visual apparatus is an important part of the decision-making process in choosing the surgical plan. Neuroimaging studies including CT, which is useful for assessing calcification in the tumor and in the cyst wall, and MRI with and without contrast, should be used. Surgical planning discussion for a patient with presumed craniopharyngioma should include a frank discussion of the risks and benefits of radical surgery versus limited surgery and radiation therapy. Radical surgery considerations may include minimal involvement of the hypothalamus with a solid tumor or thick-walled or calcified cyst, or a thin-walled cyst; a favorable chance of total removal; and an experienced neurosurgeon. Limited surgery and proton therapy considerations may include involvement of hypothalamus with solid tumor, thick-walled cyst, or both; and good vision. Methods for handling poor vision may include correcting hydrocephalus; performing cyst drainage and obtaining tissue to confirm diagnosis. There are a variety of means to perform cyst drainage including stereotaxic or endoscopic placement of an Ommaya reservoir for thin-walled cyst, or open procedure for a thick–walled cyst or when the cyst wall will not collapse. In any event, a decision must be made regarding the safety of cyst resection and avoiding resecting cyst on the hypothalamus if access is difficult. For thin-walled cysts beneath the optic chiasm, leaving a catheter in place is preferable to resection unless the surgeon can be sure that the cyst is removed, because leaving a catheter with a large amount of cyst wall remaining may allow the cyst to re-form with the catheter outside of cyst (Fig. 13.4). Other considerations regarding surgery include: (1) surgical decompression of a solid tumor compressing a nerve is often not necessary, because relief of hydrocephalus and drainage of the cyst will improve vision; (2) if an open procedure is performed, then care should be taken to preserve the pituitary stalk to avoid diabetes insipidus; and (3) care must be taken not to disturb the interface of the hypothalamus and solid tumor, or the morbidity will be the same as that of radical surgery.

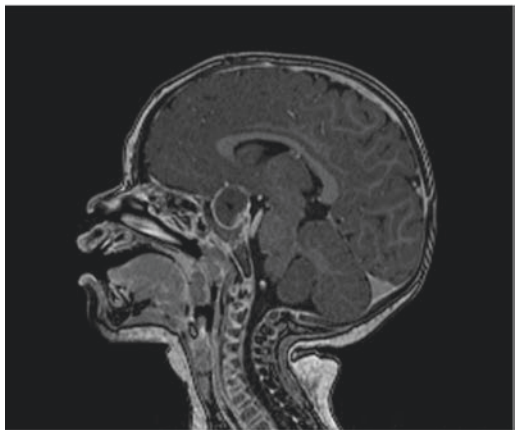
Sagittal MRI at baseline



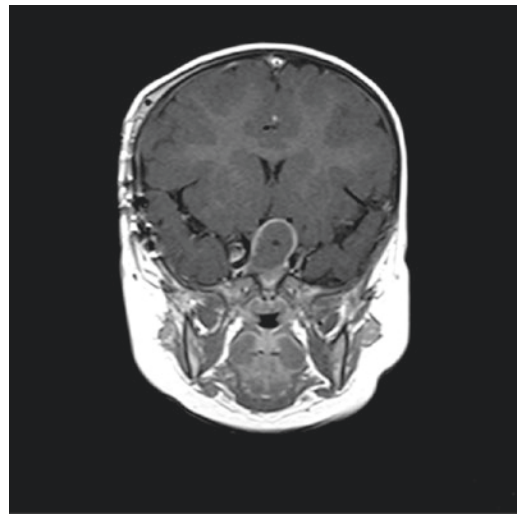
Coronal MRI at baseline



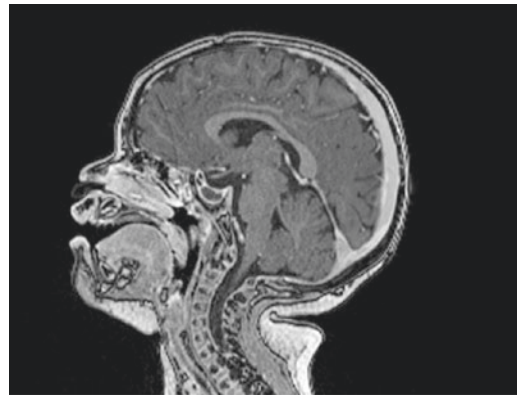
Sagittal MRI after catheter/Ommaya reservoir placement



Coronal MRI after catheter/Ommaya reservoir placement



Sagittal MRI after proton therapy



Coronal MRI after proton therapy

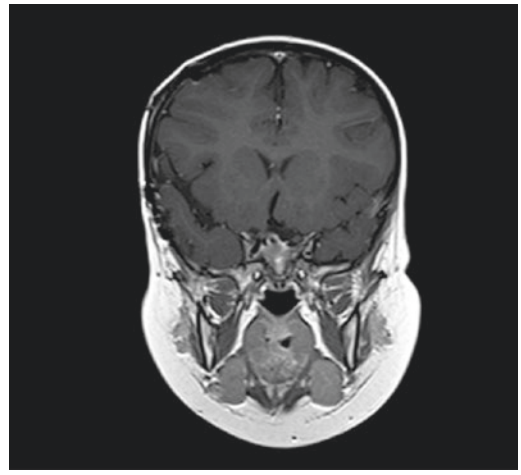


Fig. 13.4 Baseline, after catheter/Ommaya reservoir placement, and after proton therapy

13.6 Radiation Therapy

Radiation therapy has a long track record of success in the treatment of craniopharyngioma and there are a number of published disease control benchmarks reporting high rates of local tumor control with long-term follow-up. Institutional series highlight the excellent rate of tumor control and the spectrum of side effects that may arise with radiation therapy and long-term follow-up. The rationale for radiation therapy and the potential side effects include long-term disease control with limited morbidity in appropriately selected patient understanding the contribution of tumor and surgery to the latter. When tumors are left intact or minimally disturbed by surgery their borders are distinct and well-defined which permits the use of highly focused irradiation and limited margins of security around the defined target volume. Prior to the advent of 3-dimension conformal radiation therapy and later intensity-modulated radiation therapy—both using photons and eventually the application of proton therapy, children with craniopharyngioma were irradiated with parallel opposed portals and fairly large margins surrounding the perceived target in an effort to encompass the volume at risk. Not only did the lack of image-guidance risk recurrence because of the possibility that the entire tumor was not encompassed, the parallel-opposed portals encompassed a substantial amount of normal tissue including the temporal lobes, brainstem, entire circle of Willis and substantial vasculature of the middle cerebral arteries and possibly the anterior and posterior as well.

In an effort to reduce the side effects of radiation therapy, taking advantage of advances in treatment technology and the often well-defined imaging nature of craniopharyngioma, these tumors were subjected to the earliest experiences of conformal and so-called stereotactic radiation therapy using advanced methods of immobilization in cooperative patients and cone-based circular collimators apply arc methods of irradiation. In some of the earliest series craniopharyngioma was treated with margins surrounding the tumor of approximately 2 mm with the caveat that the entire tumor diameter was less than 5-6 cm. With the advent of 3-dimensional conformal radiation therapy and later intensity modulated radiation therapy investigators were able to treat tumors with conformal therapy regardless of tumor size using initially customized cerrobend collimation and later multi-leaf collimation.

There is a need to reduce side effects associated with the irradiation of young adults and children with craniopharyngioma because the tumor arises in the suprasellar region and is intimately associated with the diencephalon, optic pathways, and central cerebrovasculature. There is a need to report on long-term disease control and functional outcome for patients with craniopharyngioma and develop expanded models of radiation dosimetry that predict function outcomes. There is a need to identify factors associated with tumor progression and side effects for patients with craniopharyngioma and identify new clinical and biological correlates of outcome.

Progression-free and OS rates of 77% and 83% at 10 years and 66% and 79% at 20 years (Rajan et al. 1993) after limited surgery and radiation therapy have been reported from the Royal Marsden Hospital using doses ≥50 Gy. These are considered benchmarks for disease control and the same principals of treatment are now followed more than 50 years after their initial description. Despite its success, the side effects of photon irradiation on neurologic, endocrine and cognitive function weigh heavily when recommending irradiation because the long-term prospects for survival are excellent. Reducing dose to normal tissue should be a primary goal when radiation therapy is administered. Long-term disease control and toxicity reports from other centers support the use of irradiation and evidence of durable disease control. Investigators in Houston reported 5 and 10 year cystic (65.8% and 60.7%) and solid (90.7%) control rates for children treated with a 1 cm clinical target volume (CTV) margin and doses ranging from 49.8 to 54 Gy (Greenfield et al. 2015). Similarly, investigators reported 5, 10, and 20 year disease control (95.3, 92.1, and 88.1%) and OS (10 year—83.3% and 20 year—67.8%) highlighting

excellent local control and the concept that most patients do not die from their tumor but associated complications from treatment (Harrabi et al. 2014). This latter point is highlighted by recent data from Vancouver which demonstrates that the leading cause of late death is complications arising from tumor and treatment-related morbidity (Lo et al. 2014).

13.7 Radiation Dose and Volume

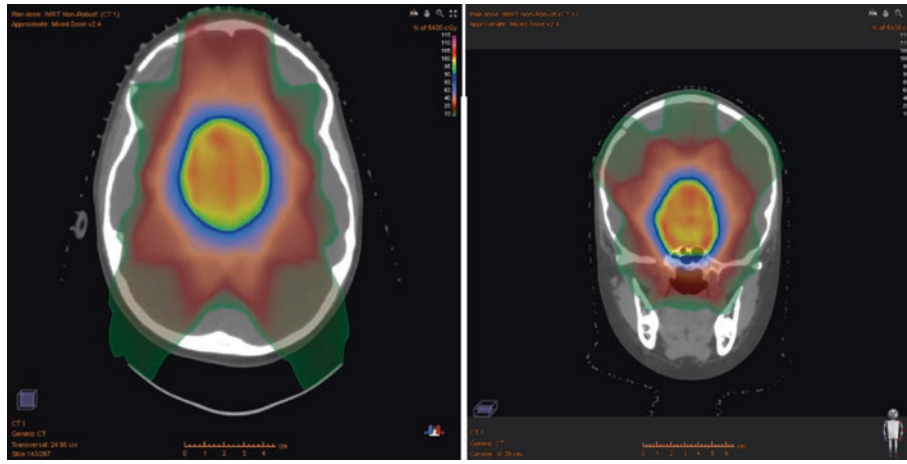
Disease control and functional outcomes have been prospectively defined for patients with craniopharyngioma using advanced methods of photon irradiation such as intensity modulated photon therapy, and investigations are now underway using intensity-modulated proton therapy with the goal of limiting side effects. Intensity-modulated proton therapy using discrete spot scanning is the newest form of proton therapy and includes intensity-modulation with iterative planning as well as single-field uniform dose methods. The potential advantages of proton therapy over photon therapy have been highlighted by a number of groups (Bishop et al. 2014; Boehling et al. 2012) despite concern by others about the costs associated with the use of protons (Leroy et al. 2016) and insufficient data which is likely related to earlier proton therapy methods (Leroy et al. 2016) (Fig. 13.5).

There have been few systematic applications of focused irradiation attempting to define targeting and treatment for craniopharyngioma. A prospective phase II trial of conformal radiation therapy was conducted at St. Jude Children's Research Hospital between 1998 and 2003. The primary objective was to estimate the local control and patterns of failure for pediatric patients treated with conformal radiation therapy using a 10 mm CTV margin. The trial demonstrated that event-free survival (EFS) with a 10 mm CTV margin and 3–5 mm planning target volume (PTV) margin was similar to treatment with conventional radiation therapy (Merchant et al. 2006). With a median follow-up of 28 months, the 3-year EFS was reported to be 85% ± 11%. This study was the first to prospectively define a minimum target volume for this disease. The secondary objective of the same trial was to estimate the incidence and time to onset of clinically significant CNS effects based on radiation dose distributions in normal tissue including deficits in neurological, endocrine and cognitive function. The impact of high-dose irradiation on functional outcomes, specifically cognition, was clearly demonstrated (Merchant et al. 2006) in younger patients. These findings and recent advances in radiation therapy have made further reductions in the irradiated volume warranted and feasible.

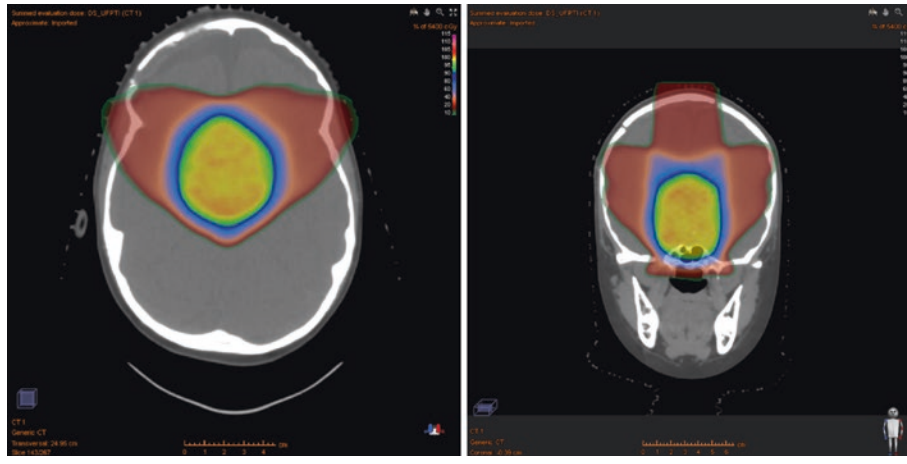
A total of 93 patients diagnosed between December 1994 and March 2010 received conformal or intensity-modulated radiation therapy at St. Jude Children's Research Hospital. This number includes patients in the original 1998–2003 prospective series (Merchant 2006). The CTV margin was subsequently reduced to less than 10 mm after 2003 yielding two groups of patients: those treated with a CTV margin greater than (>) 5 mm (n = 26) and those treated with a CTV margin less than or equal to (≤) 5 mm (n = 67). There was no significant difference in PFS distributions between these groups ($P > 0.70$) with 5-year estimates of 88.1 ± 6.3% vs. 91.7 ± 4.9%, respectively. There was no significant difference comparing patients on the basis of their PTV or combined CTV + PTV margins. The PTV was systematically reduced during this time period from 5 to 3 mm with the advent of more sophisticated methods of immobilization and verification. All cases of tumor progression were within the target volumes. While not statistically significant, factors that appeared to be associated with improved PFS included Caucasian race ($P = 0.058$) and no permanent CSF shunting requirements ($P = 0.022$). These results suggest that reductions in the targeted volume using photons and smaller margins were feasible and safe as applied (Merchant et al. 2013).

Proton therapy appears to be superior to photon therapy in reducing dose to normal tissue. It has become increasingly available for children with brain tumors and has become a preferred radiation therapy modality (Merchant et al. 2008; Luu et al. 2006; Fitzek et al. 2006; Habrand et al. 2006). Several studies have

Intensity-modulated photon therapy



3-D (passively-scattered) proton therapy



Intensity-modulated proton therapy

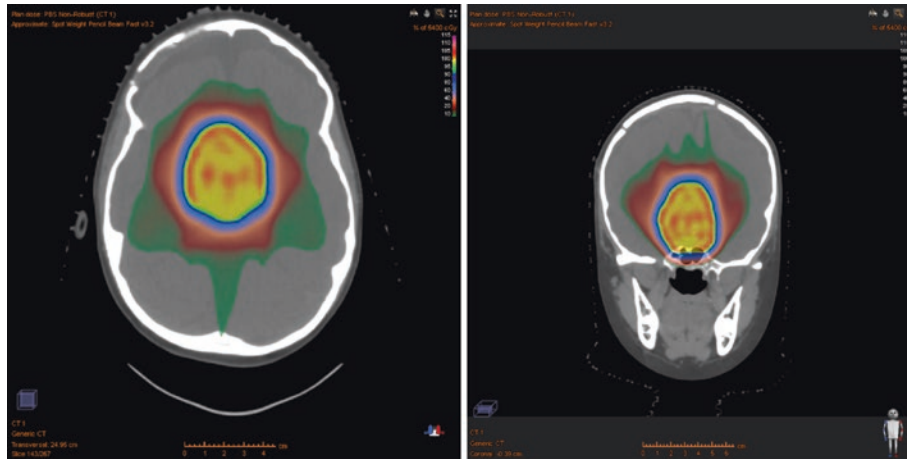


Fig. 13.5 Intensity-modulated photon therapy, 3-D (passively-scattered) proton therapy, and intensity-modulated proton therapy

shown the advantage of proton therapy to reduce dose to normal tissues irrespective of the chosen margin (Alapetite et al. 2010; Baumert et al. 2004; Fitzek et al. 2006; Merchant et al. 2008); however, a minimum CTV margin has not been defined and investigators remain concerned about idiosyncratic tumor cyst expansion during proton therapy that may lead to under-dosing of targets (Winkfield et al. 2009). We studied the differences in normal tissue dose distributions comparing protons and photons. Protons spare normal tissues better than photons, especially in patients with small tumors. Small critical structures (chiasm, pituitary, and hypothalamus) adjacent to the PTV tend to receive the prescription dose; however, those separated from the PTV (cochleae) will receive significantly less or no dose when using proton therapy. Relatively large normal tissue volumes partially (cerebellum and brainstem) or more fully subtended by the PTV (entire brain or supratentorial volumes) are expected to receive minimal reductions in the high dose volume, moderate reduction in the intermediate dose volume and significant reductions in the low dose volume using proton therapy. The differences widen as the volume of the normal tissue structure increases. The magnitude of the difference may be a factor of 3. Models suggest that cognitive function will be preserved using proton therapy in the same setting where a decline in cognitive function is expected using photons. Although the endocrine effects of radiation therapy may not be reduced, it is likely that proton therapy will reduce the risk of secondary neoplasia and vasculopathy because these late effects depend on the volume that receives both high and low doses (Merchant et al. 2008). Vasculopathy and cerebrovascular disease is a concern when considering late effects of irradiation in craniopharyngioma (Lo et al. 2014).

Apart from a number of registries, there is currently only one recently completed study in the US that deployed proton therapy for craniopharyngioma: A phase II trial of limited surgery and proton therapy for craniopharyngioma and observation for craniopharyngioma after radical resection. This study was known as RT2CR. The proton therapy delivery method for the RT2CR protocol was passive-scattering, otherwise known as double-scattering or 3-dimensional proton therapy. A 5 mm CTV margin surrounded to the post-operative tumor bed and/or residual tumor. The RT2CR protocol successfully recruited patients from 2011 to 2016. The results have not been published.

It has been shown that with on-treatment monitoring (weekly or periodic MR imaging during radiation therapy) that the targeted volume for craniopharyngioma may be safely reduced; however, these data apply only to photons which are not significantly affected by tissue heterogeneity and which have a wider gradient in therapeutic to non-therapeutic dose coverage. Craniopharyngioma is a heterogeneous cystic and solid (calcified) tumor adjacent to the base of skull. These physical properties may affect proton dose distributions which are susceptible to tissue heterogeneity. The physical characteristics of the proton beam leads to very sharp dose profiles along the lateral aspects of the beam and at the distal edge. The sharp profile may risk marginal miss of craniopharyngioma target volumes that are prone to change in size or position. The importance of monitoring these tumors during treatment has been highlighted in a number of reports (Beltran et al. 2010; Shi et al. 2012).

Proton therapy advantageously reduces dose to normal tissue in children with craniopharyngioma and should reduce or eliminate the side effects of radiation therapy. Considering the vigilance required to reduce the targeted volume using photons, the susceptibility of proton therapy to tissue heterogeneity, and the dynamic nature of the craniopharyngioma target volume, protocol-based systematic monitoring is required with the possibility of adaptive therapy to investigate the feasibility and safety of using intensity-modulated proton therapy (Yang et al. 2014).

13.8 Radiation Dose-Effects Models

The objective of using advanced methods of irradiation and monitoring dose to normal tissues is to expand the models of treatment

dosimetry and structural and functional outcome. The treatment guidelines in successive trials have included smaller target volume margins than those used in prior studies. The goals of clinical trials that include radiation therapy now seek to prospectively evaluate the use of proton therapy. The goal is to proportionally irradiate less normal tissue and define a new minimum in the irradiated volume. Longitudinal functional assessment on the aforementioned RT1 protocol included a broad range of CNS effects measures acquired before, during and after irradiation including audiometry, ophthalmology, neurology, endocrinology, neuropsychology, quantitative neuroimaging, sleep and fatigue assessments and evaluation of physical performance. With a median follow-up of 5 years, the reported incidence of neurologic complications including deficits in hearing and vision was low, endocrine deficits were found to be common before treatment and imaging changes and cognitive declines were statistically-related to treatment dosimetry (Merchant et al. 2002a, c, 2004; Dolson et al. 2009). Because of the paucity of prior prospective data for patients with this type of brain tumor (Merchant et al. 2002b), the benefit of volume reduction could not be proven; however, the acquired data now serve as a benchmark for the specified CTV and PTV margins and the irradiated volume of normal tissue. Data acquired in this study will be used for parametric modeling and future comparison with subsequent volume reductions, dose-escalation or normal tissue protection strategies for these patients.

Despite all attempts to limit dose to normal tissues, side effects will continue to be observed in these patients and it remains an important goal to identify important clinical variables and treatment factors that improve models of radiation dose. It is critical to have large numbers of patients in dose-effect modeling. The number of dose-volume intervals and correlative variables assessed depends on the number of patients. In prior studies we assessed mean dose and intervals of low (0–20 Gy), intermediate (20–40 Gy) and high dose (40–60 Gy). Correlation of radiation dosimetry with IQ has shown a statistically significant relationship with higher doses having the greatest impact. It should be a goal to evaluate more critically the effects of low dose given that this range of dose is the one most likely to differ when comparing proton and photon data. Independent of radiation dose, surgical factors have the greatest impact on cognitive function after radiation therapy. The extent of resection, number of attempts at resection, and the presence of diabetes insipidus, a surrogate marker for surgical morbidity, correlated significantly with decline in IQ (Merchant et al. 2006). These findings demonstrate the importance of considering all variables in dose-effects models. Dose models may be used to compare linear or non-linear trends in subgroups or historic data, the same models may be used to estimate the proportion of patients falling within deficient ranges on functional measures.

13.9 Radiation Therapy

The guidelines for radiation therapy have been developed to ensure coverage of the volume at risk and to minimize the side effects of treatment. The guidelines used by most centers are standard in terms of total dose (50.4–54 Gy) and fractionation (1.6–1.8 Gy/day) (Table 13.1). There is limited data concerning disease control and functional outcomes after treatment with

Table 13.1 Current guidelines for the use of proton therapy

CTV margin[a]	CTV coverage	PTV margin[b]	Prescribed dose	Dose maximum[c]
3–5 mm	95–100%	2–3 mm	50.4–54.0 CGE	100–108%

[a]Includes margin surrounding post-operative tumor bed and not surgical corridor
[b]Includes margin surrounding CTV for positional and range uncertainty
[c]Chiasm dose maximum ≤100%

new methods of radiation therapy including proton therapy and the impact of target volume reduction. None of the published reports concerning proton therapy describe in detail the method of targeting, immobilization and verification, and on treatment assessment of target volume deformity. There has never been a national or international prospective study for the treatment of craniopharyngioma that included radiotherapy. The prescribed dose for craniopharyngioma has evolved to a standard of 54 Gy when using a CTV margin of 5 mm for all children. There are ample data demonstrating that these prescribed doses and target volumes are reasonable and safe. The data suggest that further volume reductions are warranted because of the correlation between radiation dose, treatment volume and a variety of functional outcomes. With the availability of improved imaging and increased treatment accuracy the CTV and associated target volumes will be further reduced with the expectation that the dose to normal tissue will be lowered and side effects will be reduced. A single treatment plan is envisioned for most patients early in their course except for those who experience target volume change (most often cystic enlargement) early during treatment. Because of the association of the brainstem, optic chiasm and optic nerves, prior studies have not specified brainstem dose-volume constraints and few unexpected adverse events have been observed in these patients. Children with craniopharyngioma tend to be young and vulnerable from the events leading to diagnosis and neurosurgery.

Surgery performed prior to proton therapy may reduce the targeted volume depending on the extent of resection and interpretation of the treatment planning guidelines and the definitions of the gross-tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV). The GTV is defined as the edge of the residual disease as determined by pre- and post-operative neuroimaging and does not include the surgical corridor. In some instances, the resection bed may be added to the GTV when the likelihood of microscopic residual is high. The CTV is defined as the margin of security surrounding the GTV and tumor bed, when indicated, which is meant to encompass subclinical microscopic disease. Current institutional preferences include a 3–5 mm margin which is anatomically confined at interfaces where invasion is unlikely such as the boney base of skull or where a cystic structure may be pushing but not invading a normal tissue structure such as the brainstem or reduced where surgery has not been performed and a clear interface exists between tumor and normal tissue. At the boney interfaces the CTV margin is essentially zero (0 mm); however, for practical purposes it is customary for the CTV contour to appear external to the GTV. At interfaces such as the brainstem, the CTV margin may or may not be altered. A limited survey was conducted regarding target volume margins and treatment parameters at North American proton therapy sites. The survey included recommendations based on non-protocol treatment plans. The consensus is a 3–5 mm CTV margin, 95–100% CTV coverage, 3 mm margin beyond the CTV to define the PTV or equivalent, prescribed dose 54 CGE, and dose maximum 100% including point dose to the chiasm. All investigators would include the post-operative tumor bed in their targeted volume.

13.10 Alternatives to Radical Surgery and Fractionated External Beam Radiation Therapy

Investigators are keen to understand the biology of craniopharyngioma to identify aberrant pathways that might be targeted using existing agents. So far none have been found. Interferon administered systemically is currently being tested through the pediatric brain tumor consortium for newly diagnosed patients and those recurrent after prior radiation therapy. The phase II study of peginterferon alfa-2b (PEGIntron) for pediatric

patients with unresectable or recurrent craniopharyngioma was activated October 2013 (Goldman 2013, ClinicalTrials.gov Identifier: NCT01964300). Other means to treat craniopharyngioma include intracystic isotopes, bleomycin, and interferon (Bartels et al. 2012; Lafay-Cousin et al. 2007). P-32 brachytherapy can provide local control for growing cysts but does not supplant the need for surgery or external beam radiation therapy in most cases (Ansari et al. 2016). Radiosurgery may be considered for local residual disease or recurrence. Toxicity of radiosurgery is not insignificant as described (Murphy et al. 2016).

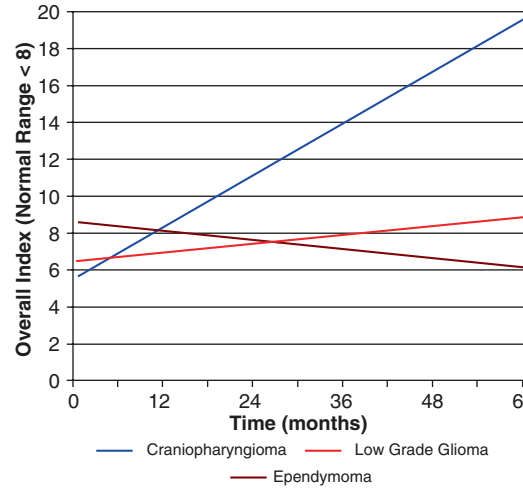


Fig. 13.6 Summary of attentional deficits in children with craniopharyngioma compared to children with other tumor types. Connor's continuous performance test overall index after surgery and radiation therapy—normal 0–8, borderline 8–10, abnormal >10

13.11 Physical Performance

Children with craniopharyngioma are at risk for physical performance limitations related to either their tumor or as a result of treatment. Limitations are likely the result of structural or physiological damage to critical normal tissue structures in proximity to the suprasellar region. Hypothalamic obesity, neuroendocrine abnormalities, visual deficits, and neuromuscular dysfunction including muscle weakness and poor flexibility may contribute to poor physical performance. Poor physical performance may be perpetuated by difficulty with movement. Movement problems encourage inactivity and sedentary behavior resulting in further deterioration in performance capacity. Reduced physical performance may be compounded by neurocognitive and emotional limitations so that participation in everyday activities is difficult and unrewarding (Fange et al. 2002). Less than optimal participation may result in social isolation and contribute to poor health related quality of life.

13.12 Cognitive Effects

Neuropsychological measures have been used to monitor function outcomes regardless of treatment strategy. The typical location of craniopharyngioma in the suprasellar region renders frontal/subcortical pathways vulnerable with respect to tumor infiltration, vascular displacement, surgical disruption (particularly with subfrontal approaches) and radiation effects. Previous studies investigating cognitive outcomes following treatment for craniopharyngioma indicate vulnerabilities in the areas of frontal lobe functioning including perseveration, inflexibility and disinhibition (Cavazzuti et al. 1983; Riva et al. 1998), attention regulation (Kiehna et al. 2006) and memory (Carpentieri et al. 2003; Niwa et al. 1996; Di Pinto et al. 2012; Dolson et al. 2009; Netson et al. 2013). Findings from the St. Jude RT1 protocol indicate that overall academic achievement may be relatively well preserved with reading achievement more vulnerable than math achievement (Fig. 13.6).

13.13 Endocrine Effects

The hypothalamus produces growth hormone releasing hormone (GHRH) and is sensitive to the effects of tumors (hydrocephalus and tumor

invasion) and treatment (surgery and irradiation). Thus, growth hormone deficiency is a common side effect in patients with craniopharyngioma. The extent and impact of growth hormone deficiency before and after irradiation is largely unknown and is, therefore, an important research focus. Estimating the extent of this underreported problem may prompt research to identify means for intervention and improvement in screening guidelines for those at risk. Growth hormone secretion has shown the highest level of sensitivity to the effects of radiation therapy on the hypothalamus. Peak growth hormone levels after radiation therapy decline as an exponential function of time based on the mean dose to the hypothalamus. This conclusion is consistent among patients with craniopharyngioma. The marked difference is that children with craniopharyngioma have a high rate of pre-irradiation growth hormone deficiency. Levels of growth hormone are often undetectable as soon as 12 months after radiation therapy. The assessment of pre- and post-irradiation growth hormone secretion abnormalities in children with brain tumors can be divided according to whether they arise from tumor-related hydrocephalus, tumor invasion, or tumor extension. Among children with craniopharyngioma, pre-irradiation growth hormone deficiency impacted both baseline and longitudinal changes in IQ and reading scores. The treatment of growth hormone deficiency may be a means to improve functional outcomes.

13.14 Ophthalmology and Audiology Effects

Vision loss and impairment from tumor and treatment is common in children with craniopharyngioma (Drimtzias et al. 2014). Worsening vision is most often a sign of tumor progression and not treatment effect. Baseline testing and serial follow-up should be considered a standard of care with the findings useful in the assessment of functional outcomes. Visual function does not necessarily impact functional outcomes (Netson et al. 2013). The incidence of hearing loss after radiation therapy for craniopharyngioma is low based on the assessment of children with this disease (Bass et al. 2016).

13.15 Sleep Disorders, Fatigue and Quality of Life in Craniopharyngioma

Survivors of craniopharyngioma are known to have neuroendocrine deficiencies, visual deficits, and hypothalamic obesity due to tumor location (Rosenfeld et al. 2014). In addition to the tumor location, damage to the hypothalamus by surgery and radiation therapy results in sleep disturbances, daytime hypersomnolence, short-term memory problems, and limited concentration (Palm et al. 1992; van der Klaauw et al. 2008). Reports of sleep disturbances and long term outcomes in survivors have been reported as case studies or small cohorts. Poretti et al. (2004) reported on patients with craniopharyngioma, who were treated with radical tumor excision, and found long-term complications including sleep disturbances and poor quality of life. Increased daytime sleepiness was noted in 6 of 21 patients with five of six of these patients having obesity. Other problems beset by this tumor have been documented in the assessment of long-term survivors (Crom et al. 2010).

13.16 Neuroimaging

Neuroimaging is critical to the treatment and follow-up of children with craniopharyngioma. The purpose of the diagnostic imaging examination is to ensure the diagnosis of craniopharyngioma, define the extent of disease for surgery and radiation therapy planning, perform surveillance for tumor progression after surgery and during and after radiation therapy,

and detect or evaluate treatment-related side effects. Diagnostic imaging should include multi-sequence, multi-planar, multi-dimensionally acquired MR imaging with and without IV gadolinium. The rationale for the chosen sequences supports their ability to differentiate between the cystic and solid tumor components, the interface between the tumor complex and the base of skull, brain parenchyma and CSF spaces. Consideration should be given to the omission of gadolinium in future clinical trials.

Weekly examinations during radiation therapy using a dedicated MR system (1.5 T or 3.0 T) are performed at major institutions during the 6-week proton therapy treatment course to monitor tumor shape and volume. MR imaging during the treatment course is essential to monitor for volumetric changes in the cystic component of the tumor that would reduce target volume coverage and/or increase normal tissue doses. Acquired imaging data during the treatment course may be used to model tumor response to treatment and dosimetry benefits of adaptive therapy. The criterion for adaptive planning consists of creating an adaptive plan when target volume coverage appears to be compromised by change in the volume or shape of the target during treatment. Some centers will perform imaging frequently during the early phase of therapy and discontinue if no change is observed. Others perform less frequently and as clinically indicated. In some instances CT is used and may be appropriate.

More advanced imaging may be performed in the follow-up of children with craniopharyngioma to monitor for response and changes in normal tissues. Diffusion-weighted imaging is the most important magnetic resonance imaging technique to investigate tumor cellularity in various brain tumors. Numerous lines of evidence support the use of DWI in studying tumor response. Uh and others used DWI to study radiation-related normal tissue effects in children with craniopharyngioma treated with proton therapy (Uh et al. 2015).

13.17 Management of Treatment-Related Effects

When early signs of progressive parenchymal changes are present on imaging representing necrosis one may consider referral for hyperbaric oxygen therapy (HBOT). HBOT should be considered when progressive parenchymal changes are associated with symptoms regardless of severity. Steroid therapy, most often dexamethasone, may be initiated and tapered according to symptoms. When the dose of dexamethasone has been tapered to approximately 0.5 mg daily, a taper of hydrocortisone will be initiated at approximately 25 mg daily administered in divided doses. Dexamethasone will be discontinued within 2–3 days of the initiation of the hydrocortisone. Patients are not required to remain on steroid therapy during HBOT. The use of HBOT for non-radiation-induced normal tissue damage resulting from mechanical, ischemic and other toxic insults is less certain (Fig. 13.7).

Vasculopathy is common among patients with craniopharyngioma and is responsible for some of the devastating effects observed after radiation therapy. The incidence and time to onset and factors predictive of severe and life-threatening vasculopathy have not been studied systematically (Bitzer and Topka 1995; Ishikawa et al. 1997; Lui et al. 2007; Mori et al. 1978; Morris 2007; Murakami et al. 2002; Pereira et al. 2002; Rossi et al. 2006; Sutton 1994). Attribution has been given to surgery for peri-operative vasospasm and ischemia whereas late events are largely attributable to radiation dose and volume. Managing vasculopathy is often difficult because medical or surgical intervention is instituted or considered after the process has become established. Three-dimensional time-of-flight MRA of the brain is the standard MRI technique for evaluation the arteries of the Circle of Willis and its branches. This technique is used to evaluate for stenosis, dilatations and aneurysms of the principle components of the intracranial arterial circulation. It should be considered the MRA is a screening tool and represents physiology as well

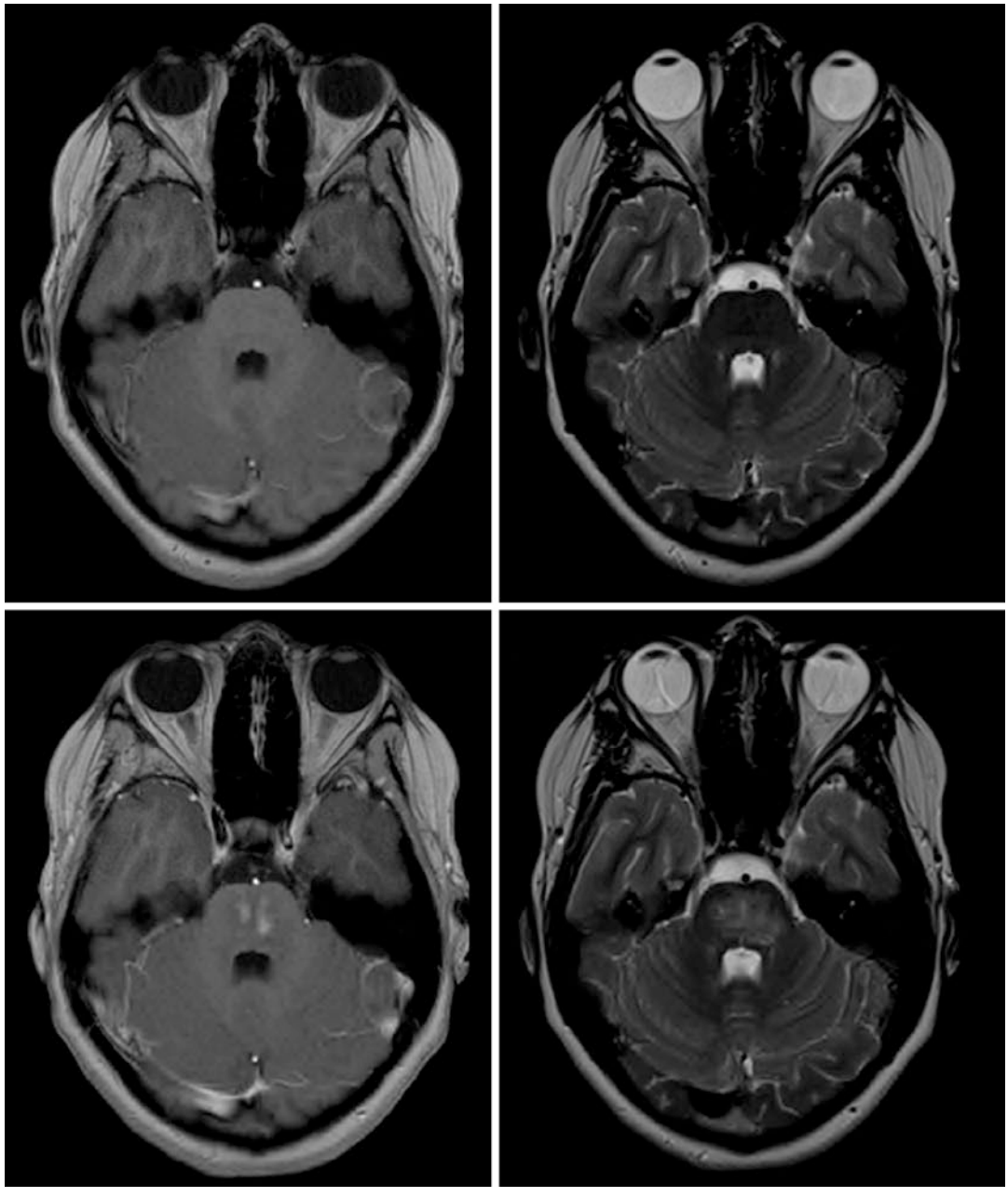


Fig. 13.7 Example of brainstem necrosis and response to hyperbaric oxygen therapy. MRI 6 weeks after the completion of proton therapy (*first row*), MRI 12 weeks after the completion of proton therapy (*second row*); MRI after 6 weeks of hyperbaric oxygen therapy (*third row*); MRI 2 years after proton therapy (*fourth row*)

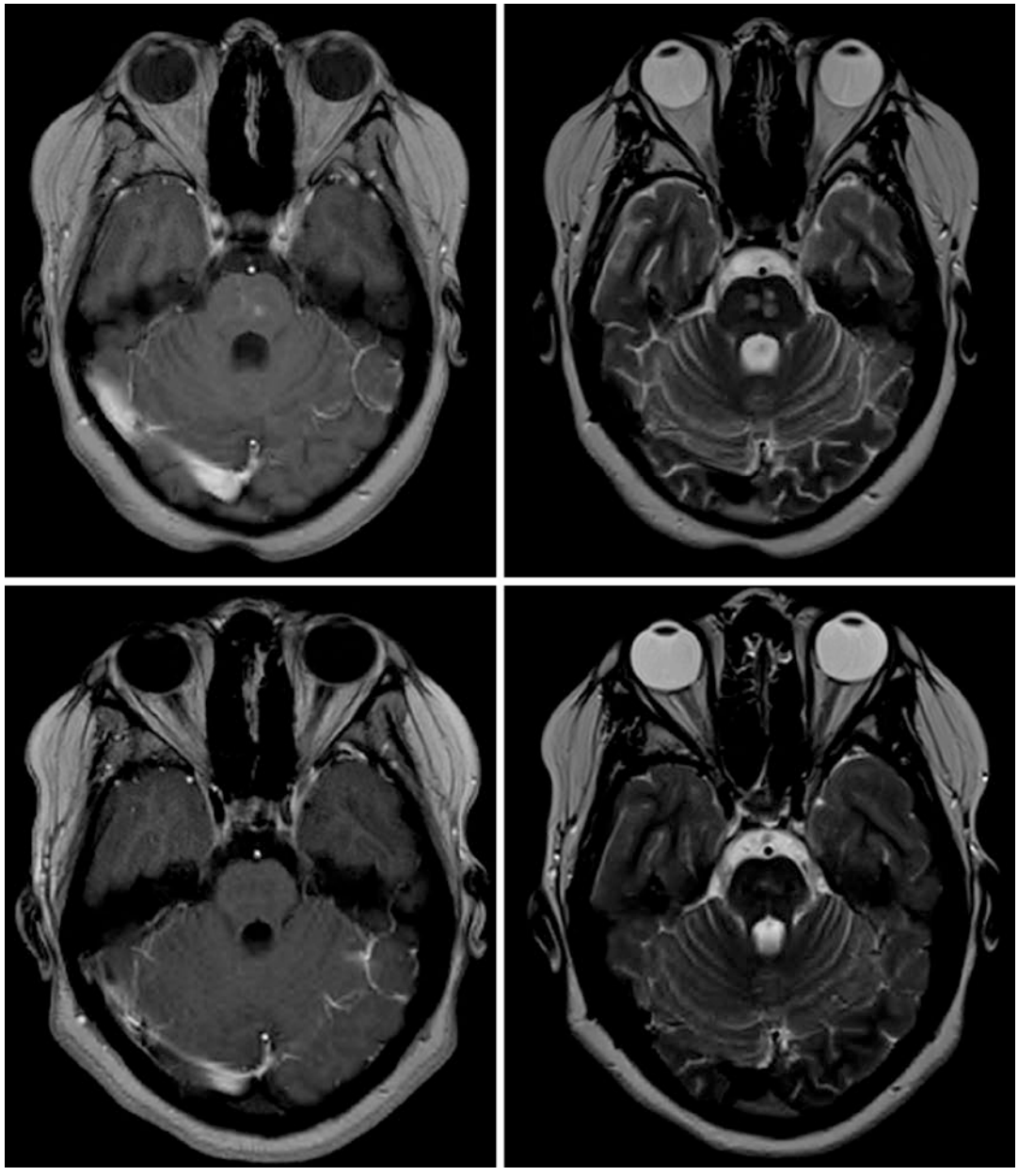


Fig. 13.7 (continued)

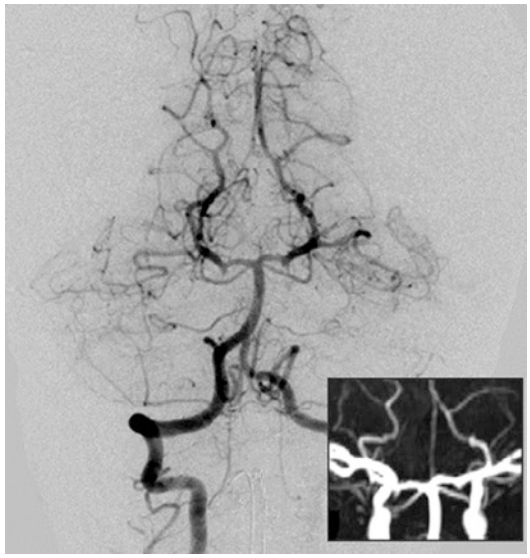


Fig. 13.8 Example of vasculopathy

as structure at the time of the examination. Abnormal MRA should be triaged by an experienced interventional team to consider evaluation of the vasculature by digital subtraction angiography or CT angiography. In some cases additional MR studies evaluating small vessels and tissue perfusion may be indicated and can be used to determine the need for revascularization surgery (Fig. 13.8).

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Hematopoietic Stem Cell Transplantation

14

Natia Esiashvili and Michael A. Pulsipher

14.1 Introduction

Introduced in the early 1970s for treatment of aplastic anemia and leukemia, hematopoietic cell transplantation (HCT) offers treatment for a growing number of patients with complex hematologic malignancies, dysfunctional or absent immune systems, inherited or acquired marrow failure, and selected genetic disorders including hemoglobinopathies and inborn errors of metabolism. The procedure involves a preparative regimen for suppression of the patient's immune system followed by infusion of hematopoietic progenitor cells. There are two major forms of HCT: allogeneic and autologous. In allogeneic transplant, hematopoietic stem cells (HSC) are obtained from related or unrelated donor source after administration of high-dose cytotoxic therapy. Because of immunologic differences between the donor and recipient, graft-versus-tumor (GVT) or graft-versus-leukemia (GVL) effect can occur. Autologous HCT involves exposing patients to myeloablative doses of cytotoxic therapy followed by infusion of the patient's previously stored hematopoietic stem cells. Current pediatric indications for autologous transplant include patients with certain lymphomas, neuroblastoma, and brain tumors.

14.2 Allogeneic HCT

There are three stem cell products currently being used from both related and unrelated donors: bone marrow (BM), peripheral blood stem cells (PBSCs) and cord blood (CB). It is very important and often challenging to achieve appropriate matching between donor and recipient HLA in the major histocompatibility complex located on chromosome 6 (Gragert et al. 2014). Some cell sources are compatible with multiple mismatches (CB), while standard related or unrelated donor BM or PBSC grafts are usually restricted to a single mismatch out of 8 or 10 alleles. Partially HLA-matched (half or more antigens [haploidentical]) related bone marrow or PBSCs can be used after *in vitro* or *in vivo* T-cell depletion.

There is some controversy remaining around selection of patients who may benefit the most from allo-HSCT (Lawson et al. 2000; Gaynon et al. 2006; Pulsipher et al. 2011) (Fig. 14.1). Allo-HCT typically offers benefit only to children at high risk of disease relapse with standard chemotherapy

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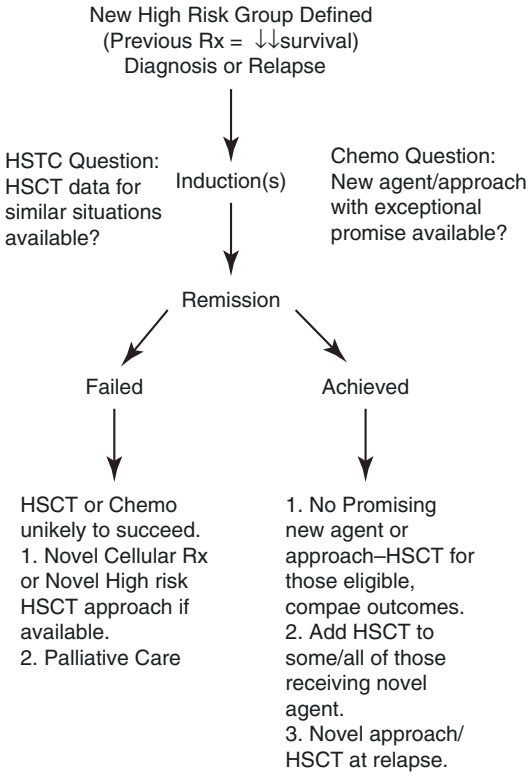

Fig. 14.1 Selection of patients appropriate for consideration of HSCT (Pulsipher et al. 2011)

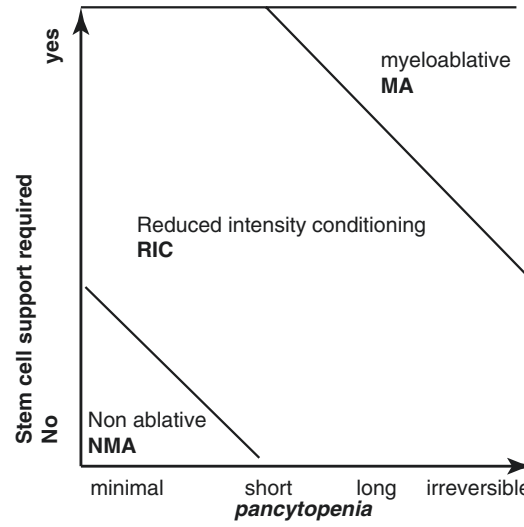

Fig. 14.2 Classification of conditioning regimens in three categories, based on duration of pancytopenia and requirement for stem cell support. Myeloablative regimens (MA) produce irreversible pancytopenia and require stem cell support. Nonmyeloablative regimens (NMA) produce minimal cytopenia and would not require stem cell support. Reduced-intensity regimens (RIC) are regimens which cannot be classified as MA nor NMA (Bacigalupo et al. 2009)

approaches and if appropriately HLA-matched donors are available (Schrauder et al. 2008). Early studies showed that allogeneic approaches led to a decreased risk of relapse caused by an immunotherapeutic reaction of the new bone marrow graft against tumor antigens. This phenomenon is called graft-versus-leukemia (GVL) or graft-versus-tumor (GVT) effect. It is very challenging to balance between GVL/GVT and graft-versus-host disease (GVHD). The best outcomes have been observed with mild or moderate GVHD (grades I-III), compared with patients who have no GVHD or patients with severe GVHD (Woods et al. 2001; Ribera et al. 2007; Pulsipher 2014; Pulsipher et al. 2014). HLA-matched sibling donors have been established to be most beneficial for allo-HSCT (Matthay et al. 1999; Woods et al. 2001; Shaw et al. 2010). However, higher-risk approaches such as haploidentical transplantation are becoming safer and more efficacious and are increasingly being used interchangeably with fully matched allogeneic approaches (Bertaina et al. 2014; Handgretinger et al. 2007; Luznik and Fuchs 2010).

While allo-HSCT is the most promising therapy for high-risk disease (e.g., cytogenetically unfavorable disease and relapsed disease), the conditioning regimen (as well as effective control of GVL effects) play an important role in reducing the incidence of relapse after transplantation. Conditioning regimens include chemotherapy/immunotherapy alone or their combination with radiation therapy that immediately precedes infusion of the stem cells. The goal of conditioning/preparative regimen is to suppress the immune system to minimize risks of rejection. It also creates bone marrow space in the recipient for the donor cells to engraft. Another major benefit of conditioning is to deliver intense treatment to residual cancer cells and to overcome therapy resistance. Based on varying degrees of myelosuppression and immune suppression, preparative treatment has been grouped clinically into myeloablative, nonmyeloablative and reduced-intensity (intensity between myeloablative and nonmyeloablative) (Fig. 14.2).

Classification of conditioning regimens in three categories, based on duration of pancytopenia and requirement for stem cell support. Myeloablative regimens (MA) produce irreversible pancytopenia and require stem cell support. Nonmyeloablative regimens (NMA) produce minimal cytopenia and would not require stem cell support. Reduced-intensity regimens (RIC) are regimens which cannot be classified as MA nor NMA (Bacigalupo et al. 2009).

14.2.1 Indications for Allogeneic HCT

Allogeneic hematopoietic cell transplantation (HCT) is the standard of care for pediatric patients with early medullary relapse of acute lymphoblastic leukemia (ALL). Most patients with B-ALL with isolated central nervous system (CNS) relapse that occurs more than 18 months after diagnosis have good outcomes when treated with intrathecal and systemic chemotherapy followed by irradiation to the neuroaxis. However, there may be a role of HCT in B-cell patients with early isolated CNS relapse (<18 months) or who have T-cell isolated extramedullary relapse at any time.

14.3 Total Body Irradiation

Total body irradiation (TBI) has been developed as a backbone preparative regiment that effectively treats residual malignancy and provides appropriate immunosuppression prior to HSCT (Vitale and Franzone 1991; Barrett 1982). It remains as an important component of many protocols commonly using it in combination with chemotherapeutic agents. There are unique features and advantages of TBI that makes it a preferred method of conditioning for some diseases: relatively homogeneous dose delivery to all sites potentially harboring disease cells, including "sanctuary" sites such as testes and the central nervous system and less chance of cross-resistance with other antineoplastic agents (chemotherapy). TBI presents a unique technical and clinical challenge and if incorrectly delivered, it may increase risks of fatal toxicities.

TBI has competing goals of disease eradication and avoidance of toxicity; attempts to find the optimal balance have led to a variety of TBI dose and fractionation schedules. While optimal regimens have not been identified based on high-level evidence, selection of TBI is made based upon patient, disease and HCT variables. Fractionated TBI regimens have shown superior outcome compared to single fraction TBI mainly due to decrease in toxicities (Deeg et al. 1986; Thomas et al. 1982; Evans 1983). The most commonly accepted total dose of fractionated TBI for myeloablative HCT ranges from 12 to 15 Gy delivered in 6–12 fractions over 3–5 days (Alyea et al. 2002; Marks et al. 2006). Dose-rate is also an important variable for reducing TBI toxicities and 5–10 cGy/min is typically acceptable to limit the risk of acute gastrointestinal and pulmonary toxicities.

The main goal of TBI technique is to achieve homogeneous dose distribution throughout the body with the exception of organs requiring shielding or boosting based on clinical goals. Extended distance from the source is typically required for achieving uniform dose coverage to the entire body with the beam pointed horizontally. Patients are either standing upright, sitting, or partially reclining (Wolden et al. 2013). Opposing anterior and posterior or lateral fields can be used with a beam spoiler to prevent skin sparing (Van Dyk J, Galvin JM, Glasgow GP, et al. AAPM Report No. 17: the physical aspects of total and half body photon irradiation. 1986). Alternatively, patients can be irradiated in a lateral decubitus position with AP-PA fields or lateral fields in a sitting or partly reclining position (Khan et al. 1980). Each position usually poses unique dosimetric challenges for achieving dose uniformity. Another potential hurdle is administration of anesthesia to younger children to maintain integrity of position of the patient in relation to the source, beam spoiler and blocks.

The treatments are complicated by constraints of radiotherapy units and treatment rooms, moreover, large dose variations across the target volume create radiotherapy uncertainties in absolute dosimetry. Centers had developed TBI methods suitable for their particular environment as well

as making it very difficult to assess clinical efficacy when comparing results from various treatment centers. TBI treatment planning and delivery requires specific quality assurance measures, determination of beam characteristic to achieve homogeneous dose distribution to the whole body. These include beam energy, beam spoiler, field size, collimator rotation, treatment distance, and beam calibration at an extended distance. Radiotherapy rooms are not usually designed to provide the long distances (usually >5 m) that may be required for large field treatments. Therefore, radiotherapy departments participating in an HCT program should consider designing at least one larger treatment room designed to accommodate TBI. Typically megavoltage beam is chosen to ensure adequate dose to the full body thickness (Fedoruk and Johns 1957; Findley et al. 1980). Single beam methods at extended distances are much preferred because application of multiple adjacent fields is another way to address the additional dosimetric problems associated with field junctions as well as the concern about cells circulating through the body and, therefore, potentially receiving a reduced dose. With single large beam techniques, some centers historically developed sweeping beam or moving couch techniques. Yet, beam collimation is usually viewed as less cumbersome and may allow more body area coverage at beam corners. But one should be careful not to underestimate the sharp dose fall off at remote points off of the beam axis. For most large field techniques, AP treatments will provide better than 15% uniformity even for cobalt-60 radiation. On the other hand, only 25 MV X-rays at a distance of 300 cm will yield a dose uniformity within 15% for a 50 cm diameter patient (Fig. 14.3) (Van Dyk J, Galvin JM, Glasgow GP, et al. AAPM Report No. 17: the physical aspects of total and half body photon irradiation. 1986).

Because of the 2-dimensional nature of treatment planning, the key information for dose calculation is based on patient body thickness measurements. These measurements should be obtained at the prescription point; often the level of the umbilicus is chosen for TBI. Thickness of other points such as head, neck, mid-mediastinum,

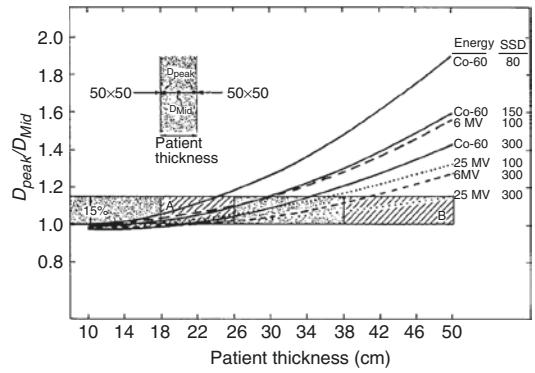

Fig. 14.3 Ratio of peak dose to midplane dose on the central ray versus patient thickness. The horizontal shaded region represents a 15% spread in this ratio. Cross hatched region A represents the typical range of adult patient diameters in the anterior-posterior direction while cross hatched region B represents the range of adult patient diameters in the lateral direction (Van Dyk J, Galvin JM, Glasgow GP, et al. AAPM Report No. 17: the physical aspects of total and half body photon irradiation. 1986). Again beam parameters are critical to consider when choosing from various TBI techniques currently available. In either case, dosimetry measurements should be performed under the operating conditions to insure accurate dose delivery

mid-lung, pelvis, knee, ankle, etc. are obtained to determine dose homogeneity (Galvin 1983). Tissue compensators may improve dose homogeneity (Galvin et al. 1980), however, some centers simplify technique by excluding head and lower limbs for part of the TBI. Overall goal is to keep dose homogeneity close to ±10%. Additionally, shielding for dose attenuation may be required for specific organs (e.g., lungs, kidneys) and boost specifications to other areas of the body (e.g., testes, chest wall). Note that the broad beam attenuation coefficient to be used will be dependent on the maximum scattering angle. For linear accelerators there is an additional problem that the attenuation coefficient changes as the point of interest moves away from the central ray due to a change in the primary beam photon spectrum. This may require attenuation coefficient measurements to be performed at various distances from the central ray. This is particularly important if attenuating materials will be used clinically to reduce the dose to organs located away from the central ray. Typically the head and neck region in patients treated with lateral fields will

be more prone to dose inhomogeneity, and tissue compensators or closing field in that region for part of treatment is recommended to keep dose homogeneity within approximately 10–15%. The simplest method to compensate for tissue curvature is to use tissue-equivalent bolus material placed directly on the skin if loss of skin sparing is not a concern. Alternatively, missing tissue compensators may be considered but use of these is not an easy task due to long treatment distance and lack of patient immobilization.

Dose variability due to inhomogeneities in tissue like lungs and bones can create a different challenge. Practical treatment planning dose calculation programs allow for corrections to a dose distribution by applying an inhomogeneity correction factor to the water-like calculations. However, such procedures produce inaccurate results (by as much as ±12% in the middle of lung) when the field sizes are extended beyond 30 × 30 cm (Van Dyk et al. 1980). The most important parameter in providing inhomogeneity corrections is the geometric outline of the inhomogeneities. CT pixel-based calculation has been the most widely adopted method (Van Dyk 1983). Calculation methods also seem to be more reliable for higher energy photons then Cobalt-60 beam (Malicki et al. 2005).

Clinically, lung injury has been noted to be the most important TBI dose limiting toxicity. Clinical aspects of acute and late pulmonary toxicity in a setting of HSCT will be discussed in later part of this chapter. Here we will examine the evidence around TBI dose contribution to interstitial pneumonitis (IP) or idiopathic pneumonia syndrome (IPS), as it has been termed recently. Even though lung toxicity was found to be the dose limiting toxicity from early TBI experience, the dose threshold question was never fully resolved. Most protocols limit lung dose to 8–10 Gy. Retrospective analysis of 20 studies published (1090 patients) evaluated IPS incidence in a setting of 26 distinct TBI/chemotherapy regiments and multivariate logistic regression was performed to determine dosimetric and chemotherapeutic factors that influence the incidence of IPS. The alpha/beta value of the linear-quadratic model was estimated to be 2.8 Gy. The dose eliciting a 50% incidence, D50, for IPS after 120 mg/kg of cyclophosphamide was 8.8 Gy; in the absence of chemotherapy, the estimated D50 is 10.6 Gy. No dose rate effect was observed (Sampath et al. 2005).

There is interest in use of helical tomotherapy and volumetric modulated arc therapy for total body or selective total marrow irradiation, which warrants further validation for dosimetric and clinical feasibility (Wong et al. 2006, 2009; Mancosu et al. 2013; Takahashi et al. 2013).

Reduced-intensity HSCT regiments have been initially investigated for older adults to reduce the risk of TRM. In children, it is most commonly utilized for patient receiving allo-HCT for an aplastic anemia. The TBI is usually given 2–8 Gy range in combination with Fludarabine and can result in successful and durable engraftment (Mcsweeney et al. 2001; Niederwieser et al. 2003; Maris et al. 2003; Tomblyn et al. 2008; Stelljes et al. 2005).

TBI requires good communication and coordination between the radiation oncologist, medical physicist, dosimetrists, nurses, and radiation therapists. Moreover, TBI has to be tightly integrated into the general HCT program. It is crucial to have detailed information exchange and documentation of choice of preparative regimen, including TBI dose, between radiation oncology and transplant team. Treatment scheduling and toxicity management measures also need to be coordinated among all subspecialties involved (hematology/oncology, radiation oncology, nurses, physicist, anesthesiologist for sedation of younger children, radiation therapy technologists, social worker, etc.). For the entire course of TBI, a physician should be in close proximity to manage any clinical issues. Physics staff also should be on standby to solve any technical or other problems to ensure uninterrupted dose delivery. Because the TBI cannot be delayed or canceled, a back-up method of treatment should be considered (alternate machine or even another near-by radiation therapy department).

14.4 Acute Complications of HCT

Failure of immune reconstitution can be a fatal complication after HCT (Antin 2005; Fry and Mackall 2005). Factors contributing to immune

recovery include stem cell source, GVHD and graft manipulation (removal of T cells) (Bunin et al. 2012).

Acute toxicities from intense conditioning regiments coupled with infections can lead to multi-organ failure and are major contributors for early post-HCT mortality. The TBI is fairly intense treatment and because of entire body been exposed to the dose, multiple acute toxicities can be anticipated. Acute side effects include fatigue, loss of appetite, nausea, emesis, parotitis, xerostomia, headache, fatigue, mucositis, and diarrhea (Buchali et al. 2000). Most of the symptoms are well-managed with supportive care in a specialized inpatient HCT unit.

GVHD is the result of immunologic activation of donor lymphocytes targeting major or minor HLA disparities present in the tissues of a recipient (Ferrara et al. 2009). Acute GVHD usually occurs within the first 3 months post-transplantation, although delayed acute GVHD has been noted in reduced-intensity conditioning and nonmyeloablative approaches, where achieving a high level of full donor chimerism is sometimes delayed. Typically, acute GVHD presents with at least one of three clinical manifestations: skin rash, hyperbilirubinemia, and secretory diarrhea. Acute GVHD is classified by grading the severity of skin, liver, and gastrointestinal involvement and further combining the individual grading of these three areas into an overall stage that is prognostically significant (Przepiorka et al. 1995). Morbidity and mortality from acute GVHD can be reduced through immune suppressive medications given prophylactically or T-cell depletion of grafts. Because of immunosuppression, patients are susceptible to infections and they been shown to account for a significant percentage (4–20%) of both early and late deaths after HSCT (Wingard et al. 2011). Implementation of proper infection control measures is paramount for reduction of risk of TRM. Patients also require prophylactic interventions, like intravenous hydration, administration of antiemetics, and antimucositis drugs. Sinusoidal obstructive syndrome/veno-occlusive disease of the liver (SOS/VOD) is the result of damage to the hepatic sinusoids, clinically presenting as the right upper quadrant pain with hepatomegaly, fluid retention and hyperbilirubinemia. This syndrome has been estimated to occur in 15–40% of pediatric myeloablative transplantation patients. The risk factors include the use of busulfan, TBI, infections, GVHD, and pre-existing liver dysfunction. Life-threatening SOS/VOD generally occurs early after transplantation and is characterized by multiorgan system failure.

Pulmonary complications are a significant cause of early mortality after bone marrow transplantation. Systemic activation of inflammatory cytokines during sepsis and cell-mediated immune injury in the lung during GVHD reactions are commonly underlying pathophysiology for acute injury of lung tissue. About 30–40% of patients experience diffuse interstitial pneumonias with no infectious etiology found (Krowka et al. 1985). Different terminologies have been used to describe this complication, including interstitial pneumonitis and idiopathic pneumonitis syndrome (IPS). IPS is defined as "evidence of widespread alveolar injury in the absence of active lower respiratory tract infection" after marrow transplantation (Sampath et al. 2005). Diagnostic criteria include clinical symptoms of pneumonia, radiographic evidence of diffuse pulmonary infiltrates, and abnormal pulmonary function, all in the absence of documented infectious organisms (Clark et al. 1993). IPS typically occurs from 14 to 90 days after the infusion of donor cells. Possible etiologies include direct toxic effects of the conditioning regimens, occult infection, TBI or GVHD (Shankar et al. 1999; Tait et al. 1991; Depledge et al. 1983; Barrett et al. 1983). Bronchoalveolar lavage, rather than lung biopsy, is recommended as the primary diagnostic approach. Several studies have reported mortality rates associated with IPS to be as high as 60–70% (Meyers et al. 1982; Wingard et al. 1988; Weiner et al. 1986; Gopal et al. 2001) (Kantrow et al. 1997), however, the incidence and outcome of this complication appears to be decreasing, possibly because of less-intensive preparative regimens, better HLA matching, and better definition of occult infections through polymerase chain reaction (PCR) testing of blood and bronchoalveolar specimens (Crawford et al. 1988).

14.5 Autologous HCT

Patients receiving autologous HCT are subjected to myeloablative therapy with intent to eliminate malignant cells, commonly in a setting of disease resistance to conventional dosing of cytotoxic therapy. Patients are initially treated with a number of chemotherapy cycles to determine their responsiveness to it and also to reduce the chance of bone marrow contamination with tumor cells. Although many techniques have been developed to remove or *purge* tumor cells from products, most studies looking into these approaches have shown no benefit to tumor purging. Subsequently, patient's stem cells (progenitor CD34+ cells) are harvested and stored after their immobilization with growth factor through the process of apheresis. Autologous HCT is typically given during the consolidation phase of high-risk regimens and involves myeloablative chemotherapy to eradicate minimal residual disease followed by infusion of patient's stem cells. TBI had been previously used in autologous HCT conditioning regimens; however, because of growth stunting and secondary solid malignancy risks, it was subsequently substituted with high dose chemotherapy. Examples of current protocols include carboplatin/etoposide/melphalan or busulfan/melphalan as conditioning regimens. Two or more sequential cycles of myeloablative chemotherapy and stem cell rescue given in a tandem fashion has been shown to be feasible for patients (Granger et al. 2012; Seif et al. 2013). Efficacy of two cycles versus one cycle of myeloablative chemotherapy with stem cell rescue for high risk neuroblastoma was recently tested in a cooperative group trial, showing improved EFS with two cycles (personal communication with Dr. Julie Park).

The most common autologous transplant indications are the following: High-risk neuroblastoma, relapsed Hodgkin lymphoma and non-Hodgkin lymphoma, High-risk and relapsed brain tumors, relapsed or refractory germ cell tumors. Autologous HCT is accepted as a salvage therapy for primary refractory or relapsed Hodgkin and non-Hodgkin lymphoma (Harris et al. 2011). Several studies suggested that allogeneic HCT may result in better outcome compared to autologous HCT for refractory/relapsed anaplastic large cell lymphoma (Gross et al. 2010; Woessmann et al. 2006; Fukano et al. 2015). For solid tumors, autologous HCT indication is somewhat limited. High-dose chemotherapy and autologous stem cell rescue has curative potential for patients with relapsed systemic non-germinomatous germ cell tumors (Siegert et al. 1994; Modak et al. 2004; Beyer et al. 1996; Motzer et al. 1996). Although there is limited clinical experience showing change of long-term survival (Burdach et al. 2000), the role of HCT in Ewing's sarcoma is controversial. Similarly, experience from rhabdomyosarcoma (RMS) and non-RMS soft tissues sarcomas showed questionable or no benefit from high dose chemotherapy and stem cell rescue compared with standard chemotherapy, although randomized trials have not been performed (Admiraal et al. 2010; Peinemann et al. 2011).

14.6 Late Mortality After HCT

The highest incidence of mortality after HCT occurs in the first 2 years, mostly caused by relapse. Late mortality in the allogeneic HCT is also primarily attributable to relapse. In contrast to studies of adult patients, non-relapse mortality is less common in children, and death caused by chronic GVHD. Given intensity of HCT, many organ systems can be affected from therapy and develop late toxicities.

Common late effects from HCT include infertility, growth stunting, cognitive dysfunction, cataracts, pulmonary fibrosis, cardiac dysfunction, endocrine dysfunction and metabolic syndrome. Second malignant neoplasms, especially solid tumors from TBI exposure tend to increase in incidence over time (Danner-Koptik et al. 2013). Overall, patients treated with HCT in childhood are at risk for decreased quality of life and on occasion can have physical dysfunction caused by therapy, thus they require careful clinical monitoring (Sundberg et al. 2013).

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Utilization of Radiation for Pediatric Hodgkin Lymphoma

15

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15.1 Background, Clinical Presentation, Pathologic Classification, Staging and Work-Up, and Prognostic Factors

15.1.1 Background

Hodgkin lymphoma (HL) was one of the first malignancies successfully managed with radiotherapy. Today, HL is highly curable, with 85–90% of children achieving long-term survival through a combination of chemotherapy and radiotherapy (Ward et al. 2014).

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15.1.2 Epidemiology

HL is relatively rare in children, representing approximately 6–7% of pediatric malignancies, (Childhood Hodgkin Lymphoma Treatment–for health professionals (PDQ®) 2016); however, it is the most common malignancy among adolescents 15–19 years old (800 cases in 2014) (Ward et al. 2014). The age distribution of patients with HL is bimodal with some geographic and ethnic variation with first peaks of incidence occurring in childhood in developing countries, and in young adults in their mid to late 20s in developed countries, with the second peak in both cohorts in those over 50 years old (Thomas et al. 2002).

HL is believed to have some association with infectious exposure. In young children with HL, risk factors for earlier exposure to infections including lower socioeconomic status, later birth order, and larger family size are evident (Westergaard et al. 1997). In young adults with HL, risk factors for late exposure to infections, including higher socioeconomic status, earlier birth order, and smaller family size are more typical (Westergaard et al. 1997). Epstein-Barr virus (EBV) has also been implicated as a cause of HL, especially in children below 10 years of age, in the immunosuppressed, and in the elderly. EBV is most commonly associated with the mixed cellularity subtype of HL (Claviez et al. 2005; Jarrett et al. 2005; Flavell and Murray 2000). There is also an increased risk of HL in immunodeficient

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patients, including patients with HIV/AIDS (Levine 1998).

Studies have also indicated a potential for an inheritable risk for HL (Kharazmi et al. 2015; Mack et al. 1995; Linabery et al. 2015). In a recent study evaluating the familial risk of HL among five Nordic countries, first-degree relatives of a patient with HL had a threefold risk of developing HL over the general population (Kharazmi et al. 2015). Interestingly, the risk was only 2.1 for parents and/or children, while it was sixfold for siblings, and 57-fold for same-sex twins.

15.1.3 Clinical Presentation

The presentation of HL is related to sites of disease and subtype of lymphoma. About 60% of pediatric patients are diagnosed with stage I-II HL, and 15–20% of patients will have stage IV disease, affecting noncontiguous extranodal sites such as the lung, liver, bones, and bone marrow (Levine 1998). B symptoms, which are characterized by drenching night sweats, weight loss of at least 10% over 6 months, or fevers of at least 38 °C over 1–2 weeks, affect approximately 25% of patients. B symptoms are more common in children over 10 years old (~30%) than in young children (20%) (Pileri et al. 2002).

Pediatric patients present with painless cervical lymphadenopathy in about 80% of newly diagnosed cases (PDQ Cancer Information Summaries 2016). In children 10 years and older, 75% will have mediastinal involvement; in patients younger than 10 years old, one-third will have mediastinal adenopathy (PDQ Cancer Information Summaries 2016). These patients may experience shortness of breath, chest pain, or cough, especially if their disease is bulky. A bulky mass can also result in superior vena cava syndrome. Isolated disease below the diaphragm is rare, occurring in less than 5–10% of patients (Vassilakopoulos et al. 2006).

The cytokines produced by the Reed-Sternberg cells and the supporting stroma within the lymph nodes, namely interleukin-6 (IL-6), are thought to be responsible for some of the symptoms associated with HL, including pruritis, urticaria, and fatigue, as well as B symptoms (Skinnider and Mak 2002). Some studies have associated elevated serum levels of IL-6 with a worse prognosis, including failure to induce a complete response to treatment and potentially poorer survival (Reynolds et al. 2002; Kurzrock et al. 1993). IL-6 production is also thought to induce anemia of chronic inflammation by elevating hepcidin levels (Hohaus et al. 2010). In rare cases, patients may present with alcohol-induced pain, setting in within minutes after ingestion of alcohol and resolving within 30 min to a few hours. The pain is typically localized to the affected lymph node region, and is more commonly seen with mediastinal lymph node involvement, female patients, and nodular sclerosing HL (Bobrove 1983). Although this symptom only affects 2–3% of patients, it is considered pathognomonic for HL. The mechanism for such pain is unclear, but may be related to the alcohol dehydrogenase pathway (Banerjee 2011).

15.1.4 Pathologic Classification

The classical pathologic finding for HL is the multinucleated Reed-Sternberg (RS) cell (Kuppers et al. 2002), which represents clonal populations of transformed germinal center B cells, although in 2% of cases these are derived from T cells (Pileri et al. 2002). The RS cells, which are characteristic of classical HL and which lose B-cell antigens, express CD30 in all cases; in 70% of cases, the cells express CD15. CD20 expression is rare (Tzankov et al. 2003). The malignant Reed-Sternberg cell elicits a reactive cellular infiltrate compromised of lymphocytes, macrophages, granulocytes, and eosinophils. Nodular lymphocyte-predominant HL (NLPHL) is comprised of lymphocytic and histiocytic cells, which are usually CD30- and CD15-negative, and CD20- and CD45-positive (Shankar and Daw 2012). Subtyping of HL should be based on pretreatment biopsy samples as chemotherapy or radiation therapy can alter the morphology to a lymphocyte-depleted-like histology (Pileri et al. 2002).

The WHO classification of HL is broadly divided into classical HL and nodular lymphocyte-predominant HL. Classical HL comprises up to 95% of all HL diagnoses. There are four subtypes

of classical HL: nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted. Nodular sclerosis is seen in 70–80% of adolescents and 50–55% of young children, although there are geographic variations in incidence (Pileri et al. 2002). Nodular sclerosing HL is characterized by "sclerosis," or fibrosis, from formation of broad collagen bands; lacunar cells, which contain polylobular nuclei and small-medium nucleoli. The mixed cellularity subtype affects 30–50% of cases in children younger than 10 years and 10–15% of cases in children 10–19 years old. Lymphocyte-rich and lymphocyte-depleted cases are rare in the pediatric population, representing less than 5% of cases (Schellong et al. 1999).

NLPHL represents a minority of all HL diagnoses and is more common in males. NLPHL is considered to have a favorable prognosis and a more indolent course, although it is also characterized by a high rate of salvageable late relapses. This subtype typically presents in a single lymph node rather than a group of nodes. Bone marrow involvement is rare in these cases.

Table 15.1 Staging criteria for patients with Hodgkin lymphoma

Stage	Description
Stage I	Single lymph node region, or lymph node and surrounding area
Stage II	Two separate lymph node regions; or lymph node or organ and second area. Both areas are on same side of diaphragm
Stage III	Disease involves both sides of the diaphragm
Stage IV	Diffuse or disseminated involvement of at least one extralymphatic organ (e.g., liver, bone marrow, lungs)
Modifiers	Description
A	Absence of constitutional (B-type) symptoms
B	Presence of B-type symptoms, including drenching night sweats, weight loss >10% in 6 months or less, or fevers >38 °C over 1–2 weeks
S	Disease involving the spleen
E	Disease is not in lymph nodes, or has spread from lymph nodes to adjacent tissue
X	Presence of bulky disease (>10 cm, or in mediastinum, >1/3 chest diameter on chest x-ray

15.1.5 Staging

Hodgkin lymphoma is staged using the Ann Arbor staging system, which was developed in Ann Arbor, MI by the Committee on Hodgkin's Disease Staging Classification (Carbone et al. 1971). As shown in Table 15.1, staging is based on both location and extent of disease as well as presence or absence of associated symptoms.

The classic lymph node groups (Fig. 15.1) have historically been defined as follows (National Institute of Health (US) 2016):

15.1.5.1 Above the Diaphragm

- Waldeyer ring (ring of lymphoid tissue encircling the nasopharynx and oropharynx)
- Cervical lymph nodes: occipital, submental, preauricular, submandibular, internal jugular, and supraclavicular (scalene)
- Infraclavicular axillary and pectoral nodes
- Epitrochlear, brachial
- Mediastinal
- Hilar

15.1.5.2 Below the Diaphragm

- Spleen
- Paraaortic
- Mesenteric
- Iliac
- Inguinal, femoral
- Popliteal

15.1.6 Workup

All patients presenting with lymphadenopathy should undergo a thorough medical history and physical examination. Duration of symptoms, sites of lymphadenopathy, presence of B symptoms, alcohol-induced pain, pruritis, and anorexia should be determined. Family history of malignancy as well as social history, including number of siblings, socioeconomic status, and personal history of infectious disease or immunocompromised conditions, should also be included. Physical examination should con-

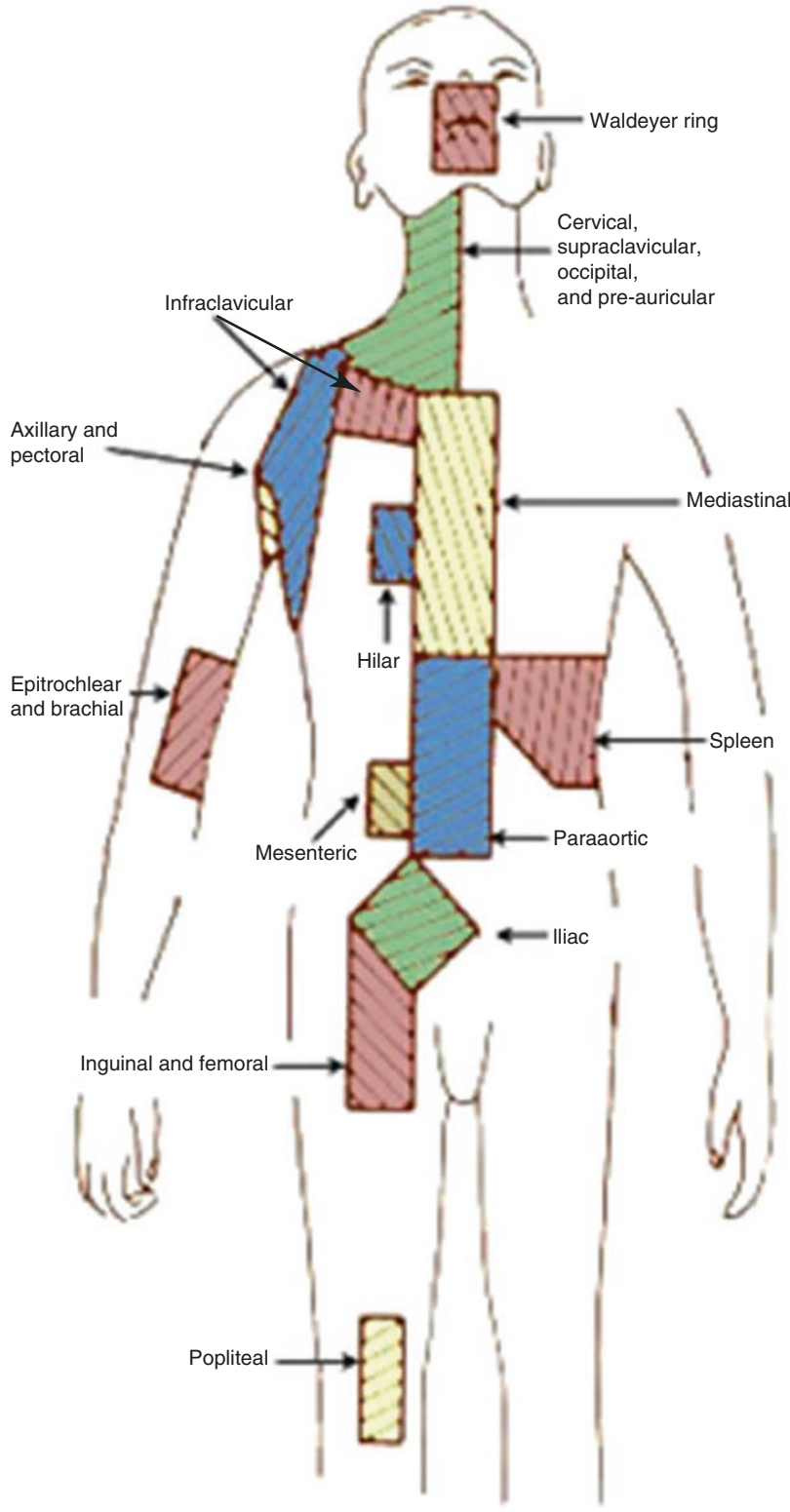

Fig. 15.1 A depiction of lymph node regions in the body. Image borrowed from Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015

centrate on all assessable lymph node regions for presence of lymphadenopathy. Assessment of extralymphatic organs at risk for enlargement, such as the liver and spleen, should also be undertaken.

The workup for patients presenting with lymphadenopathy or extranodal disease suspicious for lymphoma then involves obtaining a tissue diagnosis. The gold standard for tissue is an excisional biopsy of the largest accessible lymph node. Excisional biopsy allows full evaluation of malignant cells, especially Reed-Sternberg cells, in the context of stromal tissue with architecture intact, which is critical for diagnosis of HL. The node should be submitted intact in a dry empty container to minimize distortion. If there is a concern for non-HL, some tissue should be frozen and submitted. If an excisional biopsy is not possible, core needle biopsy should be attempted. While fine needle aspiration is discouraged for initial diagnosis of HL owing to the risk of false negatives, in the hands of an experienced cytopathologist and with the aid of immunohistochemistry it can yield a diagnosis in some cases if necessary (Hoppe et al. 2007; Das et al. 2009). If an excisional biopsy is not possible, core needle biopsy should be attempted. Biopsies of equivocal lymph nodes should be also done when possible if a positive finding will alter staging and management. Staging laparotomy is no longer recommended but suspicious nodes should be sampled if a positive finding will alter management.

FDG (^{18}fluoro-2-deoxyglucose) positron emission tomography (PET) with DICOM-registered computed tomography (CT) is considered part of the standard workup for adult patients with HL and is now standard practice for pediatric patients as well. PET-CT scanning allows for full-body staging and can help determine tumor involvement in equivocal nodes or in extralymphatic organs. In about 10–20% of cases, PET-CT will alter disease stage compared with conventional staging using CT scans alone. PET-CT is also used to determine response to therapy and can guide additional systemic or local therapy, including radiation therapy (Robertson et al. 2011; Paulino et al. 2012). However, PET-CT is subject to false positives due to infection, inflammation, or brown fat (especially in children). High-quality CT scanning of the area of interest with intravenous (IV) contrast may also be desired to help guide treatment planning as the resolution of PET scanning may not be adequate for radiotherapy planning purposes. Standard anterior-posterior projection chest X-rays are also still used in children with mediastinal involvement to determine the presence of bulky disease (>33% of the chest diameter at any vertebral body level) (Cheson et al. 2014).

Bone marrow biopsy is recommended for children with B symptoms and for all patients with stage III-IV disease. More recently, however, this has come under debate as PET-CT has been shown to detect bone marrow involvement (Chen-Liang et al. 2015; Hines-Thomas et al. 2010). Data to recommend against bone marrow biopsy for the above indications is scarce at this time, but may become more available in the near future (Cheng et al. 2011; Cheson et al. 2014).

Before initiating treatment, the following baseline laboratory tests should be obtained: complete blood count with differential; complete metabolic panel; erythrocyte sedimentation rate as a marker of inflammation; and lactate dehydrogenase as a potential indicator of bulk of disease. Premenopausal females of appropriate age should have a documented negative pregnancy test and should be counseled on the importance of appropriate contraception during treatment and for at least 1 year thereafter. Both male and female patients should be counseled on the risks of infertility after chemotherapy and radiation therapy; adolescents and young adults should be referred to a fertility specialist for consideration of sperm or egg storage. Baseline pulmonary function tests and an echocardiogram should also be completed before administration of bleomycin and adriamycin, respectively. Finally, depending on the patient's age and risk factors, HIV testing can be considered as administration of anti-retroviral therapies along with treatment of HL can improve outcomes.

15.1.7 Prognostic Factors

Risk stratification for pediatric patients with HL has been defined by the various cooperative groups. The categories of low, intermediate, and

Table 15.2 Risk stratification for pediatric patients with Hodgkin Lymphoma defined by the various cooperative groups (Friedman et al. 2014; Furst et al. 1989; Schellong et al. 1994; Tebbi et al. 2012; Weiner et al. 1997)

Risk stratification	Children's Oncology Group	St. Jude/Stanford/Dana-Farber	German studies
Low	IA-IIA non-bulky	Stage IA-IIA; non-bulky and <3 sites	IA-IIA; IB
Intermediate	IA-IIA bulky; IB-IIB or IA_E-IIA_E, bulky or non-bulky; IIIA-$IIIA_E$ bulky/non-bulky; IVA-IVA_E	IB, IA_E-IIA_E, IIIA, ≥3 sites or bulk	IIB, IIIA; IA_E, IB_E, IIA_E
High	IIIB-IVB, sometimes IIB bulky, IVA	IIB, IIIB, IV	Stages IIIB, IV; IIB_E, $IIIA_E$, $IIIB_E$

high risk are summarized in Table 15.2, and are based on stage, presence of B symptoms, and presence of bulky disease. The definition of bulky disease also varies but generally is defined as a single nodal mass greater than 10 cm or a mediastinal mass greater than 1/3 the intrathoracic diameter (Cheson et al. 2014). Risk stratification and the corresponding treatment recommendations should be carefully considered and not confused.

Multiple studies have also tried to determine which pretreatment factors portend a better or worse prognosis. Among pediatric cohorts, advanced disease with B symptoms, nodular sclerosing sub-type, extranodal extension, and elevated ESR have been associated with worse outcomes (Ruhl et al. 2001; Nachman et al. 2002; Henry-Amar et al. 1991). The Stanford group identified male sex; stage IIB, IIIB, or IV disease; bulky mediastinal disease; elevated white blood cell count (>13.5 × 10^3/mm^3); and anemia with hemoglobin below 11 g/dL as poorer prognostic factors, with diminishing disease-free survival and overall survival (OS) with each additional risk factor present (Smith et al. 2003; Metzger et al. 2008). In a retrospective analysis, Metzger et al. found that black children have lower event-free survival (EFS) than white children (although 5-year OS does not differ), despite similar presenting features and enrollment rates on clinical trials (Metzger et al. 2008). EBV infection in HL as a marker of prognosis is controversial. In a Surveillance, Epidemiology, and End Results (SEER) database study, Keegan et al. observed that EBV was associated with favorable survival in HL patients below 15 years old (Keegan et al. 2005). European retrospective data, however, show inferior survival (Jarrett et al. 2005; Claviez et al. 2005). Modern combined-modality therapy greatly diminishes the prognostic effect of EBV infection (Claviez et al. 2005; Lee et al. 2014). Lastly, the Children's Oncology Group recently reported on the development of the Childhood International Prognostic Score (ChIPS) based on the outcomes of 1721 patients with intermediate-risk HL treated on the AHOD 0031 protocol (Friedman et al. 2014). Four variables were found to be predictive of EFS: stage IV, bulky mediastinal disease, albumin < 3.5, and fevers. The EFS rates based on how many of these variables were found at presentation were as follows: 0–1, 90%; 2, 78%; and 3, 62%.

15.1.8 Interim Imaging

The extent of initial response to treatment has been correlated with relapse and survival outcomes in pediatric HL patients. The Children's Oncology Group study AHOD 0031 evaluated the role of early chemotherapy response in risk-adapted therapy. Patients were classified as rapid early responders (RERs) or slow early responders (SERs) following two cycles of ABVE-PC chemotherapy based on CT criteria. RERs had better 4-year event free survival compared with SERs (86.9% vs 77.4%, p<0.001) (Friedman et al. 2014).

While the use of PET-CT has become standard for adult HL patients in an effort to move toward risk-adapted therapy, this approach is still being investigated in the pediatric population (Iberri et al. 2015). Active lymphoma studies typically use the Deauville 5-point scale for assessing

Table 15.3 Deauville positron emission tomography response criteria [105]

Scores	Description
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions

response to treatment by PET scan (Table 15.3). Among adult patients early interim PET response has been shown to be the strongest prognostic factor with positive results strongly predictive of progression, especially in patients with advanced stage disease or extranodal extension (Gallamini et al. 2007; Hutchings et al. 2006). The predictive value of PET-CT has also been investigated in pediatric patients and appears to be a good predictor of outcome (Ilivitzki et al. 2013). Lack of FDG activity after treatment has been associated with prolonged disease-free survival (Kamal and Elsaban 2014; Miller et al. 2006), even with a residual mass present on the CT component (Miller et al. 2006). Overall, PET-CT has demonstrated high sensitivity and a high negative predictive value for treatment outcomes; the positive predictive value of PET-CT is not as strong (Evens and Kostakoglu 2014).

15.2 Therapeutic Trials

Treatment of pediatric HL has come a long way since the use of total nodal irradiation. Combined-modality treatment, introduced in the 1960s, has led to improved OS rates exceeding 90% (Ward et al. 2014). Owing to the concurrent observation of treatment-related late effects, such as infertility and secondary malignancies, chemotherapy agents have been modified and radiation doses and fields decreased over the years. Today, patient response to chemotherapy is studied to guide radiotherapy planning with the aid of modern imaging such as FDG-PET scans. While treatment group allocation varies among cooperative groups, evolving through generations of trials within each group, risk stratification remains an integral guide for all clinicians choosing the appropriate treatment for a patient. With the goal of maintaining a high cure rate and minimizing toxicity and late effects of treatment, risk-adapted therapy with response-based use of radiation is currently the backbone of most European and North American pediatric HL trials.

15.2.1 Low-Risk Disease

The majority of patients with low-risk HL experience excellent outcomes following 2–4 cycles of chemotherapy and low-dose radiation (Table 15.4). Reducing treatment-related morbidity among these patients is of particular interest considering their excellent prognosis.

The German-Austrian multicenter trial for pediatric Hodgkin disease has developed generations of trials since 1978 focusing on finding the balance between good cure rates and treatment toxicity. With reports of secondary leukemia and male sterility after MOPP chemotherapy (mechlorethamine, vincristine, procarbazine, and prednisone), they proposed substituting nitrogen mustard with doxorubicin in their induction therapy (OPPA: vincristine, prednisone, procarbazine, and doxorubicin) and with cyclophosphamide in the later cycles (COPP: cyclophosphamide, vincristine, prednisone, and procarbazine) (Schellong 1996). Nevertheless, even minimal therapy consisting of 2 cycles of OPPA was associated with elevated follicle-stimulating hormone levels in 29% of males, an indicator of impaired spermatogenesis (Schellong et al. 1994).

Addressing the gonadotoxic effect of procarbazine in boys, the German-Austrian group has designed a procarbazine-free regimen in their HD-85 trial (Schellong 1996). Unfortunately, this study was terminated early after 22 months because of high rates of early progression and relapses, especially among treatment group 2 (TG2) (intermediate-stage) and TG3 (advanced-stage) patients. The boys in remission had normal endocrine parameters for testicular function, establishing the importance of replacing procarbazine in this patient population. In the

Table 15.4 Recent studies for low-risk Hodgkin lymphoma

	Definition of risk	Treatment	EFS/PFS	OS
DAL HD-90	TG1: I, IIA	OPPA × 2 (girls) OEPA × 2 (boys) Local RT 25 Gy (30–35 Gy if residual)	5-year EFS: 94%	5-year OS: 99.6%
GPOH-HD95	TG1: I, IIA	OPPA × 2 (girls) OEPA × 2 (boys) If CR: no RT If <CR: reduced involved field 20 Gy (boost to residual bulk 30–35 Gy)	5-year PFS: 94.4%	5-year OS: 98.8%
GPOH-HD-2002	TG1: I, IIA	OPPA × 2 (girls) OE*PA × 2 (boys) If CR: no RT If <CR: IFRT 19.8 Gy (boost to residual 30–35 Gy)	5-year PFS: 92.7%	5-year OS: 99.5%
POG8625	I, IIA, $IIIA_1$	MOPP/ABVD × 4 If CR/PR: MOPP/ABVD × 2 vs. IFRT	8-year EFS: 86.9%	8-year OS: 95.4%
CCG5942	Group 1: I without RF IIA without RF	COPP/ABV × 4 If CR: randomization to 21 Gy IFRT or no RT If PR: IFRT	3-year EFS: 95%	3-year OS: 100%
P9426	I, IIA, $IIIA_1$	DBVE × 2 If CR: IFRT If <CR: DBVE × 2 + IFRT	5-year EFS: 88.3%	5-year OS: 97.6%
COG AHOD0431	IA, IIA (no bulk)	AVPC × 3 If CR: no RT If PR: 21 Gy IFRT	2-year EFS: 84%	OS2: 100%
Stanford-DFCI-St. Jude 1990–2000	I–II (no bulk, no E)	VAMP × 4 If CR after 2 cycles: 15 Gy IFRT If PR after 2 cycles: 25.5 Gy IFRT	5-year EFS: 92.7%	5-year OS: 99.1%
Stanford-DFCI-St. Jude 2000–2009	IA–IIA (no mediastinal bulk, no E, <3 involved nodal regions)	VAMP × 4 If CR after 2 cycles: no RT If PR after 2 cycles: 25.5 Gy IFRT	5-year EFS: 88.5%	5-year OS: 100%

Abbreviations: *AVPC* adriamycin (doxorubicin),vincristine, prednisone, cyclophosphamide; *COPP/ABV* cyclophosphamide, vincristine sulfate (Oncovin), procarbazine hydrochloride, prednisone, doxorubicin hydrochloride (Adriamycin), bleomycin sulfate, and vinblastine sulfate; *CR* complete remission; *DBVE* doxorubicin, bleomycin, vincristine, and etoposide; *EFS* event-free survival; *IFRT* involved-field radiation therapy; *MOPP* mechlorethamine, vincristine, procarbazine, and prednisone; *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine; *OEPA/OPPA* vincristine sulfate (Oncovin), etoposide, prednisone, doxorubicin hydrochloride (Adriamycin); *OS* overall survival; *PFS* progression-free survival; *PR* partial remission; *RT* radiation therapy

DAL-HD90 study (Schellong et al. 1999), procarbazine was substituted by etoposide in the induction therapy for boys (OEPA: vincristine, etoposide, prednisone, and doxorubicin). Girls in this study received OPPA for their first 2 cycles of chemotherapy. Radiation was delivered to the initially involved areas for a total dose of 25 Gy (20 Gy for TG3 patients with a boost to 25–35 Gy if residual disease >50 mL and/or >25% of the initial tumor volume was observed). For TG1 (early-stage) patients, the 5-year EFS rates were 94% for boys and 95% for girls ($P = 0.70$). Initial response to the different chemotherapy regimens (OPPA vs. OEPA) was also identical, confirming etoposide as an alternative to procarbazine for the induction

phase of therapy. In their subsequent study (GPOH-HD95) to lower the risk of radiation-induced late effects, the German group decided to examine the omission of radiotherapy for patients in complete remission (CR) after chemotherapy as well as examine the reduction of radiation dose (20 Gy) for those in good partial remission (PR) (Dorffel et al. 2013). This response-adapted strategy has shown good results for low-risk patients, with 10-year progression-free survival (PFS) rates of 92.2% for patients receiving radiation and 97.0% for those treated without radiation ($P = 0.21$) in the TG1 group following 2 cycles of OPPA (females) or OEPA (males). The excellent outcomes observed among TG1 patients in CR (32% of the TG1 cohort) after induction chemotherapy without radiotherapy was confirmed in the GPOH-HD-2002 study (Mauz-Korholz et al. 2010). CR was defined as ≥95% tumor reduction and ≤2 mL of the initial volume.

In North America, the Pediatric Oncology Group (POG) 8625 trial aimed to compare combined-modality therapy with chemotherapy alone (Kung et al. 2006). Patients with stage I, IIA, and IIIA1 disease received 4 initial cycles of alternating MOPP/ABVD (nitrogen mustard, vincristine, prednisone, and procarbazine/doxorubicin, bleomycin, vinblastine, and dacarbazine) after which, if in complete or PR, they were randomized to 2 supplementary cycles of chemotherapy or 25.5-Gy of IFRT. Outcomes at 8 years were no different when using chemotherapy only versus combined-modality therapy (EFS rate, 82.6% vs. 91.1%, $P = 0.151$; OS rate: 93.6% vs. 96.8%, $P = 0.785$). Early response to therapy was, however, associated with improved EFS (92.7% vs. 76.7%, $P = 0.006$), paving the way to a generation of trials examining the response-adapted strategy. From 1995 to 1998, the Children's Cancer Group (CCG) 5942 trial evaluated the role of low-dose IFRT for patients achieving CR (≥70% mass reduction and negative Gallium scan) after completion of chemotherapy (Nachman et al. 2002; Wolden et al. 2012). Patients in group 1, defined as stage I or IIA without risk factors (hilar disease, >4 nodal regions, bulky mediastinal mass, bulk >10 cm), received 4 cycles of COPP/ABV (cyclophosphamide, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, and vinblastine). Patients in CR were randomized between 21-Gy IFRT or no radiotherapy. Patients in PR (50–70% tumor reduction) received IFRT. In the "as treated" analysis for patients in group 1, the estimated EFS rate at 3 years was 100% with IFRT and 89% without IFRT. This difference of EFS was confirmed as statistically significant in the long-term results of this study ($P = 0.001$). These findings are in contrast to the findings from the GPOH-HD95 study wherein patients in the TG1 stratum did not benefit from the addition of radiotherapy when in CR after chemotherapy. The difference may be partly attributable to the more stringent definition of CR in the German protocol.

In the P9426 study evaluating the role of dexrazoxane as a cardioprotective agent (Tebbi et al. 2012), patients with stage I, IIA, and $IIIA_1$ HL were initially treated with 2 cycles of DBVE (doxorubicin, bleomycin, vincristine, and etoposide). Patients in CR (i.e., those with a negative Gallium scan) after 2 cycles proceeded directly to 25.5-Gy of IFRT, while patients in less than CR received 2 additional cycles of DBVE before radiotherapy. In this study, a large proportion of the patients (55%) were in CR after induction chemotherapy, demonstrating that about half of low-risk patients can be saved from additional chemotherapy toxicity. This reduction of therapy based on early assessment of chemosensitivity was achievable with a satisfactory outcome, as illustrated by comparable 8-year EFS rates after 2 versus 4 cycles of chemotherapy (86.7% vs. 85.8%; $P = 0.78$). In the more recent Children's Oncology Group (COG) AHOD 0431 single-arm study, patients with stage IA-IIA without bulk disease received 3 cycles of AVPC (doxorubicin, vincristine, prednisone, and cyclophosphamide) (Keller et al. 2010). After initial therapy, patients in CR (defined by a ≥ 80% reduction in the size of each node or a return to normal size and negative FDG-PET or Gallium scan) received no further treatment, while patients in PR were given 21-Gy of IFRT. At 2 years, the patients in CR (no RT) had an EFS rate of 80%, while those in PR receiving radiation had an EFS rate of 88%.

Evaluation of response after 3 cycles of AVPC does not seem adequate to tailor the use of radiation in this low-risk population. Fortunately, OS at 2 years remains excellent at 100%, likely due to the effectiveness of salvage therapy. Nevertheless, this study was able to demonstrate that an earlier assessment of chemosensitivity with the use of FDG-PET scan after 1 cycle (PET1) can identify patients with a good prognosis. In the no-radiation group, patients with a negative PET1 had a 2-year EFS rate of 87% versus 65% for those with a positive/equivocal PET1 ($P = 0.005$). Similar findings were revealed when evaluating the prognostic value of PET1 for the radiotherapy group (96% vs. 82%, $P = 0.047$).

A risk-adapted response-based approach has also been tested by the Stanford-Dana Farber-St. Jude consortium. In 2007, Donaldson et al. published their experience using 4 cycles of VAMP chemotherapy (vinblastine, doxorubicin, methotrexate, and prednisone) for 110 children with low-risk HL (Donaldson et al. 2007). Patients in CR after 2 cycles were given 15-Gy of IFRT, while those in PR received 25.5-Gy. At 5 years, the EFS and OS rates were 92.7% and 99.1%, respectively. Early response to VAMP chemotherapy was associated with better EFS at 10 years ($P = 0.02$), but with a marginal difference for OS ($P = 0.07$). Their subsequent study evaluated the efficacy of 4 cycles of chemotherapy (VAMP) with the omission of radiation therapy for early-stage patients in CR after 2 cycles (Metzger et al. 2012). Patients who did not require radiotherapy had a 2-year EFS rate of 89.4%, compared to 92.5% for patients receiving radiation ($P = 0.61$). This again suggests that some patients responding early to chemotherapy might have a good outcome when radiation is omitted.

15.2.2 Intermediate-Risk Disease

The criteria for intermediate-risk HL vary widely among groups and trials, especially with regard to stage IIB bulky patients (Table 15.5). For these children, the balance between maintaining a high cure rate and minimizing late effects is usually achieved by slightly de-intensifying the treatment as compared with patients with high-risk disease. Three to six cycles of dose-intensive chemotherapy are recommended and the use of radiation might be tailored by early-response assessment for patients achieving CR (Terezakis et al. 2014).

In the GPOH-HD95 study, patients in the TG2 group initially received 2 cycles of OPPA(girls)/OEPA(boys) followed by 2 cycles of COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) (Dorffel et al. 2013). Patients in CR at completion of chemotherapy did not receive any radiotherapy. The 10-year PFS rate for those patients was fairly disappointing when compared with TG-2 children who were irradiated (68.5% vs. 91.4%; $P < 0.0001$). In their subsequent study (GPOH-HD-2002), boys with intermediate-risk disease received 2 cycles of OEPA followed by 2 cycles of COPDAC (cyclophosphamide, vincristine, prednisone, and dacarbazine), while girls received 2 cycles of OPPA and 2 cycles of COPP (Mauz-Korholz et al. 2010). All patients received IFRT and the 5-year PFS rate was 93.4% for TG2 patients.

Intermediate-risk patients in the CCG-5942 study received 6 cycles of COPP/ABV (Nachman et al. 2002). Patients in CR were then randomly assigned to 21-Gy of IFRT or observation. The long-term value of radiotherapy for this group of patients was small and non-significant (10-year EFS rates, 84.0% vs. 78.0%) (Wolden et al. 2012).

The P9425 study introduced ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone), a novel dose-dense chemotherapy protocol, as an alternative to MOPP and ABVD (Schwartz et al. 2009). Intermediate- and high-risk patients both received 3 cycles of chemotherapy, after which early response was assessed. Children in rapid early response (RER; ≥50% reduction of lesions and negative Gallium scan) received 21-Gy of extended-field radiotherapy (EFRT), while patients with slow early response (SER) proceeded to 2 additional cycles of ABVE-PC before EFRT. In the intermediate-risk group, 67% achieved RER. The 5-year EFS rate was 84% for the intermediate-risk cohort (RER, 82%; SER, 88%).

With the goal of minimizing treatment-related side effects for chemosensitive patients and

Table 15.5 Recent studies for intermediate-risk Hodgkin lymphoma

	Definition of risk	Treatment	EFS/PFS	OS
DAL HD-90	TG2: IIB, IIIA ($+I_E$, II_EA)	OPPA × 2 + COPP × 2(girls) OEPA × 2 + COPP × 2 (boys) Local RT 25 Gy (30–35 Gy if residual)	5-year EFS: 93%	5-year OS: 97%
GPOH-HD95	TG2: IIB, IIIA ($+I_E$, II_EA)	OPPA × 2 + COPP × 2 (girls) OEPA × 2 + COPP × 2 (boys) If CR: no RT If <CR: reduced involved field 20 Gy (boost to residual bulk 30–35 Gy)	5-year PFS: 87.8%	5-year OS: 97.3%
GPOH-HD-2002	TG2: IIB, IIIA ($+I_E$, II_EA)	OPPA × 2 + COPP × 2 (girls) OE*PA × 2 + COPDAC × 2 (boys) IFRT 19.8 Gy (boost to residual 30–35 Gy)	5-year PFS: 93.4%	5-year OS: 98.5%
CCG5942	Group 2: I with RF II with RF IIB III	COPP/ABV × 6 If CR: randomization to 21 Gy IFRT or no RT If PR: IFRT	3-year EFS: 82%	3-year OS: 93%
P9425	IB, IIA/IIIA1 with mediastinal bulk, IIIA2	ABVE-PC × 3 If RER: 21 Gy RT If SER: ABVE-PC × 2 + 21 Gy RT	5-year EFS: 84%	5-year OS: 95% (intermediate-and high-risk combined)
COG AHOD0031	IA with bulk, IAE, IB, IIA with bulk, IIB, IIAE, IIIA, IVA	ABVE-PC × 2 RER: ABVE-PC × 2; if CR: 21 Gy IFRT vs. no-RT; if <CR: 21 Gy IFRT SER: DECA × 2 + ABVE-PC × 2 vs. ABVE-PC × 2; 21 Gy IFRT for all	4-year EFS: 85%	4-year OS: 97.8%

Abbreviations: *AVPC* adriamycin (doxorubicin),vincristine, prednisone, cyclophosphamide; *COPP/ABV* cyclophosphamide, vincristine sulfate (Oncovin), procarbazine hydrochloride, prednisone, doxorubicin hydrochloride (Adriamycin), bleomycin sulfate, and vinblastine sulfate; *CR* complete remission; *DBVE* doxorubicin, bleomycin, vincristine, and etoposide; *EFS* event-free survival; *IFRT* involved-field radiation therapy; *MOPP* mechlorethamine, vincristine, procarbazine, and prednisone; *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine; *OEPA/OPPA* vincristine sulfate (Oncovin), etoposide, prednisone, doxorubicin hydrochloride (Adriamycin); *OS* overall survival; *PFS* progression-free survival; *PR* partial remission; *RT* radiation therapy

improving the cure rate for patients with a suboptimal response to initial chemotherapy, COG AHOD 0031 was a response-adapted study evaluating the role of therapy reduction for patients with RER, and chemotherapy intensification for those with SER (Friedman et al. 2014). All patients began therapy with 2 cycles of ABVE-PC followed by an early response assessment. Children with RER (≥60% reduction of all target lesions on CT scan) continued with 2 additional cycles of the same chemotherapy. CR (≥80% reduction) was then evaluated after the fourth cycle, and patients meeting criteria for CR were randomized between 21-Gy IFRT and no further treatment. RER with less than CR all received radiotherapy. Patients with SER were randomly assigned to augmentation with DECA (dexamethasone, etoposide, cisplatin, and cytarabine) for 2 cycles and 2 supplementary cycles of ABVE-PC versus 2 additional cycles of ABVE-PC only. All SER patients were given radiotherapy. At 4 years, the benefit from adding radiotherapy for RER/CR patients was modest, with an absolute difference of 3.6% (87.9% vs. 84.3%; $P = 0.11$). When restricted to RER/CR children with a negative PET scan after 2 cycles, the 4-year EFS rate was 86.7% for the IFRT group versus 87.3% for the no-radiation group ($P = 0.87$). The benefit from adding DECA for SER was also small in terms of the 4-year EFS rate (79.3% vs. 75.2%; $P = 0.11$), but increased for patients with a positive PET scan after 2 cycles (PET2) (4-year EFS rate, 70.7% vs. 54.6%; $P = 0.05$). Early response to dose-intensive chemotherapy appears to be an adequate prognostic factor for tailoring therapy for children with intermediate-risk HL.

Table 15.6 Recent studies for high-risk Hodgkin lymphoma

	Definition of risk	Treatment	EFS/PFS	OS
DAL HD-90	TG3: IIIB, IV ($+II_EB$, III_E)	OPPA × 2 + COPP × 4(girls) OEPA × 2 + COPP × 4 (boys) Local RT 20 Gy (25–35 Gy if residual)	5-year EFS: 86%	5-year OS: 94%
GPOH-HD95	TG3: IIIB, IVA ($+II_EB$, III_E)	OPPA × 2 + COPP × 4 (girls) OEPA × 2 + COPP × 4 (boys) If CR: no RT If <CR: reduced involved field 20 Gy (boost to residual bulk 30–35 Gy)	5-year PFS: 86.4%	5-year OS: 94.4%
GPOH-HD-2002	TG3: IIIB, IVA ($+II_EB$, III_E)	OPPA × 2 + COPP × 4 (girls) OE*PA × 2 + COPDAC × 4 (boys) IFRT 19.8 Gy (boost to residual 30–35 Gy)	5-year PFS: 87.4%	5-year OS: 94.9%
POG8725	IIB, IIIA2, IIIB, IV	MOPP/ABVD × 8 ± TNI	5-year EFS: 79%	5-year OS: 92%
CCG-521	III–IV	MOPP/ABVD × 12 vs. ABVD × 6 + 21 Gy EFRT	4-year EFS: 82%	4-year OS: 87%
CCG5942	Group 3: IV	Multidrug intensive chemotherapy × 2 cycles If CR: randomization to 21 Gy IFRT or no RT If PR: IFRT	3-year EFS: 83%	3-year OS: 93%
P9425	IIB, IIIB, IV	ABVE-PC × 3 If RER: 21 Gy RT If SER: ABVE-PC × 2 + 21 Gy RT	5-year EFS: 85%	5-year OS: 95% (intermediate-and high-risk combined)
AHOD 0831	IIIB-IVB	ABVE-PC × 2 If RER: ABVE-PC × 2 If SER: IFOS/ VINO × 2 + ABVE-PC × 2 21 Gy IFRT to initial site of bulk and/or regions of SER	4-year EFS: 80.2%	4-year OS: 95.9%

Abbreviations: *AVPC* adriamycin (doxorubicin),vincristine, prednisone, cyclophosphamide; *COPP/ABV* cyclophosphamide, vincristine sulfate (Oncovin), procarbazine hydrochloride, prednisone, doxorubicin hydrochloride (Adriamycin), bleomycin sulfate, and vinblastine sulfate; *CR* complete remission; *DBVE* doxorubicin, bleomycin, vincristine, and etoposide; *EFS* event-free survival; *IFRT* involved-field radiation therapy; *MOPP* mechlorethamine, vincristine, procarbazine, and prednisone; *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine; *OEPA/OPPA* vincristine sulfate (Oncovin), etoposide, prednisone, doxorubicin hydrochloride (Adriamycin); *OS* overall survival; *PFS* progression-free survival; *PR* partial remission; *RT* radiation therapy

15.2.3 High-Risk Disease

Despite being in the highest risk category, children presenting with advanced-stage HL can still achieve long-term survival and good outcomes (Table 15.6). Their treatment usually consists of 4–6 cycles of dose-intensive chemotherapy with low-dose radiation therapy (Terezakis et al. 2014). The large volume of normal tissue exposed to radiation when irradiating all initial tumor involvement has led investigators of the most recent trials to focus on the selective use of radiation to the initial site of bulk and slow-responding lesions for high-risk HL.

In the GPOH-HD95 study, patients in the TG3 group were treated similarly as those in the TG2 group yet they received 6 (2 + 4) cycles of chemotherapy in total (Dorffel et al. 2013). Ten-year PFS was worse for the non-irradiated patients, but with less magnitude than in the TG2 group (TG3, 82.6% vs. 88.7%; $P = 0.259$). Among those who received radiation in the GPOH-HD2002 study, TG3 patients had an EFS rate of 87.4% and an OS rate of 94.9% at 5 years (Mauz-Korholz et al. 2010).

Started in 1986, the CCG521 study investigated if MOPP chemotherapy can be safely omitted for advanced-risk HL patients with the use of ABVD and low-dose EFRT (Hutchinson et al. 1998). Patients with stage III-IV disease were randomized between MOPP/ABVD for 12 cycles and ABVD for 6 cycles plus 21-Gy of EFRT. At 4 years, patients in the combined modality treatment arm had an EFS rate of 87%, compared to 77% for the patients in the chemotherapy alone arm ($P = 0.09$), suggesting that children with high-risk HL can be treated without MOPP when radiation is added to ABVD. In parallel, the POG8725 trial studied from 1987 to 1992 if advanced-stage patients (stages IIB, IIIA2, IIIB, and IV) benefit from low-dose total-nodal irradiation (TNI) after 8 cycles of MOPP/ABVD (Weiner et al. 1997). At 5 years, the EFS rates were comparable, at 80% for the combined-modality group and 79% for the chemotherapy-only group. In the CCG-5942 trial, stage IV patients received 2 courses of intensive multidrug chemotherapy (Nachman et al. 2002; Wolden et al. 2012). Patients in CR after completion of chemotherapy were randomly assigned to receive low-dose IFRT versus no radiotherapy. Long-term results of this study demonstrated that for high-risk patients (n = 66) the benefit of adding radiation was not significant (10-year EFS rate, 88.5% vs. 79.9%; P = not significant). The intensive chemotherapy regimen used, or the small patient sample size in this group, might have rendered the value of adding radiation more difficult to demonstrate.

In the P9425 trial, outcomes for high-risk patients were similar to those for intermediate-risk patients (Schwartz et al. 2009). RER was attained by 61% of advanced-stage children. The 5-year EFS rate was 85% for the high-risk group (RER, 88%; SER, 82%). However, patients with stage IVB disease (n = 51) had a 5-year EFS rate of only 74%. The most recently completed high-risk study by the COG (AHOD 0831) included patients with stage IIIB-IVB HL. High-risk patients were given 2 initial cycles of ABVE-PC chemotherapy, after which early response was assessed by FDG-PET imaging. Patients with RER (negative PET2) continued with 2 additional cycles of the same chemotherapy, while SER patients were intensified with 2 cycles of ifosfamide-vinorelbine before receiving the third and fourth cycles of ABVE-PC. In this protocol, radiation was limited to site of initial bulk or regions of SER for a dose of 21-Gy. A preliminary report for this study showed that the primary endpoint, the 4-year second-EFS rate, was 89.8% (RER, 91.9%; SER, 87.8%), which was below the projected rate (Kelly et al. 2015). About half of the patients were RER. At 4 years, the EFS rate was 80.2%, while the OS rate was 95.9%. These results are similar to the outcomes in the POG9425 trial, despite a more limited use of radiation. The currently enrolling COG AHOD 1331 trial is investigating the use of brentuximab vedotin, an anti-CD30 monoclonal antibody, in the treatment of high-risk HL (stages IIB with bulk, IIIB, IVA, and IVB). In this study, radiation is restricted to initial large mediastinal adenopathy and sites of slow-responding lesions (PET2-positive). Radiation is administered using involved-site radiation therapy (ISRT) to limit further the irradiated volume.

15.3 Radiation Simulation and Treatment Planning

15.3.1 Patient Positioning for Simulation

Patient positioning for simulation and treatment cannot be standardized and requires customization based on various factors including patient's age, sex, disease distribution, etc. The advantages and disadvantages to different set-up approaches must be considered for each patient and require input from physicists, dosimetrists, therapists, and the physician. Care especially must be taken to determine arm positioning and neck positioning (Fig. 15.2).

15.3.2 CT Simulation Fusion with Pre-chemotherapy Imaging

Owing to the immense response to chemotherapy, most patients undergoing simulation for HL will not have disease present at the time of simulation in all the regions initially involved at presentation. Consequently, modern radiation field

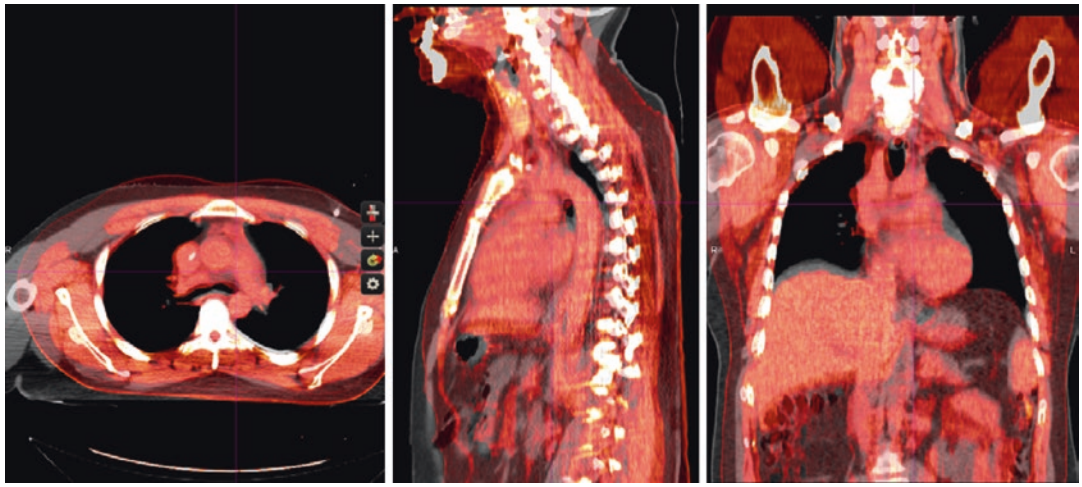

Fig. 15.2 Image fusion of the computed tomography (CT) component of the prechemotherapy positron emission tomography (PET)/CT scan (*pink*) with the post-chemotherapy CT simulation/planning CT scan (*grey*). Although fusion appears to be good according to the carina on the axial image, the chin and neck are quite off on the sagittal image due to flexion on the PET/CT scan and extension on the simulation scan. Furthermore, the coronal image can demonstrate how the axilla and supraclavicular regions would be off based on the PET/CT scan being done with the arms above the head and the CT simulation with the arms akimbo

designs using ISRT necessitates appropriate image fusion with prechemotherapy imaging to identify the initial sites of involvement (Hodgson et al. 2015). Smaller clinical target volume (CTV) expansions are allowed when fusions are more precise; however, larger CTV margins are needed when fusions are poor. In particular, when disease involves the axilla, supraclavicular, and/or infraclavicular region, arm position (above head, akimbo, or at the side) can greatly impact fusion with the prechemotherapy imaging. This uncertainty and consequently larger CTV may lead to increased dose to the breast (in a female) and lung. In our practice, when these regions are involved, we attempt to reproduce the arm positioning used during prechemotherapy imaging. More flexibility in choosing the arm position may be allowed if the prechemotherapy PET/CT scan and pre-chemotherapy CT scan with IV contrast involved different arm positions.

15.3.3 Simulation Position

When treating the neck, the impact of head flexion, extension, and hyperextention must be considered. Head flexion may help in fusion with prechemotherapy scans, but often places the chin and salivary glands in the treatment field for cases with neck involvement, thereby increasing the risk of xerostomia and mucositis. However, there are some instances with proton therapy for which this approach may allow reducing the dose to the brain. Head extension is generally the preferred way to simulate and treat a patient to maximize patient comfort and avoid the salivary glands, oral cavity, and brain. Hyperextension is the most uncomfortable position, but it may be preferred in some instances when the oral cavity and salivary glands can be better avoided. A potential disadvantage is that some of the brain may enter into the radiation field. When treating the neck, we generally use a face mask to help align the patient and prevent the chin from dropping into the field.

In the thorax, arms above the head can pull the breasts superiorly and medially, which, depending on the location of the disease, can be helpful or harmful. Arms above the head generally help pull the axilla and infraclavicular regions above the lung field, which can help reduce the dose to the lungs. When considering treatment with lateral fields or arc therapy, the arms above the head can

help avoid radiation beams passing through the arms. However, this position may not be as reproducible and may require larger planning target volume (PTV) margins for set-up errors. In our experience, despite wing boards, patients experience difficulty with treatments when they are required to lay with their arms above their heads for extended periods of time. A more comfortable and reproducible position for patients is with their arms at their sides or slightly akimbo. This position may allow the breasts to fall inferiorly and laterally, which, in certain circumstances, can reduce the amount of breast tissue receiving radiation. Since most patients prefer this position, at our institution, all staging PET/CT scans in this population are performed with the patient's head extended and arms at their side to aid in CT simulation fusion.

15.3.4 CT Simulation

All patients should undergo a CT simulation using IV contrast to help identify sites of interest. If IV contrast would alter the treatment planning, a non-contrast CT scan should be done, additionally. When the mediastinum or abdomen is involved, breathing motion may affect treatment. A 4-dimensional CT scan can help determine breathing motion and the appropriate involved tumor volume (ITV) margin. Alternatively, the deep-inspiration breath-hold technique can be used to greatly reduce breathing motion of the mediastinum with a full breath.

15.3.5 Target Delineation

Many patients will be treated on cooperative group protocols or per a protocol, outlining specific instructions for target delineation. For IFRT, modern radiation treatment planning should be incorporated to develop involved-site radiotherapy (ISRT) targets according to the guidelines of the International Lymphoma Radiation Oncology Group for pediatric HL (Hodgson et al. 2015). Elective treatment of uninvolved nodal regions, such as EFRT, subtotal lymphatic irradiation (STLI), or total nodal irradiation (TLI) should rarely, if ever, be used in the management of HL.

The ISRT guidelines rely on the International Commission on Radiation Units and Measurements (ICRU) reports 62 and 83 to detail the concepts of target volumes and organs at risk (OAR). These ISRT volumes, however, can vary depending on whether the patient received chemotherapy and whether radiation is being used to all sites of involvement or to sites of bulky disease as well as slowly responding disease. Table 15.7 provides contouring guidelines.

15.3.6 Definitive ISRT

ISRT is rarely, if ever, used as definitive treatment in pediatric HL without chemotherapy. If such a case arises, as may occur with early-stage nodular lymphocyte-predominant HL, target planning is as follows: The gross tumor volume (GTV) includes the nodal disease visualized on the planning CT simulation and PET/CT scan. To create the CTV, a 2–4 cm margin is added to encompass the adjacent nodal stations and account for subclinical disease, with normal structures excluded. An ITV margin is added depending on the degree of motion expected for the region at risk, which may be none in the head and neck region and 1–2 cm in the thoracic or abdominal region. A PTV margin for set-up uncertainties ranging from 0.3 to 1.5 cm should be incorporated, depending on the region at risk and whether daily image guidance is used.

15.3.7 Consolidative ISRT

Consolidative ISRT is the most common post-chemotherapy radiation treatment for patients with pediatric HL. The prechemotherapy GTV, or GTV(prechemo), is defined as the disease seen on the prechemotherapy PET/CT scan and diagnostic CT scan. The postchemotherapy GTV, or GTV(postchemo), is defined as the disease seen at the time of CT simulation following chemotherapy. GTV(postchemo) can be further defined as GTV(postchemo, PET+) defined as residual PET-avid disease seen on the postchemotherapy PET/CT

Table 15.7 Contouring guidelines for involved-site radiotherapy

	Definitive ISRT	Consolidative ISRT	Consolidative ISRT to bulky disease
GTV (prechemo)	Gross disease as seen on PET/CT scan and planning CT sim	Gross disease as seen on prechemo PET/CT scans	Gross bulky and adjacent connected disease as seen on prechemo PET/CT scans
GTV (postchemo)	Not applicable	Residual disease seen at the time of CT simulation that may be PET negative (GTVPET Negative) or PET positive (GTVPET Positive)	Residual disease seen at the time of CT simulation that may be PET negative (GTVPET Negative) or PET positive (GTVPET Positive)
CTV	GTV + 2–4 cm margin within nodal stations to encompass sites of subclinical disease	GTVpostchemo + margin that includes sites of involvement of GTVprechemo, while respecting normal tissue and OAR boundaries (ie if the lung was not involved, do not extend CTV into lung) + margin to account for fusion uncertainties between pre-chemo imaging and CT simulation + margin to account for subclinical involvement (ie connecting uninvolved nodal stations lying between 2 involved sites within 5 cm of each other)	GTVpostchemo + margin that includes sites of involvement of GTVprechemo, while respecting normal tissue and OAR boundaries (ie if the lung was not involved, do not extend CTV into lung) + margin to account for fusion uncertainties between pre-chemo imaging and CT simulation + margin to account for subclinical involvement (ie connecting uninvolved nodal stations lying between 2 involved sites within 5 cm of each other). Adjacent non-bulky well responding sites of prior involvement can be excluded if they may lead to excessive irradiation of an OAR if included
ITV	CTV + margin for motion (0–2 cm)		
PTV	ITV+ margin for Set up uncertainties (0.3–1.5 cm)		

Abbreviations: *CTV* clinical target volume; *GTV* gross tumor volume; *ISRT* involved-site radiation therapy; *OAR* organs at risk; *PET/CT* positron emission tomography/computed tomography

scan and GTV(postchemo, PET–) defined as residual gross disease that is PET negative on the post-chemotherapy PET/CT scan. To determine the CTV, the CT simulation scan is fused to the pre-chemotherapy PET/CT scan and diagnostic CT scan. The CTV includes the entire GTV(postchemo) volume and nodal sites initially involved at presentation as defined by the GTV(prechemo). The CTV should be modified as the nodal disease shrinks, and exclude normal structures that may have fallen into these regions. For example, the GTV(prechemo) on the fused prechemotherapy PET/CT and CT simulation scan may extend far into the lung once disease has shrunken considerably. The CTV should adapt to such changes and exclude the lung so that the CTV is smaller than the GTV(prechemo) in transverse dimension in certain regions (Fig. 15.3). If anatomy prevents the prechemotherapy PET/CT scan from fusing well with the CT simulation scan, a more generous CTV should be drawn; when the scans fuse extremely well, smaller margins, such as those used for involved-node radiation therapy field design, can be used. The CTV should also encompass the adjacent uninvolved nodal stations between the two involved sites if they are within 5 cm of each other. An ITV margin is added depending on the degree of motion expected for the region at risk, which may be 0 cm in the head and neck region or 1 to 2 cm in the thoracic or abdominal region. A PTV margin for set-up uncertainties should also be incor-

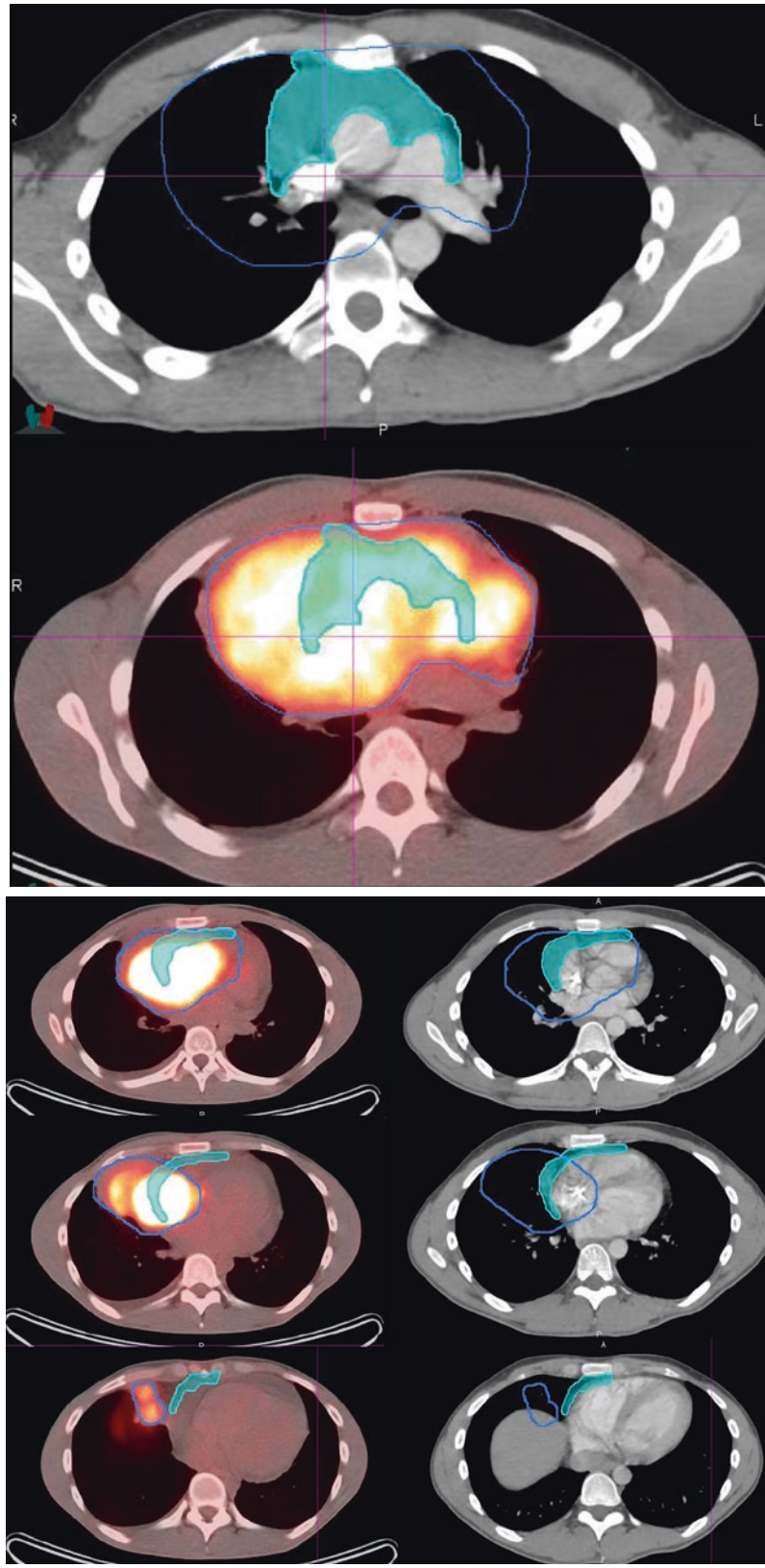

Fig. 15.3 Fused transverse images from the prechemotherapy positron emission tomography (PET)/computed tomography (CT) scan (*bottom figure*) and the CT simulation (*top figure*). The gross tumor volume (GTV) prior to chemotherapy is outlined in *blue*, while the clinical target value (CTV) is contoured in aqua. Notice that the normal anatomy (i.e., the lung and major blood vessels) would be treated if we used the prechemotherapy volume from the original GTV. The CTV, however, excludes these normal structures from the volume

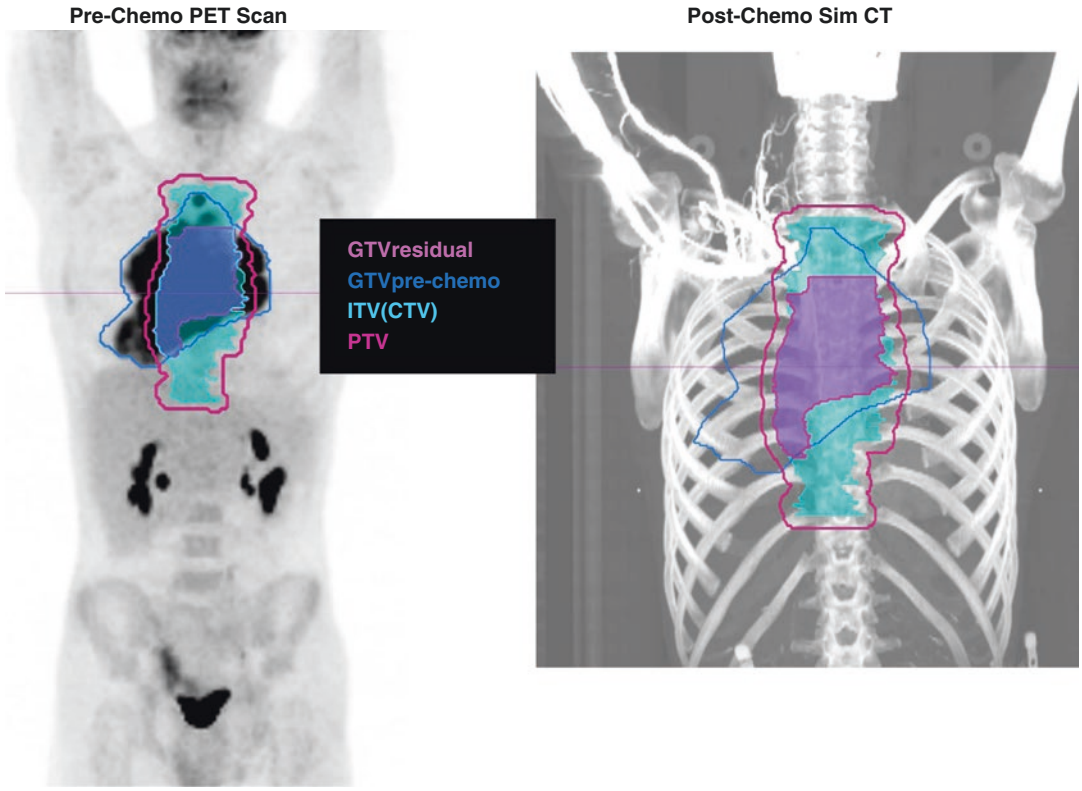

Fig. 15.4 A prechemotherapy positron emission tomography (PET)/computed tomography (CT) scan is shown on the left and the planning CT simulation on the right for a 17-year-old male with stage IB bulky nodular sclerosing Hodgkin lymphoma who had a partial response after 4 cycles of ABVE-PC chemotherapy and received 21-Gy of ISRT. The prechemotherapy gross tumor volume (GTV) is shown in *dark blue*, post-chemotherapy GTV is shown in *pink*, the clinical target volume (CTV)/internal target volume (ITV) in aqua, and planning target volume (PTV) in magenta. Contours shown on the original prechemotherapy PET maximum intensity projection (MIP) image (*left*) and reconstruction on a CT simulation scan (*right*)

porated, which will depend on the region at risk and whether daily image guidance is being used; this margin can range from 0.3 to 1.5 cm. In some situations, a boost may be delivered to a higher dose to the GTV(postchemo) or GTV(postchemo, PET+) with an appropriate PTV margin. Figure 15.4 shows several slices from a case example.

15.3.8 Consolidative ISRT to Bulky Disease

Consolidative ISRT is the most common radiation treatment for patients with stage III/IV HL. In these patients, irradiating the full ISRT field, as stated earlier, could lead to large radiation fields reminiscent of the STLI and TLI used in the prechemotherapy era. Nevertheless, because the predominant site of failure for these patients is generally within the sites of bulky mediastinal involvement, irradiation to the site of bulky disease can provide a clinically meaningful reduction in the risk of recurrence without causing significant toxicities. Depending on the potential risk of late toxicity, the target is the bulky mediastinal disease with consideration of immediately adjacent disease, rather than splitting the radiation field through disease.

15.3.9 OAR Delineation

Modern radiation treatment planning utilizes conformal radiation techniques to help spare the OARs while treating the PTV. OAR delineation for each

specific case will depend on the region of involvement. The following structures should be considered for contouring in each plan if they are likely to receive doses >1-Gy: eyes, lens, brain, salivary glands, oral cavity, mandible, larynx, thyroid, esophagus, breast, heart (consider substructures of the heart, such as coronary vessels, chambers, and valves), lungs, stomach, bowel, pancreas, bladder, kidneys, and liver (Feng et al. 2011).

15.3.10 Treatment Planning

Current National Comprehensive Cancer Network guidelines for treatment planning suggest utilizing the treatment planning system that best allows for sparing of the OARs while maintaining appropriate coverage of the target volume. Such planning may be done adequately with electrons, photons, or protons.

Several recent studies have evaluated the dosimetric impact of using proton therapy compared with either 3-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT) and all have found a benefit to using proton therapy in reducing the radiation dose to different OARs (Hoppe et al. 2012a, b; Maraldo et al. 2013a, b, 2014; Sachsman et al. 2015). Figure 15.5 demonstrates comparison plans using 3DCRT, proton therapy, and IMRT for a 16 year old female with stage IIIA Hodgkin lymphoma. In particular, when disease is located in the mediastinum, proton therapy has been shown to help reduce the radiation dose to the heart, lungs, and breast. Reports of early results with proton therapy have shown similar recurrence rates as photon-based approaches (Hoppe et al. 2014; Wray et al. 2014). Although not specific to lymphoma, a study from Massachusetts General Hospital (Boston, Massachusetts) found that, when matched to similar patients in the SEER registry, patients treated with proton therapy had an approximately 50% reduction in secondary cancers compared with patients treated with photons (Chung et al. 2013). Proton therapy is currently allowed on the most recent COG AHOD 1331 study. Unfortunately, many patients do not live close to a center that offers proton therapy or their insurance will not reimburse proton therapy treatment.

IMRT is photon-based strategy that also helps reduce the radiation dose to OARs. With IMRT, the radiation dose is re-distributed in an effort to improve conformality of the dose in the high-dose region. IMRT, however, leads to an increased volume of tissue receiving low-dose radiation. Depending on the method for predicting second cancers the use of IMRT may or may not reduce the risk of second cancers compared with 3DCRT. Consequently, investigators should be aware of the potential trade-offs of the low-dose bath associated with IMRT when determining the best treatment approach for a given patient (Weber et al. 2011; Cella et al. 2013).

The deep inspiration breath hold is another method to potentially reduce radiation dose to the OARs and can be combined with proton therapy, IMRT, or 3DCRT. In selected patients, deep inspiration breath hold can help facilitate pulling the heart away from the mediastinal disease, allowing for a reduced dose to the heart and larger lung volume, which helps limit the percent of lung irradiated (Charpentier et al. 2014; Paumier et al. 2012; Aznar et al. 2015). However, care must be taken with the reproducibility of this treatment technique to ensure the target is always being treated. This approach may be more difficult to utilize in younger pediatric patients, due to the complexity of reproducing the same deep breath consistently.

15.3.11 Treatment Planning Guidelines

The radiation dose delivered for pediatric HL is low (~20–30-Gy). Attempts should be made to cover the PTV completely. In general, we try to achieve a $PTV_{D95} = 100\%$ and a $PTV_{V95} = 100\%$; however, due to the concern of OAR dose, we will accept $PTV_{D95} > 95\%$.

Since patients with PHL receive lower radiation doses, we generally do not expect many, if any, major acute toxicities. While some patients may develop fatigue, skin erythema, minor esophagitis, mucositis, hair loss, and dry mouth, the toxicities are rarely greater than a grade 2. The predominant concern for these patients is late side effects years after treatment.

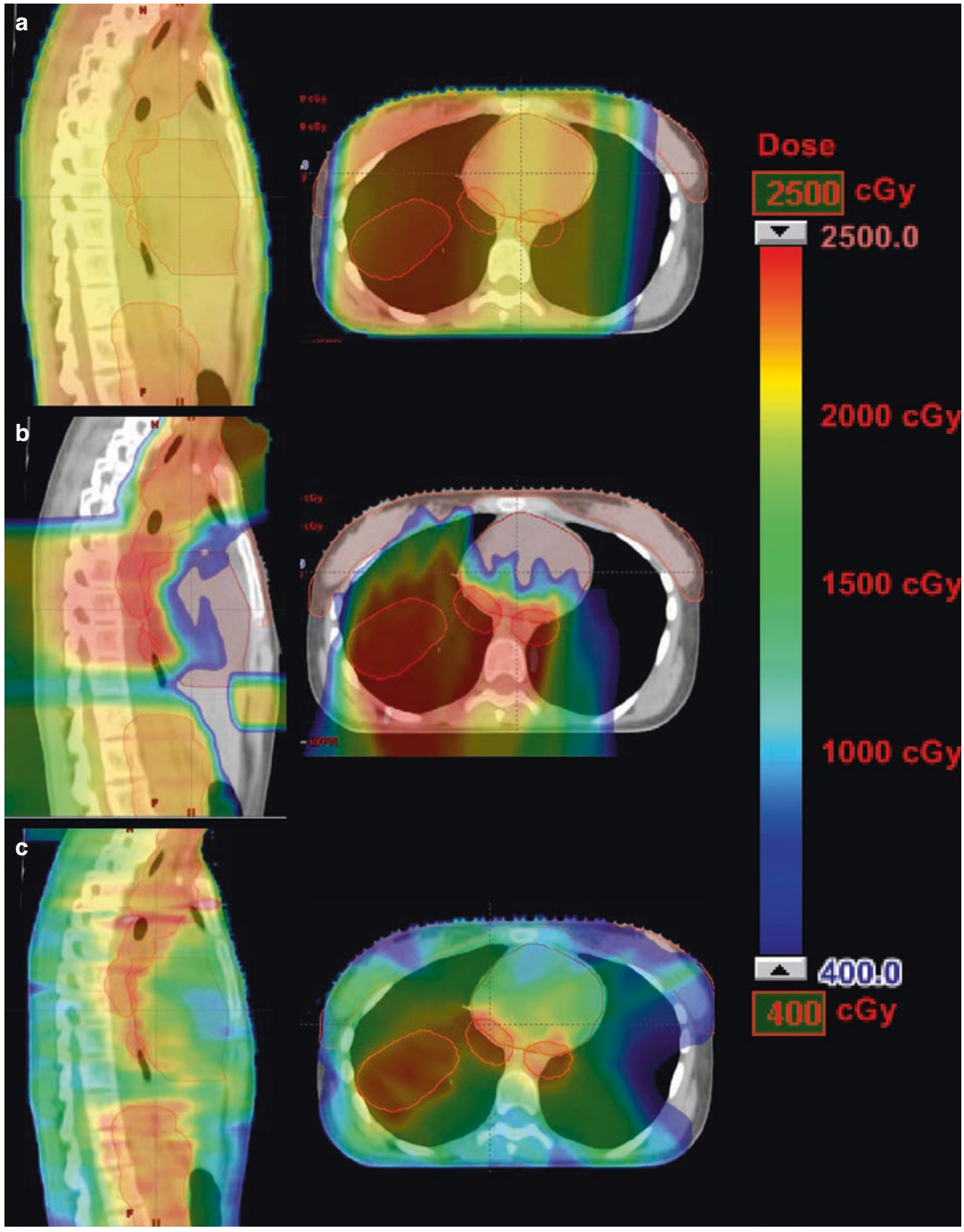

Fig. 15.5 Comparison of the dose distribution of (**a**) 3-dimensional conformal radiation therapy (3DCRT), (**b**) proton therapy (PT), and (**c**) intensity-modulated radiation therapy (IMRT) plans. The clinical target volume (CTV; *red*), heart (*brown*), and breasts (*pink*) are outlined. Borrowed from Holtzman A, Hoppe BS, Li Z, Su Z, Slayton WB, Ozdemir S, Joyce M, Sandler E, Mendenhall NP, Flampouri S. Advancing the Therapeutic Index in Stage III/IV Pediatric Hodgkin Lymphoma with Proton Therapy. Int J Particle Ther. 2014;1(2):343–356

15.4 Radiation .Toxicities and Corresponding Radiation Doses

15.4.1 Second Cancers

Second cancers related to treatment are, perhaps, the most concerning late side effect for survivors of HL (Castellino et al. 2011). Although hematopoietic neoplasms generally occur within a few years of treatment, solid tumors typically develop decades after treatment. In a report of the Childhood Cancer Survivor Study, among survivors of pediatric HL, the most frequently observed second malignancies were breast cancer, thyroid cancer, and soft tissue sarcoma (Castellino et al. 2011). Radiation has been associated with an increased risk of solid tumor development with the risk of malignancy development generally following a direct linear relationship with the amount of radiation delivered to the OAR, as seen in breast cancer (Travis et al. 2003), lung cancer (Travis et al. 2002), brain tumors (Neglia et al. 2006), gastric cancer (Morton et al. 2013), and sarcoma (integral dose to body) (Tukenova et al. 2011). On the other hand, thyroid cancer appears to peak after doses between 10 and 30-Gy and then decline with increasing doses of radiation, albeit the risk is still elevated for doses >50-Gy (Veiga et al. 2012). Although no threshold dose exists for any of these tumors, increasing risks were seen with doses as low as 4–5-Gy for breast, lung, and thyroid cancer. Consequently, we attempt to minimize the radiation dose exposure to all of these OARs to the best of our ability while considering the mean OAR dose and the volume receiving low doses of radiation (such as doses >5-Gy).

15.4.2 Heart

Cardiovascular complications are the second most common serious side effect of treatment for HL. However, when evaluating all toxicities, including second cancers, by organ systems, cardiac injury is the primary cause of organ-specific toxicity (Ng et al. 2002). Heart damage is a combination of injury from anthracycline chemotherapy and unintentional radiation to the heart. Hancock et al. reported one of the first studies demonstrating that the use of lower radiation doses (≤30-Gy) and a heart block helped reduce the risk of cardiac death and cardiac disease, respectively (Hancock et al. 1993). Hull et al. demonstrated an increased risk of cardiac valvular surgeries and coronary revascularization procedures among survivors of HL who had been irradiated with higher doses of radiation associated with increased risk of coronary artery disease (Hull et al. 2003). More recently, Mulrooney et al. evaluated the cardiac outcomes among adult survivors from the Childhood Cancer Survivor Study, which demonstrated increased risk of congestive heart failure, pericardial disease, and valvular abnormalities with exposure to ≥250 mg/m^2 of anthracyclines, as well as increased risk of congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities with cardiac radiation doses of ≥15-Gy (Mulrooney et al. 2009). Similarly, Tukenova et al. demonstrated among 5-year survivors of childhood cancer in France and the UK that there was an increased risk of cardiac death with radiation doses starting at 5-Gy (Tukenova et al. 2011). They found a linear relationship between average dose to the heart and risk of mortality, with an estimated excess relative risk at 1-Gy of 60%. Most recently, a study by van Nimwegen et al. evaluated the risk of coronary heart disease among 5-year HL survivors and found that this risk increased linearly with increasing mean heart dose (Van Nimwegen et al. 2016). The excess relative risk per Gy was 7.4%, resulting in a 2.5-fold increased risk after 20-Gy compared with those who didn't receive radiation.

Based on the data listed above, in practice, we try to limit the radiation dose as much as possible to the heart, which can be quite difficult because of disease distribution. Although a mean dose to the heart <5-Gy is ideal, we are often forced to deliver higher doses. In general, we try to keep the mean radiation dose to the heart below 15-Gy and make exceptions when necessary. When using modern radiation techniques, such as IMRT, VMAT, or proton therapy, it is important

to limit the dose to the more critical areas of the heart, such as the coronary vessels, cardiac valves, and left ventricle.

15.4.3 Lungs

Pulmonary toxicity from radiation for lymphoma is a concern, but the rate of toxicity has reduced considerably with the use of smaller field radiation and lower radiation doses. One recent study by Hua et al. evaluating radiation pneumonitis among pediatric patients receiving thoracic radiation found that lung V24 was associated with increased risk of any pneumonitis, grade 1 or 2, reaching 5% with a V24 of 30% (Hua et al. 2010). In another study evaluating pulmonary damage among HL survivors, Cella et al. found that a left-lung V30 of 32% predicted the risk of Radiation Therapy Oncology Group grade ≥ 2 pulmonary toxicity (Cella et al. 2014). In a study by Koh et al., the lung V20 was evaluated as a predictor for pneumonitis (Fox et al. 2012). The rate of Radiation Therapy Oncology Group grade 2+ pneumonitis was 12.5% with lung V20 ≥ 36% and 11.8% for a mean lung dose >14-Gy. The risk of clinically meaningful lung toxicity appears to increase among patients undergoing high-dose therapy and transplant for relapsed or refractory disease.

Lung cancer risk as a late side effect of radiation is also an important toxicity to consider. The rate of secondary lung cancers has decreased significantly with the decline in tobacco use among survivors. In a case-control study by Travis et al. among HL survivors, the risk of developing a secondary lung cancer was increased with radiation doses starting at 5-Gy (Travis et al. 2002). Importantly, the risk of lung cancer was 20-fold higher among smokers.

Based on the overall data, we try to keep the lung V20 below 35% and mean lung dose below 14-Gy to minimize the risk of pneumonitis. Because rates are still reasonably low above these doses, we can use higher doses for patients in more critical need for radiation. When considering the risk of secondary lung cancer, we minimize the lung V5 and counsel patients to not smoke.

15.4.4 Thyroid

According to the Childhood Cancer Survivorship Study (Castellino et al. 2011), the risk of thyroid dysfunction and second cancer is quite high among HL survivors (it is the second most common second cancer). In a study of HL survivors by Cella et al. (2012), a thyroid V30 of ≤62.5% was associated with an 11.5% risk of hypothyroidism; the risk was 70.8% for those treated with a V30 over 62.5%. Bolling et al. found that children who received doses >15-Gy to the head and neck region had an increased risk of thyroid dysfunction (Bolling et al. 2011). In a study examining the risk of secondary thyroid cancers by radiation dose to the thyroid, Veiga et al. found a linear dose-related increase for doses <10-Gy, which leveled off between 10 and 30-Gy at 10–15 fold, and moderately declined for doses over 50-Gy (Veiga et al. 2012). Bhatti et al. similarly found that thyroid cancer risk increased linearly to doses of 20-Gy with a 14.6-fold increase before a downturn (Bhatti et al. 2010).

Based on the data, we try to keep the thyroid dose as low as possible, which is complicated by the thyroid's location. Because of the therapies available for managing thyroid dysfunction and the excellent outcomes among patients with secondary thyroid cancer (Podda et al. 2014), we generally caution our patients about the risk, but rarely compromise coverage of our target to achieve a specific thyroid dose constraint.

15.4.5 Breast

Breast cancer, the primary secondary cancer following HL, is a significant late effect from radiation of great concern to female patients (Castellino et al. 2011). Fortunately, breast cancer-specific mortality among patients who develop secondary breast cancer after HL is just as favorable as the general public (Elkin et al. 2011). Radiation dose to the breast has been associated with an increased risk of breast cancer. A study by Travis et al. showed an increased

risk of breast cancer after 4-Gy to the breast, with a 3.2-fold increased risk with dose increases (for example, there was an eightfold increase for doses of 40-Gy) (Travis et al. 2005). Fortunately, the volume of breast being irradiated in HL patients has significantly decreased with modern radiation field design (De Bruin et al. 2009). Breast hypoplasia is a concern among pediatric survivors who have received radiation. Little data exist, but one study by Furst et al. suggested an increased risk with increasing radiation dose and no identified threshold dose (Furst et al. 1989). Accordingly, we attempt to minimize the breast dose as much as possible while considering the breast V5. Consequently, we must be careful when using IMRT and VMAT owing to the impact of the low-dose radiation bath to the breast.

15.4.6 Bone

Bone radiation can compromise growth among young children before the epiphyseal growth plate has closed. In a study from Stanford University (Stanford, California), children with HL irradiated to the whole spine were found to have a 7.7% height impairment equating to a 13-cm height loss. While treating the whole spine is rare, some concern does exist for partial radiation to vertebral bodies and the impact of dose gradients, potentially increasing the risk of scoliosis. Modern radiotherapy techniques can create these dose gradients through the effort to be more conformal and reduce dose to other OARs. In our practice, we have generally accepted these dose gradients. Patients and their parents are warned of possible risks. If there is significant concern, the entire vertebral body can be included in the higher dose region to avoid a dose gradient.

15.4.7 Ovaries

Although rare, subdiaphragmatic radiation in HL may put the ovaries at risk of irradiation. Depending on the region that requires radiation, an oophoroplexy, whether medial or lateral, can help reduce the radiation dose to the ovaries. Current data suggest that doses >6-Gy to the ovaries may increase the risk of premature ovarian failure.

15.5 Follow-Up Imaging

Patient follow-up is necessary to promptly identify treatment-toxicities when interventions are possible. In a longitudinal COG study of HL survivors (Voss et al. 2012), few patients had relapses identified >12 months after treatment by routine imaging. Consequently, surveillance imaging without symptoms may not be necessary >1 year after treatment.

15.6 Follow-up Late Side Effects

Long-term follow-up assessing treatment side effects should include those effects that can develop both from chemotherapy and radiation, specifically in the area that received radiation. When the thyroid is irradiated, recommendations are for yearly thyroid examinations, including thyroid function tests and ultrasound and FNA as needed for palpable nodules. After thoracic radiation, yearly breast exams should begin at puberty with mammograms beginning at age 25 years or 8 years following treatment (whichever occurs last) and breast magnetic resonance imaging (Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers 2014). Baseline pulmonary function should be assessed during the first follow-up visit and repeated as needed depending on pulmonary complaints. Cardiovascular evaluation should include fasting blood glucose and lipid profile every 2 years with baseline EKG and ECHO performed during the first follow-up visit and repeated as clinically indicated. The COG's Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer, which is continually updated on their website, is an excellent resource for following HL survivors (Kelly 2012; Barrington et al. 2014).

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16 Basic Principles and Advances in Technology Used for Pediatric Radiotherapy

Arthur J. Olch and Chia-Ho Hua

16.1 Introduction

Modern radiotherapy is a highly complex process utilizing the accurate application of computerized treatment planning coupled with particle acceleration and photon emitting systems providing precisely positioned and accurate beam delivery. Treatment planning has been transformed over the past couple decades, enhanced by advanced imaging for target and normal structure definition, previously impossible radiation dose sculpting, and highly accurate 3-dimensional (3D) dose calculations that allow the minimization of normal tissue dose while conformally treating the tumor. The radiotherapy community has aggressively employed these normal tissue sparing techniques for pediatric cancer patients as will be shown in this chapter. Therefore, (Marks et al. 2010) late effects outcomes reported in the literature for patients treated decades ago should not be relied upon for formulating expectations of such effects in currently treated patients.

The radiotherapy physics and dosimetry team must understand the difference between treating a child and an adult. Although refining radiation dose-tolerance limits is still an area of investigation for adults and children, data from the literature can be used to support specific dose limits for normal organs (Marks et al. 2010; Mertens et al. 2008), and, for certain organs in children, to doses below what we would allow for adults. Examples of differences in pediatric vs. adult normal organ tolerance doses include musculoskeletal tissues, heart, endocrine glands, brain, reproductive system, and that which can produce secondary malignancies. The treatment of children with radiotherapy demands a heightened concern for late effects, which can have a tremendous cost in quality of life for the survivor (Mertens et al. 2008). The technologies we can now bring to bear provide us with a remarkable degree of control over non-target dose and are described below. At the same time, our ability to define the location and sometimes the aggressiveness of tumor tissue has improved dramatically over the last decade and continues to advance.

The successful utilization of technology requires input from the entire radiotherapy team which consists of radiation oncologists, radiation physicists, dosimetrists, therapists, and

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nurses, all working together through a complex process that includes the patient consult, computed tomography (CT) simulation, treatment planning, and treatment delivery.

16.2 Modern Radiotherapy Workflow

16.2.1 Precision Immobilization Device Creation

After diagnosis and the decision to treat is made, a special CT scan called a planning CT or CT simulation is performed. Prior to the scan, a special device is constructed for each patient to replicate as precisely as possible the patient's body "pose" at the time of the scan and for each radiation treatment. For the head, this device would include a custom formed head cushion and either a plastic mask formed to the patient's face and head or a custom mouthpiece with dental impression which in some implementations has a vacuum applied to hold it in position accurately (Olch and Lavey 2002). For the body, the patient lies on a plastic bag filled with small foam beads which is then evacuated, compressing the beads and allowing the bag to maintain a very accurate mold of the patient's body. The immobilization device is crucial in allowing the patient's body pose to be replicated on a daily basis during radiotherapy. We can then minimize the size of radiation fields while still accurately targeting the tumor and thus reduce the volume of normal tissue irradiated. The immobilization device is perhaps more important for the awake child than for an adult due to the greater chance of patient movement during the treatment. An immobilization device is always used, even for sedated children because it is important to reproduce the patient's position as well as reduce movement. These devices can typically reduce the variation in daily patient position relative to the beam to less than 2 mm for the head and less than 4 mm for body sites (Olch and Lavey 2002; Fuss et al. 2004). In addition to having the immobilization device, the device can be precisely docked to a specified location on the treatment couch by special hardware. This is called indexed immobilization and has the advantage of allowing computer control of the couch to drive it to the identical position each day, lessening the chance for human error.

16.2.2 Basic CT Simulation

During the planning process, a 3D model of the patient is created based on the CT simulation images. The CT scan is performed with 1–3 mm thick slices over a region several centimeters longer than the affected volume, with or without contrast as appropriate. These scans are then imported into a special treatment planning computer system (TPS) used for planning treatment. Other relevant imaging studies are also imported, such as the pre-and post-operative magnetic resonance imaging (MRI) scans and positron emission tomography-computed tomography (PET-CT) scans. Often the tumor volume is seen best on these other scans. Software is used to register the diagnostic scans to the treatment planning scan.

16.2.3 Target and Normal Tissue Segmentation

The tumor volume or tumor bed can be drawn on each diagnostic image slice where it is seen and passed through to the planning CT scan based on the registration of the images. If there is gross tumor seen on the pretreatment images, this volume is carefully drawn on each CT slice and becomes the "gross tumor volume" (GTV). If there is no gross tumor left after prior treatments, a volume of tissue is constructed by drawing slice-by-slice the bounds of tissue that was once in contact with tumor and therefore, must be treated. When there is a GTV, or in the case of gross total resection where there is a cavity wall, a 3D expansion is performed to create the "clinical target volume" (CTV). This expansion is to include microscopic cancer cells that can be assumed to be present adjacent to the tumor itself. The expansion radius is based on our

understanding of microscopic cancer cell extension and is based on the specific tumor type. Finally, a second expansion is preformed of the CTV to create the "planning target volume" (PTV) which accounts for our inability to perfectly reproduce the patient's position each day and the possibility of movement of the tumor itself on a daily basis. During the planning process, it is the PTV that we enclose with the prescribed dose. This guarantees that the CTV will be covered as long as we obtain the patient position reproducibility upon which we based the PTV margin. It is this margin that can be reduced by good immobilization methods and daily patient position imaging prior to each treatment. In addition to drawing the tumor on each CT slice and creating the CTV and PTV, all normal organs which need to be protected are drawn slice-by-slice. The patient's skin contour is also drawn and together, all these drawings form a 3D model of the patient and the internal structures of interest. This 3D volume set can be viewed and rotated in the TPS to help visualize the geometric relationships between structures.

16.2.4 Treatment Planning

The TPS also has a very accurate model of each radiation producing treatment machine (linear accelerator, also known as linac, or proton therapy unit) and knows the penetrability of each type of radiation beam, the degree of uniformity of the beam, and all the mechanical limits and capabilities of the treatment unit. With this information, the TPS can be used like a "flight simulator" in that an arrangement of radiation beams can be aligned to the center of and shaped to the PTV and the 3D radiation dose can be calculated. Optimization and tailoring of the dose distribution can be made for each patient and the result reviewed in advance of the start of treatment. Here is where techniques like Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) can be utilized. The Radiation Oncologist can view the dose to the target volume and to all critical structures and can review dose-volume histograms which quantitate the dose given to any particular partial volume of an organ. The goal of the planning process is to cover at least 95% of the PTV by at least 95% of the prescribed dose, but most often more than 98% of the PTV receives more than 98% of the prescribed dose. Variation in PTV coverage is due to the proximity of normal organs to the PTV and the ratio of prescribed dose to normal organ tolerance dose. The parameters of each radiation beam can be adjusted to optimize the PTV coverage while staying below normal organ tolerance doses.

Treatment approaches for pediatric patients span the range of complexity, from single fields, to opposing fields, to highly conformal multifield arrangements. These approaches are a consequence of the physician's intent, the geometry of the target and normal tissues, the magnitude of the prescribed dose vs. the normal tissue dose limits, and practical factors.

16.2.5 Quality Assurance

IMRT and VMAT of X-ray treatments not only require the 120 or so MLC leaves to move to specified positions to within 1 mm but also to be synchronized with the dose rate and gantry position during rotation. The TPS needs to calculate the dose accurately to within 3% for this complex mechanical dance. To ensure this accuracy is being achieved, medical physicists perform hundreds of radiation dose measurements of each patient's plan cast onto a rectangular block of water-equivalent plastic embedded with dosimeters. These measurements are compared to the TPS calculations in this same geometry. This comparison and analysis takes place prior to the start of first treatment. Although good agreement is generally found, if a dosimetric mismatch is seen, the plan or the linac can be adjusted and remeasured before treatment begins. A similar quality assurance process is performed for particle therapy. Examples are confirmation of manufacturing accuracy of patient-specific devices (e.g., range compensators), beam measurements with ionization chamber array detectors, independent dose calculation with separate software,

and/or analyses of the treatment log file of individual proton beam positions. Quality assurance of the imaging equipment is also very important and is performed on a regular basis.

16.3 Recent Advances in Technology

16.3.1 Imaging for Treatment Planning, Setup Verification, Adaptive Therapy, and Response Assessment

The use of medical imaging is essential in every aspect of radiation therapy for children and adults. CT, MRI, PET-CT, ultrasound, and optical surface imaging all play a unique and important role. Nowadays, almost every radiation oncology department is equipped with a dedicated CT scanner for acquiring 3D imaging data for treatment planning and radiation therapy simulation. Major academic radiation oncology departments have their own MR and PET-CT scanners for assisting tumor boundary delineation. The others may utilize the scanners in radiology departments. Scanners dedicated to radiation oncology applications have a larger bore size, higher-precision flat table tops, external laser bridges/posts for patient positioning, and unique imaging capabilities and software specifically designed for radiation oncology.

The use of MRI for tumor and critical organ delineation is vital in treating pediatric brain tumor and soft tissue sarcoma due to its superior soft tissue contrast compared to other imaging modalities. Recent advances in magnetic field homogeneity and pulse sequence design have improved the geometric distortion that arises from the imperfection in magnetic field and gradient linearity. This provides the treating physician a higher confidence in the exact location of the tumor. The availability of thin-slice 3D pulse sequences with millimeter isotropic resolution is very helpful in tumor delineation and can be easily reformatted into other imaging planes for better visualization. 4D MRI techniques are now being developed for pediatric patients to determine the extent of tumor motion and surrounding critical organs due to respiration (Uh and Hua 2015). 4D MRI produces 10-phase-bin 3D MRI datasets, each corresponding to a specific phase in a respiratory cycle. More precise safety margins to account for tumor motion during the irradiation can be designed based on 4D MRI (Tryggestad et al. 2013; Deng et al. 2015). It is an excellent alternative to 4D CT for pediatric patients because of the lack of ionizing radiation exposure (Pai Panandiker et al. 2012).

Multimodality image registration algorithms have been significantly improved and the spatial registration is now commonly performed in the process of treatment planning. Multiple anatomical and functional MRI and PET images can be quickly and accurately aligned to the treatment planning CT scan. Tumor boundary and subregions of high tumor burden can be delineated by simultaneously inspecting fused multimodality images. Higher radiation doses can be given to the more aggressive subvolumes while the standard dose is given to the remainder of the tumor. Deformable registration is also available as a commercial tool to assist registering image datasets acquired with the patient in different postures. A useful application is to deform images acquired at two time points years apart and accumulate radiation doses accordingly in a growing child previously treated with radiation and requiring a second course of radiation therapy due to recurrence. Doses delivered to surrounding critical organs from the previous course can be more accurately added to the new treatment plan for determining if the radiation tolerance would be exceeded.

Image-guided radiation therapy (IGRT) is a new technological advance in better localizing the tumor with imaging and improving the patient positioning on the treatment table immediately before delivering the radiation. This can be achieved by taking 3D or orthogonal 2D images of the patient using kV or MV cone beam CT (CBCT), digital X-ray, conventional fan-beam CT, MRI, and ultrasound. Among them, kV CBCT is the most popular technique which acquires volumetric images of the patient using a separate X-ray source and a flat panel detector

mounted on the linear accelerator and spatially registers them to the treatment planning CT scan (Boda-Heggemann et al. 2011). The calculated patient setup deviations are then corrected by automatically moving the treatment table. Daily IGRT has been performed for pediatric radiation therapy patients to achieve millimeter accuracy and obviate the need for a large safety margin for setup uncertainty around the tumor (Beltran et al. 2010b; Pai Panandiker et al. 2013; Alcorn et al. 2014). A large discrepancy in anatomy found in spatially registered CBCT and planning images can trigger a replan. This is sometimes seen in pediatric patients who experience weight loss, a swollen face or body due to weight gain or steroid use, or early tumor regrowth or shrinkage. This process to modify the treatment plan to account for anatomical changes during the treatment course is termed adaptive radiation therapy (Yan et al. 1997). Adaptive therapy can also be accomplished with frequent MR imaging to detect tumor changes, for example, closely monitoring the craniopharyngioma cyst growth in children receiving radiation therapy (Winkfield et al. 2009; Beltran et al. 2010a).

In addition to guiding tumor delineation, verification of treatment position, and monitoring anatomic changes during the treatment course, imaging is also instrumental in assessing treatment response of pediatric patients after radiation therapy. Imaging end points in therapeutic trials continue to evolve, such as WHO and RECIST for tumor size, EORTC and PERCIST for tumor metabolic activity. MRI and PET-based imaging biomarkers assessed during the first few weeks of radiation therapy course have shown promise in predicting tumor response for different types of adult cancers (Mayr et al. 2012; Muruganandham et al. 2014; Jeraj et al. 2015). For children, standard-of-care treatment of Hodgkin lymphoma has included fluorodeoxyglucose (FDG) PET-CT in radiation field design and treatment response assessment (Robertson et al. 2011; Paulino et al. 2012; Walker et al. 2015; Hodgson et al. 2015). There is some evidence that FDG PET-CT may have prognostic value in childhood rhabdomyosarcoma (Dharmarajan et al. 2012; Norman et al. 2015). Its use for assessing early response is being incorporated into prospective cooperative group therapeutic trials. Imaging can also be used for measuring radiation effects on pediatric normal tissues (Sabin et al. 2013). For example, changes in cerebral white matters and brainstem fibers can be detected with diffusion tensor imaging (Hua et al. 2012; Uh et al. 2013). PET imaging may help identify metabolic defects in the pediatric brain before and after radiation therapy and monitor the longitudinal development of those defects after treatment (Hua et al. 2015). Functional MRI has been applied to characterize the neurocognitive deficits and the impact of rehabilitative interventions in pediatric patients (Zou et al. 2012, 2015).

16.3.2 Treatment Planning and Delivery Advancements

Prior to about 2000, most radiotherapy centers were using "3D conformal" planning and treatment techniques. This method relies on the treatment planner to design the shape and intensity of each radiation field and then the TPS computed the resultant dose. If the dose distribution was not optimal, adjustment of beam shapes and intensities would be manually performed. Also around 2000, the multileaf collimator (MLC) integrated into the linear accelerator was becoming widely available and adopted in clinics. This device allowed computer controlled complex beam shaping with 80–120 independent tungsten blades (leaves) replacing the old hand-made lead-alloy apertures previously used to shape the radiation fields. When these leaves are inside the field, they entirely block the radiation, allowing complex shaping of the radiation field. With the advent of the MLC, computer software was created which took advantage of the dynamic motion of the independent leaves so that differential blocking of each radiation field could be performed, allowing complex radiation dose sculpting, including delivering concave dose distributions and multiple prescribed dose levels in one treatment. This type of treatment is called Intensity Modulated Radiation Therapy (IMRT)

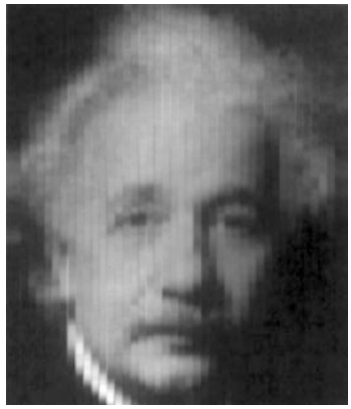

Fig. 16.1 Radiographic film irradiated with an IMRT plan, painting out a picture of Einstein with radiation

and is now the common mode of treatment. During IMRT, these leaves move during the time the beam is on, partially blocking the field in a manner determined by the TPS based on dose requirements (for targets) and limits (for normal structures) input into the system. IMRT provides highly conformal dose to the target volume while also allowing us to control the shape of the low and medium dose volumes. This process is so sophisticated that we can paint a picture of Einstein on film using the radiation output of an IMRT beam (Fig. 16.1)! Complex shaped dose distributions can be created in the patient that typically protect normal tissues two to fivefold better compared to 3D conformal treatment methods. The clinical examples below utilize these capabilities which were impossible before the IMRT era.

More recently, additional degrees of freedom of the linear accelerator radiation delivery system have been exploited to further advance IMRT. IMRT is performed with a group of radiation fields stationary in their beam direction. IMRT typically uses 5–9 beams spaced somewhat evenly in the plane around which the linear accelerator gantry (nozzle) rotates. With the newest advancement, the gantry can continuously rotate as the beam is delivered, the MLCs continuously move, and the dose rate can also be dynamically controlled. This delivery mode is called Volumetric Modulated Arc Therapy (VMAT). This technique produces similar complex dose distributions as IMRT but takes only 1–2 min to deliver instead of about 5 min with IMRT.

With the advent of 3D treatment planning, we were able to take advantage of the ability to rotate the treatment bed that the patient lies on during treatment. Especially for brain tumors, this allows beam entry directions in a superiorly oriented full hemispherical space around the patient's head and results in more conformal and protective dose distributions than if all the beams were oriented in the axial plane of beam rotation.

Computational advances in the mid 2000s have led to ever more accurate 3D dose calculations. These advances include "Monte Carlo" calculation algorithms that more accurately take into account the absorption, scatter, and attenuation properties of the various tissues in the body, including those very different than muscle and fat, such as air and even metal parts surgically implanted to support the spine or extremities (Vassiliev et al. 2010). Also, the software used for IMRT planning continues to evolve. Special software allows the input of our dosimetric goals for the targets and normal organs and then optimizes the radiation intensity pattern of each beam to best achieve these goals. This optimization process also has to calculate the position of the MLC leaves for each beam at each moment during the radiation delivery to achieve the calculated intensity patterns. As optimization software advances, we have even better control of the radiation dose outside the target volume and the treatment unit can more accurately deliver the dose that was calculated.

16.3.3 Motion Management Methods

For tumors located adjacent to the lungs or diaphragm, tumor motion during treatment may be large enough to need special consideration. Also, motion of critical organs we wish to spare needs to be considered (Li et al. 2012; Rietzel et al. 2005; Sarker et al. 2010). An example is soft-tissue sarcoma of the diaphragm. In the past, fluoroscopy was the only way to roughly estimate

such motion. PTV margins would be increased significantly to approximately account for motion to avoid target miss, thus irradiating a large portion of surrounding normal tissues. With modern CT simulators capable of 4D CT (Moorees and Bezak 2012; Kwong et al. 2015), we can take a series of CT scans whose slices are binned by phase of the breathing cycle. This effectively stops the motion in each phase-based CT scan set. One can use software to define the entire trajectory of the tumor motion in an accurate way and create a PTV that envelopes the motion (Pai Panandiker et al. 2012, 2013). Alternatively, one can choose to deliver the treatment only at moments where the patient is in a defined part of the breathing cycle, enabling a much smaller field size. This method is referred to as respiratory gating, where the treatment beam is turned on only when the specified phases are reached and turned off otherwise. A version of this method is called deep inspiration breath hold, where the beam only turns on when the patient has inhaled a specific air volume. The breathing phases of the patient are determined by detecting changes in signals generated by external devices such as reflective markers placed on abdomen or chest, a pneumatic belt around the abdomen, or a spirometer (Moorees and Bezak 2012).

16.3.4 Hypofractionated/ Stereotactic Treatment Methods

In certain situations, it is advantageous to deliver the course of radiotherapy in very few or even just one treatment fraction. This is more common for adults than children, due to the potentially greater late effects of large doses per fraction on developing organs and tissues. For small targets in the brain, we can deliver the entire dose in one fraction, which is an ablative dose. The Gamma Knife or linac can be used to deliver such treatments which are referred to as stereotactic radiosurgery (SRS). Additional care is taken to precisely position the patient for such a treatment and often an invasive head fixation system is used. For sites in the body, an alternative to treatment usually taking 5–6 weeks is to apply just 1–2 weeks of 5 daily or every other day fractions. This method is referred to as stereotactic body radiation therapy (SBRT). A Children's Oncology Group (COG) Ewing sarcoma protocol allows SBRT for metastatic sites. These treatments are given using the conventional noninvasive immobilization devices. As with SRS, additional quality assurance steps are taken to ensure high precision patient positioning, including CBCT before each fraction.

16.3.5 Radiation Treatment Delivery Equipment

16.3.5.1 X-Ray Linear Accelerators

Although X-ray and electron beam therapy have been used for radiotherapy for over 50 years, new delivery platforms and computerized technology provide us with precision control over the dose distribution in the patient. Most radiation treatments are given with a medical linear accelerator. This device has evolved over that time to be a highly precise, computer driven device with integrated imaging capabilities. The basic operation of the linear accelerator hasn't changed much over the years, which is to accelerate a pencil beam of electrons to high energies, usually between 6 and 20 million electron volts, and smash into a tungsten target, creating high energy X-rays. For superficial targets, the electrons can be directly used, first being spread out over a wide user-defined field. Electrons lose their energy rapidly and deposit virtually no dose distal to a relatively short depth determined by their energy. X-rays, on the other hand, are highly penetrating, and control of dose distal to the target is accomplished by using beams from many directions to smear out and reduce the dose away from the target. One of the significant advances to linac design over about the past 10 years has been the integrated kilovoltage imaging capability. Attached to the sides of the gantry of the linac, at 90 ° from the treatment beam, are a diagnostic type kV X-ray source and an opposing digital image receptor panel, both robotically controlled by the operator (Fig. 16.2).

Fig. 16.2 Modern linear accelerator with integrated kilovoltage imaging, the arm on the left is the X-ray source and on the right is the flat panel image receptor. (Image courtesy of Varian Medical Systems, Inc. Copyright [2017]. All rights reserved)

One of the key quality assurance steps that must be taken before each treatment or on a periodic basis during the course of treatment is to take an image of the patient through the portal that will be used for treatment (portal image). This image is compared to a synthetically created image made by the TPS called a digitally reconstructed radiograph (DRR). The congruence of the bony anatomy of the DRR and the portal image of the day is used to introduce shifts in the couch to perfectly align the two images and thus the patient before treatment. Due to the high energy of the treatment beam, the contrast of portal images is poor. By rotating the gantry 90 ° from the actual treatment angle, the kV source can be used to take a high contrast image which is much clearer and with much less radiation dose. In addition, the linac can be operated in a pseudo CT mode such that kV images are taken every degree or so as the gantry rotates, and then software reconstructs a CT image called a cone beam CT (CBCT). This CBCT can be compared to the planning CT and much more accurate shifts of the treatment couch can be made to perfectly align the radiation beam to the planned position in the patient, including the ability to use pitch, roll, and yaw of the couch if the couch is capable of those motions (called a 6-degree-of-freedom couch). The ability to see a 3D view (axial, sagittal, and coronal planes) of the patient just before each treatment also allows assessment of soft tissues not seen before with either portal images or static kV image projections. Radiation treatments can now be delivered with sub-millimeter precision, allowing much less normal tissue irradiation and therefore, less acute and late effects of treatment.

A relatively new feature for the linac is for the control system to temporarily remove the flattening filter from the beam. This is the conical metallic device that transforms the otherwise more centrally intense radiation field into a highly uniform field. This leads to an up to four-fold increase in dose rate which is especially advantageous for cases with large daily doses (to reduce treatment time) or for treating small moving targets. Although the useful (fairly uniform) field size is only about 7 cm wide, metastatic targets and small primary tumors can quickly be treated, reducing sedation time and the uncertainties of target motion. This mode is called Flattening Filter Free (FFF) mode.

16.3.5.2 Proton Accelerators

Hospital-based proton therapy became available in 1990s after decades of laboratory-based experiments and refinement. Currently, there are approximately 20 operating proton therapy centers in the United States and this number is expected to exceed 30 by 2020. Almost every proton center now offers pediatric proton therapy for selected diseases. Traditionally, a hospital-based proton therapy center was built to contain a proton-accelerating cyclotron or synchrotron, beam transport system, and multiple treatment rooms (gantry or fixed beam rooms). Medical cyclotrons typically accelerate protons to a fixed energy of 230–250 MeV and subsequently reduce the proton energy to the desired treatment energies via an energy selection system. In contrast, synchrotrons only accelerate the protons to the desired energy between 70 and 250 MeV in each acceleration before being extracted into the beam transport system. Because of the high cost and space required for

proton accelerators, multiple treatment rooms usually share the same accelerator and the proton beam can only be directed through the beam transport system into one room at a time. To reduce cost and space, compact single-room proton therapy systems have been developed and installed in many academic and community hospitals in the past few years. Because of the affordability and scalability, such systems may become popular and make proton therapy more accessible for pediatric patients outside metropolitan areas. Two techniques for proton beam delivery are passive scattering and active scanning. The former has been the dominant technique until now but the latter is being considered the state-of-the-art and gaining popularity quickly. Many new centers are scanning beam only facilities. Passive scattering, also known as double scattering, relies on scattering materials to broaden a narrow incoming beam into a uniform and large treatment field. Custom-made compensators and apertures further conform the beam to the tumor shape before reaching the patient. Active scanning, also known as pencil beam scanning, only irradiates a small region of the tumor at a time. Steered by a pair of scanning magnets in the nozzle, the beam is swept across the tumor either in discrete spots (spot scanning) or continuously (raster scanning) and irradiates the entire tumor layer by layer like a paintbrush. Passive scattering produces higher neutron dose due to the proton interaction with scattering materials and increases the undesirable total body dose (integral dose) to patients (Halg et al. 2014; Schneider and Halg 2015). Active scanning reduces the integral dose but is susceptible to missing parts of the tumor as it moves during respiration. The sensitivity to organ motion is often mitigated by "repainting" the target multiple times or with respiratory gating when the motion is large (>1 cm) (Rietzel and Bert 2010; Schatti et al. 2013). The spot size of the pencil beam for active scanning has been significantly reduced over the years, making sculpting the dose distribution for complex-shape tumors more easily achieved.

Intensity modulated proton therapy (IMPT) is the most advanced form of proton therapy. It can be achieved by controlling the dwell time of the pencil beam scanning at each tumor sub-region. The intensity of each of the multiple fields of different angles can be non-uniform and modulated to produce a uniform dose distribution when contributions from all fields are added together. Alternatively, the combined dose distribution can be designed to selectively boost the high tumor burden regions while keeping the rest of the tumor at a lower dose. This technique is known as multi-field-optimization (MFO) IMPT (Yeung et al. 2014; Kooy and Grassberger 2015). MFO IMPT has been offered to pediatric cancer patients in selected proton therapy centers. The technique is highly sophisticated, therefore, quality assurance checks to ensure the agreement of the delivered dose distribution and the planned one is performed on phantoms for each patient prior to first treatment.

Two new developments, 6 degree-of-freedom (DOF) patient position system (PPS) and volumetric image guidance system, have been recently implemented in new proton therapy facilities. The 6 DOF PPS was initially introduced for photon therapy systems, which allows the couch to move in three principal axes (X, Y, Z) and three rotation directions (pitch, roll, yaw) for correcting patient setup error before each treatment. Conventional couches only correct for translational errors. Proton therapy PPS is designed to have a higher degree of positioning accuracy and reproducibility by mounting the table top on a high precision robotic arm (Nairz et al. 2013). Since proton dose distributions have sharp dose gradients adjacent to the target volume, the delivered dose is more sensitive to errors in daily patient positioning than photon treatments. Volumetric image guidance systems in proton centers acquire 3D images of the patient in treatment position immediately before proton beams are delivered. Required 3D corrections to the patient position are implemented by the 6 DOF PPS. These image guidance systems can be gantry-, nozzle-, or ceiling-mounted CBCT or a fan-beam CT scanner installed in the treatment room. Extremely high accuracy in patient positioning can be achieved with these imaging systems.

16.3.5.3 Brachytherapy

HDR for Soft Tissue Sarcomas

High-dose rate (HDR) brachytherapy is an alternative treatment approach to external beam radiation therapy for selected cancers. The main advantage to brachytherapy over external beam is that there is a smaller volume of normal tissue irradiated to high doses. Surgeons first carefully place an applicator or multiple catheters in the tumor bed in the operating room after resection of the tumor. On a separate visit to the radiation oncology department, a high-activity (up to 10 Ci) radioactive source is remotely controlled by a computer and advanced inside the catheters within the tumor for a predetermined time via source transfer tubes. After the prescribed dose has been delivered in seconds to minutes, the source is retracted from the tumor and returned to a lead-shielded safe. HDR brachytherapy is delivered using hypofractionation, i.e., a large dose per fraction and only a few treatment fractions in less than a week. The use of HDR brachytherapy alone or as a local boost for childhood sarcoma is not new (Viani et al. 2008; Folkert et al. 2014). However, improvement has been made in catheter design, image fusion tools and dose calculation in the treatment planning system, and the development of new electronic brachytherapy systems. Electronic brachytherapy uses a miniaturized 30–50 keV X-ray source as opposed to the 350 keV Ir-192 radionuclide source (Rivard et al. 2005). It has an advantage of turning radiation on and off easily and requires less room shielding while the constantly emitting radiation from Ir-192 systems has to be contained inside a heavily-shielded safe when not in use. It does not require quarterly source exchange. Electronic brachytherapy delivers a higher dose near the source and care should be taken to minimize the risk of tissue necrosis.

Eye Plaque for Retinoblastoma

Episcleral plaque radiotherapy, also known as eye plaque brachytherapy, is an effective option for focal therapy for small localized retinoblastoma. The advantage over external beam IMRT is far less normal tissue irradiation. The eye plaque is a small gold cupped disk that can be custom sized for each child with radioactive seeds such as Iodine-125 or Palladium-103 glued to the inner surface of the plaque (Astrahan et al. 2005; Merchant et al. 2004; Shields et al. 2006). Alternatively, instead of using radioactive seeds, plaques can be purchased which have their entire surface plated with Ru-106, a beta particle emitter (Reddy et al. 2010). Methods of designing the radioactive source placement to optimize the dose to the tumor and precise positioning of the plaque relative to the tumor have been developed (Astrahan et al. 1990a, b). The plaque is sewn onto the surface of the eye over the location of the tumor and left inside the patient for several days as calculated to deliver the prescribed dose. In recent years, dedicated treatment planning systems for eye plaque dosimetry are now available for more precise 3D modeling of the eye and tumor as well as visualization of calculated dose distribution (Astrahan et al. 1990a). Better localization of the tumor before plaque placement is accomplished with fundus photograph, CT, MRI, or intraoperative ultrasound guidance. Advanced calculation algorithms take into account the backscatter from the gold plaque, and the non-uniform exposure pattern from the radioactive seeds, resulting in ever improving dose accuracy (American Brachytherapy Society—Ophthalmic Oncology Task Force. Electronic address: paulfinger@eyecancer.com; ABS—OOTF Committee 2014).

16.4 Clinical Examples

Radiotherapy, like surgery, is a local treatment, but is often used when the tumor is unresectable or as adjuvant therapy after partial or total resection. The adjacency of tumor and normal tissues in sites such as the head and neck, pelvis, and brain, are challenging but are approached in a much more elegant way than decades ago. In the past, treatment to these sites would have been performed using two opposing radiation fields which were large enough to encompass the large uncertainty in

the location of the target tissues. Today, with image registration of MRI and PET-CT images, we have much better knowledge of where we need to direct the dose. With our advanced delivery techniques such as IMRT, VMAT, and IMPT, we can sculpt the high dose volume away from normal structures which in the past would have received the same dose as the tumor. Thus, late effects of modern treatment will likely be much less than what was seen from treatments given decades ago. The following section provides some examples of modern vs. earlier treatment methods for medulloblastoma, parameningeal rhabdomyosarcoma, pelvic rhabdomyosarcoma, heart-sparing whole lung irradiation, and vertebral body sparing treatment for neuroblastoma.

16.4.1 Medulloblastoma

Medulloblastoma and other CNS tumors often necessitate the treatment of the entire craniospinal axis along with a tumor bed boost. In the past, cranial-spinal axis irradiation (CSI) was carried out by irradiating the entire brain with opposing lateral X-ray beams and the entire spinal canal with one or two abutted posterior beams (Thomadsen et al. 2003). The spinal portion of the treatment resulted in all tissues anterior to the spinal cord getting more than 70% of the prescribed dose (Parker et al. 2007). The risk of late cardiac toxicity, in particular, is a concern (Parker et al. 2007). Also, the dose to the intestines frequently causes nausea, sometimes so severe that treatment has to be interrupted. VMAT and IMPT treatment techniques have been developed and clinically implemented and can meaningfully reduce the dose to these anterior organs. Figure 16.3 shows a comparison of radiation dose with the conventional, VMAT, and IMPT techniques. For VMAT vs. conventional, the mean dose to the heart is reduced by 75%, the thyroid by 65%, and the intestines by 65% (Parker et al. 2007, 2010). The dose is increased to other structures such as the lungs and kidneys due to the

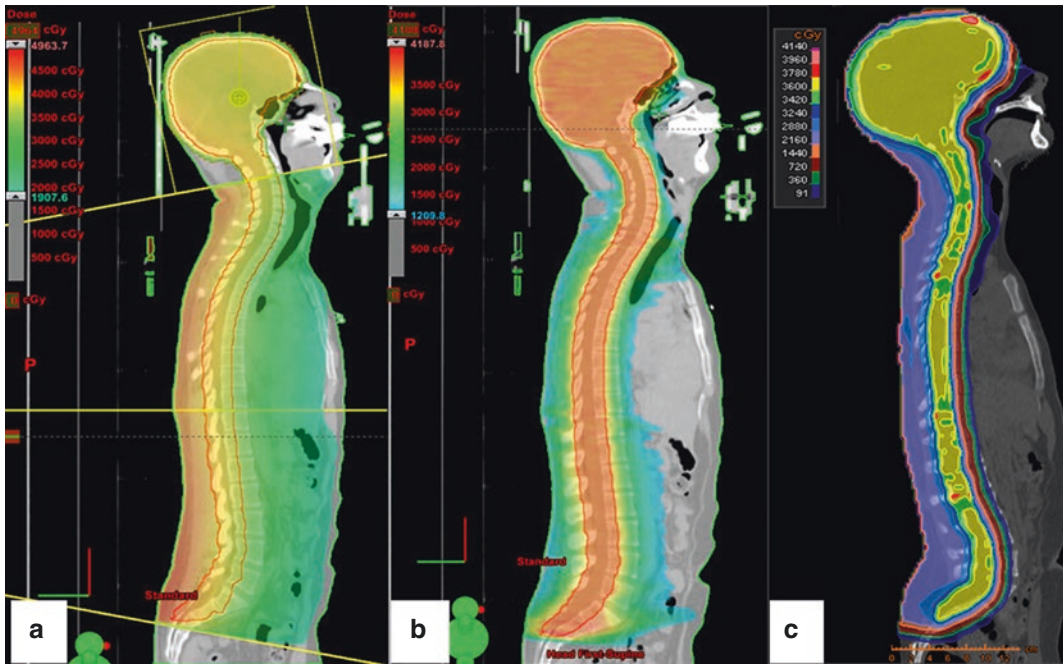

Fig. 16.3 Comparison of (**a**) Conventional (opposed lateral brain with PA spine), (**b**) VMAT, and (**c**) Proton doses for CSI. For a, the colorwash is 19–49 Gy, for **b**, it is 12–42 Gy, for **c**, it is 4–40 Gy

omnidirectional delivery but these remain significantly below organ tolerances. For proton treatment, the dose to structures anterior to the vertebral bodies is nearly zero. For CSI with VMAT and IMPT, it is also possible to spare sensitive structures adjacent to the brain, for example, the lenses and cochlea (Cochran et al. 2008; Hua et al. 2008).

Up to about the late 1990s, a common way to deliver the whole posterior fossa boost was through opposed lateral beams shaped to irradiate that compartment. This also gave high doses to large volumes of the temporal lobes. With modern techniques, radiation dose can be sculpted away from the temporal lobes, cochlea and hippocampi, reducing mean doses by more than 50%, potentially greatly reducing late effects (Breen et al. 2004; Chen et al. 2007; Olch and Lavey 2003; Rembielak and Woo 2005).

16.4.2 Rhabdomyosarcoma of the Head and Neck

Rhabdomyosarcoma and other sarcomas in the parameningeal and periorbital region are extremely challenging to both adequately irradiate and at the same time, minimize normal organ dose and associated late effects. In the era before IMRT, tumors in these locations were treated with simplistic field arrangements with limited ability to spare normal tissues. Protection of critical structures came at the cost of underdosage of the tumor. With modern techniques, normal brain, lenses, retina, and endocrine glands can be greatly spared. Often these tumors are complexly shaped and yet are amenable to conformal irradiation with IMRT or proton techniques. Figure 16.4 shows an example dose distribution from a VMAT plan for treatment of a tumor that extended from above the eyes to below the mandible. Compared to a typical plan from the 1990s for this type of case, significant sparing of brain, lenses, eyes, cochlea, parotid glands, and spinal cord can be achieved.

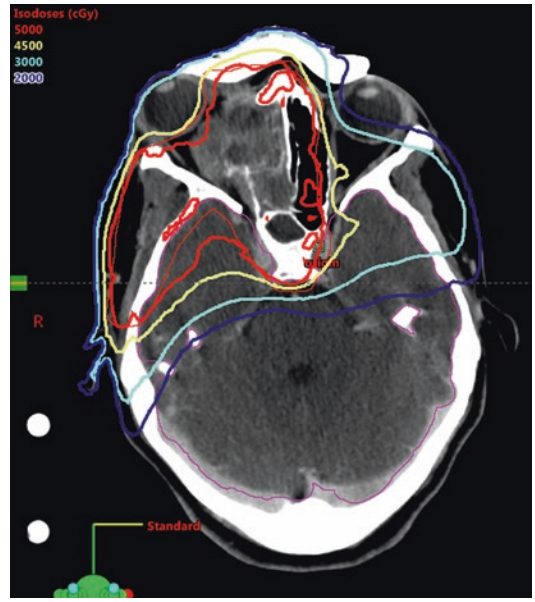

Fig. 16.4 Periorbital rhabdomyosarcoma with extension into the oral cavity and right neck. The dose distribution using VMAT is shown, with isodose lines representing the region receiving 50, 45, 30, and 20 Gy. Note the dose sculpting away from the eyes and brain

16.4.3 Pelvic Rhabdomyosarcoma

Sarcomas arising in the pelvis come with the challenge of sparing rectum, bladder, femoral and pelvic bone deformity, ovaries, and intestine. In previous decades, opposed lateral beams or a combination of opposed lateral and opposed anterior-posterior beams were used to irradiate these tumors. With modern organ sparing techniques, radiation dose can be carved around these normal organs, greatly lessening their absorbed dose while retaining adequate dose coverage to the tumor. Gonadal structures, bones, bladder and rectum can be spared in a meaningful way. Figure 16.5 shows the dose distribution from a helical tomotherapy plan (HT), a VMAT plan,

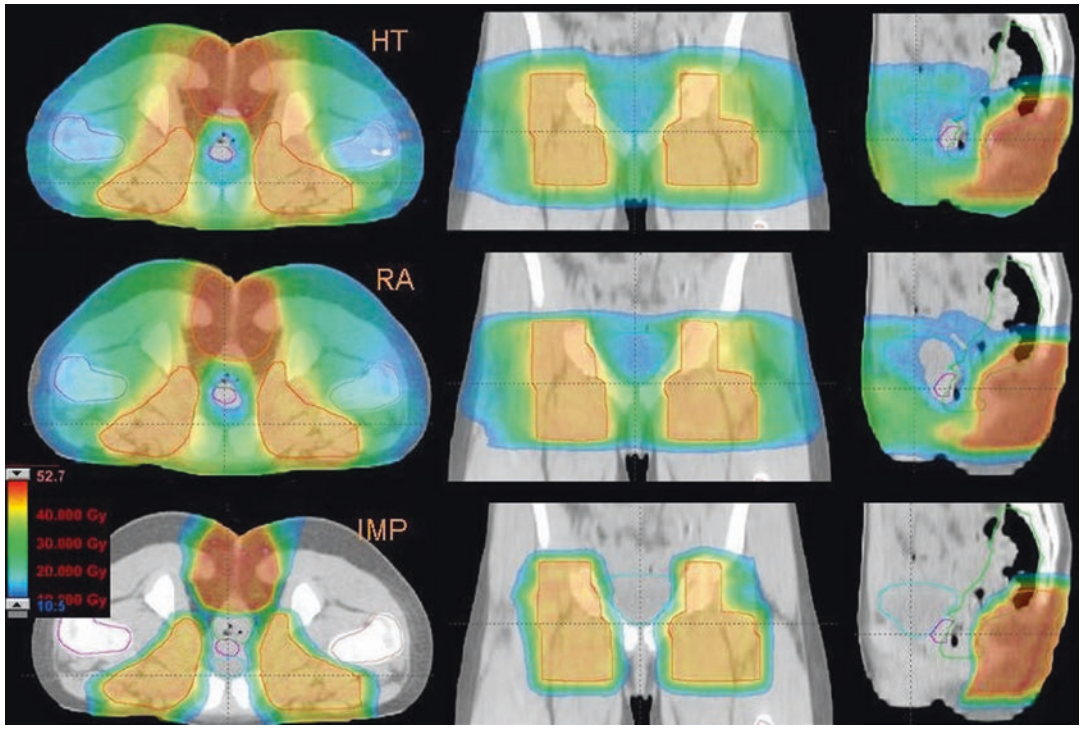

Fig. 16.5 Dose distribution in axial, coronal, and sagittal views for HT, RA (VMAT), and IMPT for pelvic rhabdomyosarcoma. From Radiation Oncology 2009, 4:2 doi:10.1186/1748-717X-4-2, Fig. 16.4

and an IMPT plan. Although all three techniques produced normal tissue sparing well below tolerances, the proton plan gave doses 40–90% less than the photon plans. Whether this additional sparing beyond what is already considered safe is meaningful to the patient is unknown. Compared to what would have been delivered in the 1990s, any of the three techniques dramatically spare normal tissues in a meaningful way.

16.4.4 Heart-Sparing Whole Lung Irradiation

For Wilms tumor or Ewing sarcoma, the presence of lung metastases require treatment by whole lung irradiation to 12–15 Gy. Traditionally, this treatment has been given through opposed anterior-posterior fields covering the whole lungs and all tissues inside the field boundary. This approach delivers the full prescribed dose to the heart. Heart irradiation can cause a wide range of disorders affecting the heart muscles, valves, and arteries. Although 12–15 Gy has historically been thought to be tolerable, newer studies indicate this dose level can be harmful decades after treatment (Darby et al. 2010; Gagliardi et al. 2010; Mulrooney et al. 2009; Stewart et al. 1995).

The National Wilms Tumor Studies (NWTS) showed an increased relative risk (RR) for 10 Gy (RR 1.6) (Green et al. 1989, 2001). A French and British study of 4122 cancer survivors demonstrated a RR of 12.5 for cardiac doses between 5–14.9 Gy and 25 for greater than 15 Gy (Tukenova et al. 2010). In a study by Kalapurakal, an intensity modulated X-ray technique was

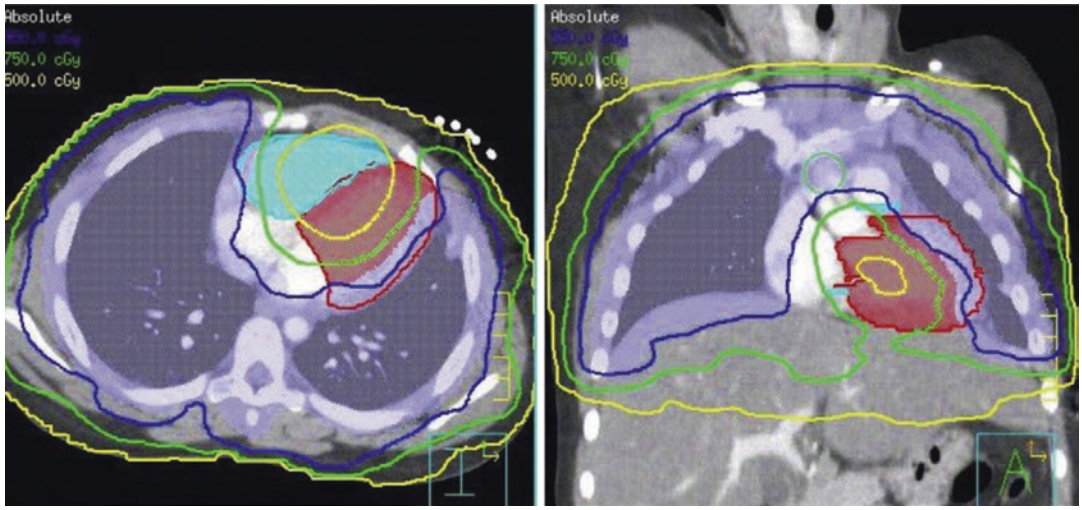

Fig. 16.6 Heart sparing, the *blue line* represents 12 Gy, *green* 7.5, and *yellow* 5. Int J Radiation Oncol Biol Phys, Vol. 85, No. 3, pp. 761e767, 2013 0360–3016$ - see front matter 2013 Elsevier Inc. All rights reserved. http://dx.doi.org/10.1016/j.ijrobp.2012.05.036

shown to deliver the prescribed dose to the whole lungs while decreasing the mean heart dose by 36% and the left and right ventricular dose by 35% and 63%, respectively compared to the conventional AP/PA plan (Kalapurakal et al. 2013). This reduction is hypothesized to be meaningful in reducing late cardiac effects. Figure 16.6 shows an example dose distribution from an IMRT plan, demonstrating the heart sparing, the blue line represents 12 Gy, green 7.5, and yellow 5 (Kalapurakal et al. 2013). The feasibility of cardiac-sparing whole lung irradiation is being studied in an NIH sponsored trial with the potential to make it the standard of care.

16.4.5 Vertebral Body and Kidney Sparing Treatment for Neuroblastoma

Prior to the era of intensity modulated treatments, opposed oblique fields were commonly employed when treating neuroblastoma, with inclusion of the ipsilateral kidney and vertebral bodies along the length of the field. Figure 16.7b shows the dose distribution for this beam arrangement for a prescribed dose of 21.6 Gy. This treatment may result in a high likelihood of kidney damage. With VMAT or protons, both kidneys can be spared from late effects without compromising tumor coverage; the ipsilateral kidney volume receiving more than 18 Gy can usually be kept to less than 25% compared to 50–100% for conventional opposed oblique fields (Fig. 16.7a). Because neuroblastoma is typically adjacent to the vertebral bodies, they have been included in the volume getting the prescribed dose of 21.6 Gy to avoid partial irradiation which could cause scoliosis or kyphosis and growth arrest of the vertebral bodies contained within the field (Fig. 16.7b). When the target volume is anterior to the vertebral bodies, bone growth halting doses can be sculpted away using IMRT or protons (Fig. 16.8). When the target volume wraps from anterior to along the side of the vertebral body, inclusion of the entire vertebral body in the 18 Gy or higher dose volume should uniformly arrest growth and avoid kyphosis or lordosis (Hartley et al. 2008; Probert and Parker 1975).

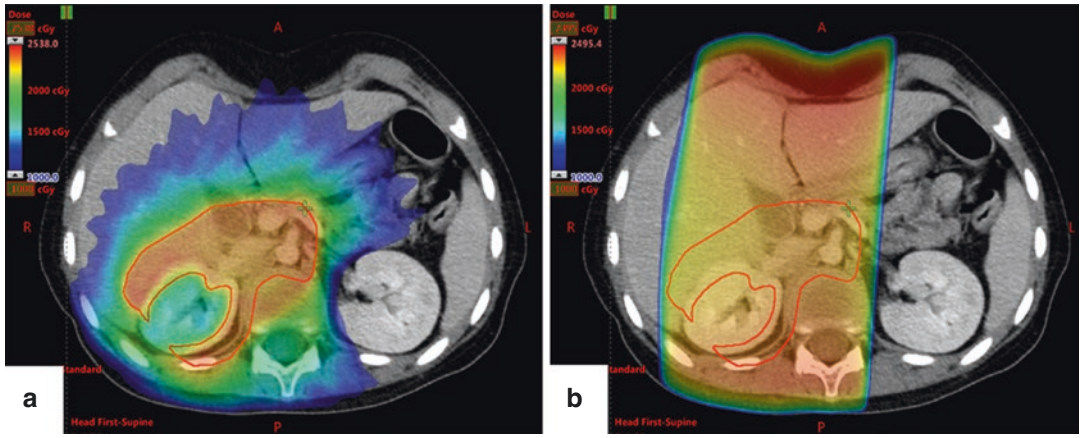

Fig. 16.7 (**a**) IMRT for neuroblastoma sparing the right kidney. (**b**) Opposed oblique fields used prior to the IMRT era. The *red* color represents the prescribed dose of 21.6 Gy and shades of *green* to *blue* represent doses down to 10 Gy

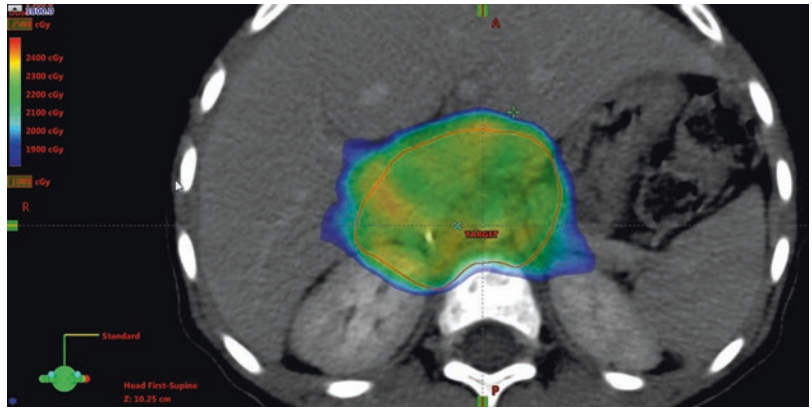

Fig. 16.8 Vertebral body sparing IMRT for neuroblastoma

16.4.6 Protons vs. X-rays?

As more proton centers get built and start operating, capacity for pediatric patients has increased while the distance to the nearest center has decreased. The question of whether a particular patient would be better treated with protons than IMRT/VMAT is being commonly asked, especially by patients and parents who have seen information about proton therapy on the web. Although each case is unique, there are some generalizations that can be made about the comparison between the two modalities. With protons, the dose a few centimeters outside the target volume will generally be less than with X-rays, and will be zero where there is non-zero dose with X-rays. With proper IMRT/VMAT planning, doses to normal organs are typically much less than their tolerance dose. It is not known whether there is a meaningful benefit to the patient for the dose to a given normal organ to be 20% instead of 50% of the tolerance dose. If everything were equal, one could speculate that less is always better. This is particularly relevant for normal tissues whose tolerance doses are not yet clearly understood such as pediatric brain. There are certainly cases where only by

treatment with protons would a patient's tumor be adequately treated while avoiding significant late effects. It should also be noted that proton plans are generally more susceptible to patient setup error and proton range uncertainty than X-ray plans with small changes in the patient position or anatomy during the course of treatment. As more children are treated with protons, studies are and will continue to be done to demonstrate the magnitude of the benefit from decrements in dose to normal organs achieved with protons. Over the last 15 years, there have been several dosimetric comparison papers published studying the head to head comparison between protons and IMRT or VMAT (Barten et al. 2015; Cotter et al. 2009; Fogliata et al. 2009; Grant et al. 2015; Olch et al. 2010; Isacsson et al. 1997; Kozak et al. 2009; Lomax et al. 1999; St Clair et al. 2004; Weber et al. 2004; Yock et al. 2005). We direct the interested reader to those papers for further information but actual patient outcome data from prospective proton trials is still being generated.

16.4.7 Secondary Cancer Considerations

With the advent of intensity modulation using X-rays, either with fixed beam angles or rotational delivery, large volumes of normal tissue are irradiated to low doses which would have received no dose with opposing fields of the prior era. This has led to concern over increasing the risk of secondary cancer formation, an unintended consequence of better normal tissue sparing in the intermediate and high dose regions. Olch performed an extensive study of this topic and concluded that the risk-benefit ratio is in favor of intensity modulated treatments. This is because of several observations from reports in the literature involving tens of thousands of childhood cancer survivors. First, the risk of secondary cancer increased with radiation dose, generally in a linear fashion. Second, secondary cancers were overwhelmingly found in the high dose region. These two factors together indicate that the low dose region contributes little to the secondary cancer risk. In fact, the smaller, more conformal high dose region produced by modern techniques may lessen the risk (Olch 2013). The use of protons may somewhat reduce the risk over X-ray methods due to the fact that the high dose region is the same for either modality. To the extent that the intermediate dose region is smaller for protons may provide some reduction in risk. The most effective way to reduce the risk of secondary cancers is to reduce the prescribed dose and/or target volume which is being done or tested for some diseases principally to reduce normal tissue damage.

16.5 Summary

Advanced imaging methods both better define normal and target tissues for more accurate treatment planning but also improve our ability to follow post radiotherapy changes which allows for a better understanding of dose-response relationships. New imaging methods and immobilization techniques assist in 1–2 mm daily reproducibility for most sites, allowing smaller margins and reduced normal tissue damage.

Modern radiotherapy for children includes an arsenal of high precision planning and delivery tools that will result in fewer late effects than treatments prior to the IMRT, VMAT, and proton era due to more precise targeting, delivery, and better normal tissue sparing. Oncologists should recognize that literature describing late effects of radiotherapy given in the decades prior to 2000 will overestimate those effects from modern delivery.

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17 Proton Therapy for Pediatric Malignancies

Matthew D. Hall, Daniel J. Indelicato, Ronny Rotondo, and Julie A. Bradley

17.1 Introduction

In the United States, approximately 12,000 children are newly diagnosed with cancer each year (Siegel et al. 2013). For these patients, improvements in cytotoxic systemic agents, the growth in multidisciplinary tumor boards, and the availability of more optimal therapies developed through clinical trials have led to improvements in 5-year overall survival (OS) rates, increasing from 58.0% in the 1970s to 75.8% in the early 1990s to 83.4% in the early 2000s (Table 17.1) (Howlader et al. 2015). Despite these successes, however, two-thirds of childhood cancer survivors will develop treatment-related illnesses, and 20% will die from treatment-related causes, such as secondary malignancies (Armstrong et al. 2009, 2010, 2011; Friedman et al. 2010). Therefore, reducing toxicity while continuing to improve treatment efficacy remains the primary goal of pediatric radiation oncologists (Merchant et al. 2013).

To this end, proton therapy has become a more widely used treatment option for childhood cancers owing to its unique physical properties. Although still considered a new technology by many, proton therapy was proposed by Robert Wilson in 1946. In 1958, the first patients to receive it were treated at the Lawrence Berkeley National Laboratory (Berkeley, CA) (Wilson 1946; Lawrence et al. 1958). As of 2014, more than 118,000 people have received proton therapy worldwide; 15,400 of whom were treated in 2014 (Jermann 2015). Yet, despite its increased use, high facility start-up costs and high treatment delivery costs have drawn scrutiny from insurance providers and healthcare reporters who demand that physicians demonstrate better clinical outcomes with proton therapy over less-expensive forms of radiotherapy (Mitin and Zietman 2014). Consequently, there has been a recent growth in the number of published studies on proton therapy. The purpose of this chapter is to discuss the physical and economic rationale

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Table 17.1 Five-year overall survival rates for selected cancers in children less than 15 years old

Site	Ages 0–14										
	1975–1977	1978–1980	1981–1983	1984–1986	1987–1989	1990–1992	1993–1995	1996–1998	1999–2001	2002–2004	2005–2011
All sites											
All races	58.0	62.4	67.0	68.1	71.6	75.8	77.4	79.1	80.7	82.7	83.4[b]
Whites	57.9	63.0	67.7	69.8	72.4	76.8	78.2	80.5	81.7	84.7	84.5[b]
Blacks	57.3	57.7	62.2	57.0	65.3	70.7	73.2	75.6	73.9	73.3	79.5[b]
Bone and joint	49.9[a]	47.8	56.8[a]	57.3[a]	66.8[a]	67.4	74.1	70.3	70.0	77.5	76.8[b]
Brain and CNS	56.9	57.7	56.7	61.7	64.3	64.4	70.7	75.2	73.9	75.3	74.2[b]
Hodgkin lymphoma	80.9	86.8	88.1	89.9	87.1	96.8	94.6	96.1	94.4	97.5	97.6[b]
Leukemia	49.7	58.0	62.7	63.6	71.0	75.5	75.9	80.3	82.7	86.0	87.2[b]
Acute lymphocytic	57.2	65.7	71.1	72.2	77.7	83.1	83.8	86.9	88.5	91.9	91.2[b]
Acute myeloid	18.8	25.8	26.7[a]	30.6[a]	37.1[a]	42.2	40.6[a]	48.7	58.2	61.1	66.5[b]
Neuroblastoma	52.5	56.6	54.5	52.3	63.2	76.0	66.8	65.6	72.1	73.4	74.2[b]
Non-Hodgkin lymphoma	43.2	52.7	66.9	69.8	70.7	76.9	80.7	83.2	89.8	84.6	88.2[b]
Soft tissue	61.3	74.2	69.2	72.9	66.4	79.8	76.7	70.5	76.9	84.5	79.0[b]
Wilms' tumor[c]	73.1	79.0	86.7	90.7	92.2	91.9	91.7	91.6	93.8	89.2	93.5[b]

Overall survival has steadily increased over time from 1975 to the present

From Table 28.8 in Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015

[a]The standard error is between 5 and 10% points

[b]The difference between 1975–1977 and 2005–2011 is statistically significant ($p < 0.05$)

[c]Wilms' tumor is defined as histologies 8959–8960

for using proton therapy and review the literature on the use of proton therapy in the treatment of childhood malignancies.

17.2 The Physical Properties of Proton Therapy

Conformal radiation therapy that uses megavoltage photons has allowed for greater dose deposit at the target and reduced how much radiation is deposited in non-targeted normal tissue. Yet in many settings, photon-based radiotherapy is still limited by the high dose deposition beyond the target (Merchant 2013). In contrast, proton therapy eliminates radiation dose deposition beyond the target through a characteristic known as the Bragg peak. A high-energy proton beam can travel linearly through tissue with minimal loss of velocity; linear energy transfer (LET) is low along the track of the beam until the proton reaches its maximal depth where most of its energy is deposited. The dose deposited before the Bragg peak is approximately 30% of the maximum dose, and no dose is delivered beyond the Bragg peak (Goitein 2007). As a result, owing to its unique dose distribution, proton therapy may achieve greater sparing of normal tissue than photon therapy while still delivering high doses to the tumor.

A single Bragg peak is too constraining for most clinical scenarios. The treatment of most solid tumors requires that the proton beam energy is manipulated to superimpose multiple Bragg peaks of variable energies and create a uniform dose region at the depth of the target volume referred to as the spread-out Bragg peak (SOBP). Although this modulation increases the entrance dose, the SOBP dose distribution still delivers lower doses in the normal tissue

proximal to the target and no distal dose compared to photons. In addition to the Bragg peak, protons have a sharper beam penumbra, or more rapid dose falloff at the lateral edges of the beam, which can improve the delivery of high radiation doses to targets near dose-limiting critical structures. This benefit can be further enhanced by the use of customized apertures.

Protons reduce the total integral dose to the patient by approximately 60% compared to conventional 3-dimensional conformal photon radiation therapy (3DCRT) (Mitin and Zietman 2014). In pursuit of improved target conformality, the additional beams used in photon-based intensity-modulated radiation therapy (IMRT) distribute more low and intermediate doses outside of the target (Hoffman and Yock 2009). This increased dose to normal tissues increases the risk of late adverse effects and may increase the risk of secondary malignant neoplasms (SMNs). This risk is magnified in pediatric patients and especially those with long expected survival due to cumulative risk-years (Hall 2006).

Because of a proton's physical properties, the initial focus of clinical research in proton therapy was on dose escalation in the treatment of adult tumors with poor local control following photon-based radiotherapy. In particular, uveal melanomas and base-of-skull sarcomas received considerable interest by early investigators, and the best long-term clinical outcomes data supporting the use of proton therapy still reside with these specific cancers. In a series of more than 3000 patients treated with proton therapy rather than enucleation for ocular melanoma at Massachusetts General Hospital (Boston, MA), the 5-year local control and eye preservation rates were 96% and 90%, respectively (Munzenrider 1999). In a prospective series of 2645 consecutive patients treated at the Paul Scherrer Institute (Villigen, Argau, Switzerland) from 1984 to 1999, proton therapy yielded eye preservation rates of 88.9% at 5 years and 86.2% at 10 years (Egger et al. 2003). Cyclotron technology has also continued to mature, and new proton devices now feature higher energy beams, field sizes that are comparable to linear accelerators, rotational gantries, and pencil-beam scanning. Increasingly, proton therapy research protocols have shifted aims to reduce treatment morbidity in patients for whom photon therapy has proven valuable but resulted in adverse effects.

17.3 Biological Properties of Proton Therapy

Both photons and protons kill cancer cells through DNA double-strand breaks. Also, both photon radiotherapy and proton therapy are characterized by their low LET. The relative biological effectiveness (RBE) of protons, which is extrapolated from cell survival curves, is approximately 1.1 (Mitin and Zietman 2014), but this is not constant along the entire beam path. The RBE increases at the end of the path in the Bragg peak region. Cell survival assays suggest that tissue cell lines irradiated by protons yield more single- and double-strand DNA breaks within the SOBP region compared to photons. In addition, the size of the repair foci for double-strand breaks generated by protons are larger, suggesting more complex DNA damage (Girdhani et al. 2013; Goetz et al. 2011). In radiotherapy, cell kill may depend on the tumor histology or the biology of the irradiated tissue. Animal studies have demonstrated that proton therapy can result in longer G2-phase cell cycle arrest in human melanoma and glioblastoma cell lines than in thyroid cell lines (Moertel et al. 2004; Ristic-Fira et al. 2007; Green et al. 2001). Differences in the radiobiology of photons and protons, and their implications on clinical outcomes, continue to be examined through single- and multi-institutional clinical trials.

Radiation-induced secondary malignancies are a known late effect of radiation therapy. One of the foremost advantages cited to support the use of proton therapy is the potential reduction in secondary cancers. Miralbell et al. examined the potential reduction in SMNs with proton therapy by generating photon and proton treatment plans a patient with medulloblastoma and a patient with paranasal sinus rhabdomyosarcoma (RMS) case. They estimated the absolute excess risk of

developing a radiation-induced SMN based on dose-volume distributions for normal organs and International Commission on Radiologic Protection benchmarks. For the patient with RMS, they found that protons reduced the expected incidence of secondary cancer by a factor of 2.4 when compared to conventional radiation therapy. In the patient with medulloblastoma, proton therapy reduced the risk by 15 times when compared to photon-based 3DCRT and by eight to nine times when compared to IMRT (Miralbell et al. 2002).

These findings have been corroborated using different models and after considering the impact of neutron contamination in the proton beam (Zhang et al. 2013; Taddei et al. 2010; Newhauser et al. 2009). Brodin et al. compared the predicted risk of SMNs in ten patients treated with craniospinal irradiation (CSI) to doses of 23.4 and 36 Gy (RBE) with volumetric-modulated arc therapy (VMAT), 3DCRT, and intensity-modulated proton therapy (IMPT) (Brodin et al. 2011). As with other studies, they found that the estimated risk of SMNs is significantly lower with proton therapy regardless of age, sex, or radiation therapy technique, even when secondary neutron contamination is considered (Brodin et al. 2011). This modeling data provide strong radiobiological rationale for the use of proton therapy in pediatric patients who require radiation therapy.

To estimate the comparative risk of SMNs using clinical data, Chung et al. performed a retrospective matched-pairs analysis of 558 patients treated with proton therapy and 558 patients from the Surveillance, Epidemiology and End Results (SEER) database (Chung et al. 2013). Of these, 44 matched patients were treated for pediatric cancers. With a median follow-up of 6.7 years, the hazard ratio for developing an SMN was 0.52 with proton therapy compared to photon-based radiation. The authors also noted that no pediatric patients who received proton therapy developed an SMN within the treatment field (Chung et al. 2013).

Secondary neutron contamination may add to the potential risk of radiation-induced SMNs (Kirsch and Tarbell 2004). Monte Carlo simulations suggest that the risk of induction of SMNs is associated with treatment technique, field characteristics, patient sex, patient age, and the organ at risk irradiated. For example, the rate of secondary neutrons is lower with IMPT than with 3-dimensional (3D) proton therapy. The secondary neutron dose from 3D proton therapy was found to be comparable to that of IMRT. As a result, the lifetime attributable risk of SMNs may be lower with IMPT compared to photon therapy and conformal proton therapy. In males, the lifetime attributable risk is greatest for lung cancers, thyroid cancers, and secondary leukemia compared to other tumor histologies, whereas the lifetime attributable risk was greatest for hematologic and breast cancers in females <14 years of age (Jarlskog and Paganetti 2008). Further research, including clinical studies on pediatric patients, will continue to determine whether the increase in volume of tissue receiving low-dose radiation with multibeam intensity modulation with protons results in improved clinical outcomes and reduced toxicity rates.

17.4 Pediatric Central Nervous System Tumors

With long expected survival, childhood cancer survivors are susceptible to the long-term adverse effects of radiation and chemotherapy, which can upset organ growth and function and lead to SMNs (Mitin and Zietman 2014). By reducing the volume of irradiated tissue and lowering the integral dose, proton therapy should reduce the rate of risks observed with photon-based therapy. Survivorship research, however, is not straightforward, and data accumulation requires long and deliberate follow-up. Nonetheless, the past 5 years have yielded important findings in the study of late effects in pediatric patients treated with proton therapy. While a comprehensive review of each disease subsite is beyond the scope of this chapter, selected disease sites are considered below to highlight the advantages to using proton therapy in the treatment of pediatric malignancies.

17.4.1 Craniopharyngioma

Craniopharyngiomas represent 3–6% of pediatric central nervous system (CNS) tumors. Although benign, craniopharyngiomas are locally aggressive. Because of their midline suprasellar location, both tumor expansion and therapeutic interventions are associated with a significant risk of adverse visual, endocrinological, neurological, and neurocognitive sequelae. Radiation therapy, either alone or following maximal safe resection, is associated with local control rates exceeding 85%, which are superior to rates observed with more aggressive surgical resection. Radiation therapy is also associated with lower rates of endocrine dysfunction and preservation of intelligence quotient (IQ) (Merchant et al. 2002b). As a result, radiation therapy is the standard of treatment at many institutions. While historical reports on patient outcomes have tended to explore older radiation therapy techniques, the current standard of care at most institutions is photon-based IMRT (Sreeraman and Indelicato 2014).

Dosimetric evidence suggests a benefit to proton therapy with the potential to reduce the neurocognitive deficits observed following photon therapy. Endocrinopathies and vasculopathies are two main concerns in this population. The midline location of craniopharyngiomas often dictates that full dose radiation will cover the hypothalamus and important vasculature; these risks exist with photons or protons. Even when there is sufficient space between the tumor and normal tissue, hypothalamic and pituitary function as well as growth hormone secretion (Merchant et al. 2002a) are sensitive to the effects of radiation at low doses (Chemaitilly et al. 2015). Therefore, the benefit of proton therapy over IMRT in these domains may be limited by target volume design.

With proton therapy, however, reduced total integral doses may provide a significant improvement in neurocognitive domains by reducing how much normal tissue receives low to intermediate doses of radiation (Fig. 17.1). In one retrospective analysis by Beltran et al., IMRT, double-passive-scatter proton therapy, and IMPT plans were created for 14 children with

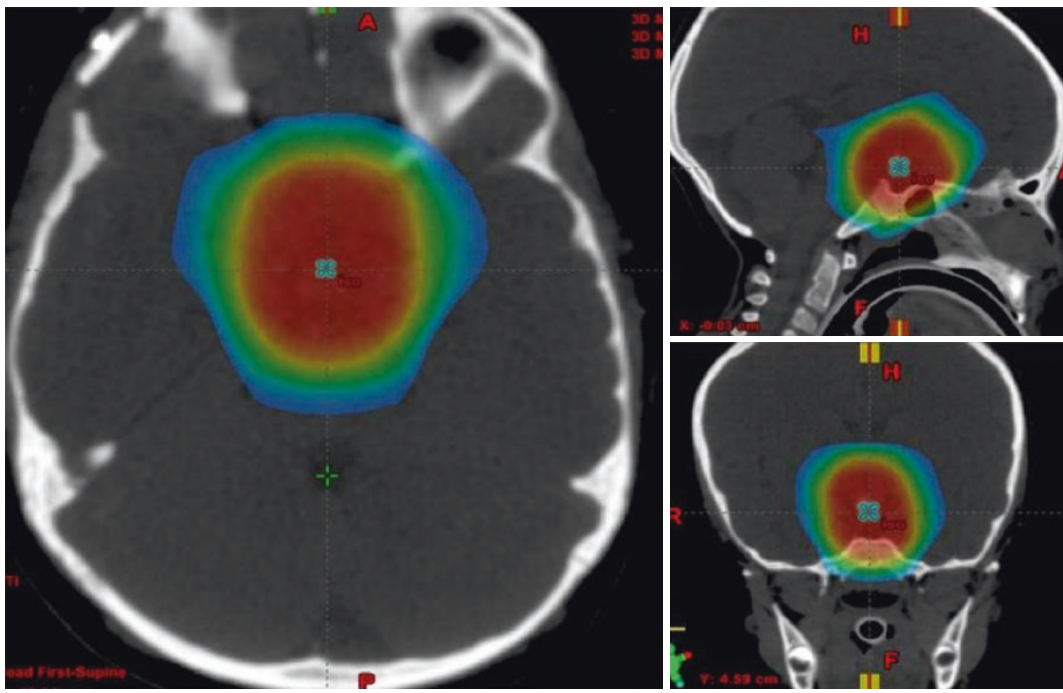

Fig. 17.1 Proton therapy treatment plan for a child with a craniopharyngioma

craniopharyngioma (Beltran et al. 2012). The children had a mean age of 5.1 years and received 54 Gy (RBE). Cyst evolution was monitored through weekly magnetic resonance imaging (MRI) and target volumes were contoured on each weekly scan for adaptive modeling. The investigators reported that proton therapy significantly reduced the normal tissue dose delivered to the whole brain, whole body, cochlea, and optic chiasm compared to photon-based IMRT (Fig. 17.2). Across various studies, IMPT delivers a significantly lower integral dose to critical structures compared to conformal proton therapy, 3DCRT, and IMRT (Beltran et al. 2012; Yeung et al. 2014; Amsbaugh et al. 2012).

Reporting the comparative effectiveness of proton therapy versus IMRT is complicated by preexisting morbidities and competing risks related to the underlying diagnosis. In a prospective phase 2 study, Merchant et al. reported that cognitive outcomes were adversely affected by younger age, more extensive surgery, multiple surgical procedures, diabetes insipidus, hydrocephalus at diagnosis, cerebrospinal fluid shunt and shunt revisions, and cyst aspirations (Merchant et al. 2006). While the percentage of total brain, supratentorial brain, and left temporal lobe volumes receiving doses >45 Gy were associated with longitudinal declines in IQ, the impact of these other pretreatment and surgical risk factors dramatically influenced patient neurocognitive outcomes (Merchant et al. 2006). Until data is available from a clinical trial with meticulous baseline and interval testing, it will remain difficult to quantify the relative value of proton therapy.

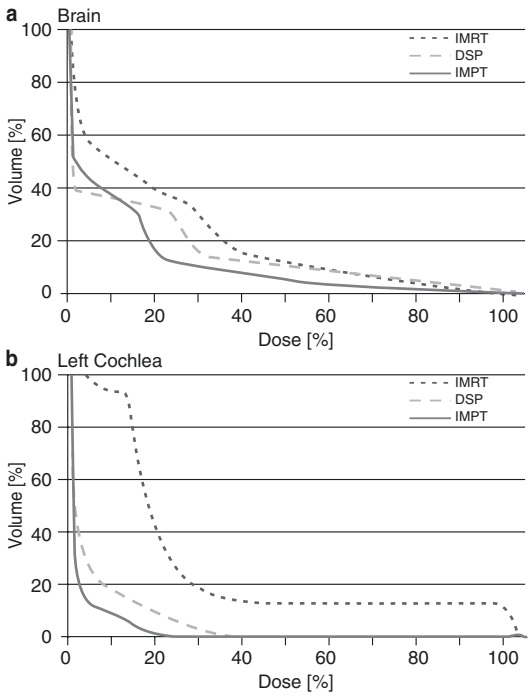

Fig. 17.2 Mean dose–volume histograms for whole brain (**a**) or left cochlea (**b**) for 3 planning methods: intensity-modulated radiation therapy (IMRT) (*dotted line*), double-scatter photon (DSP) therapy (*dashed line*), and intensity-modulated photon therapy (IMPT) (*solid line*)

17.4.2 Low-Grade Glioma

Low-grade gliomas (LGGs) are the most common pediatric CNS tumors (Ostrom et al. 2013). Radiation therapy is a standard treatment for tumors not amenable to gross total resection, which typically includes infiltrative tumors and midline tumors located near critical structures. For supratentorial parenchymal tumors, the mean dose delivered to the pituitary gland and bilateral temporal lobes is lower with proton therapy than IMRT (Greenberger et al. 2014). Brower et al. similarly reported significantly lower doses to the bilateral temporal lobes, posterior nasopharynx, hypothalamus, pituitary gland, and right hippocampus with proton therapy compared to IMRT for LGG in the posterior fossa (Brower et al. 2013). Comparably favorable dosimetric profiles and a reduction in dose to normal tissues have also been demonstrated with proton therapy for optic-pathway gliomas (Fig. 17.3) (Fuss et al. 1999).

Mature clinical outcomes for patients treated with proton therapy for LGG suggest comparable treatment efficacy with less treatment-related adverse effects in comparison to photon-based therapy. For context, the large phase 2 trial by Merchant et al. reported favorable 5- and 10-year OS rates of 98.5% and 95.9%, respectively, in 78 pediatric patients with non-brainstem LGG and a median age of 8.9 years who were treated to

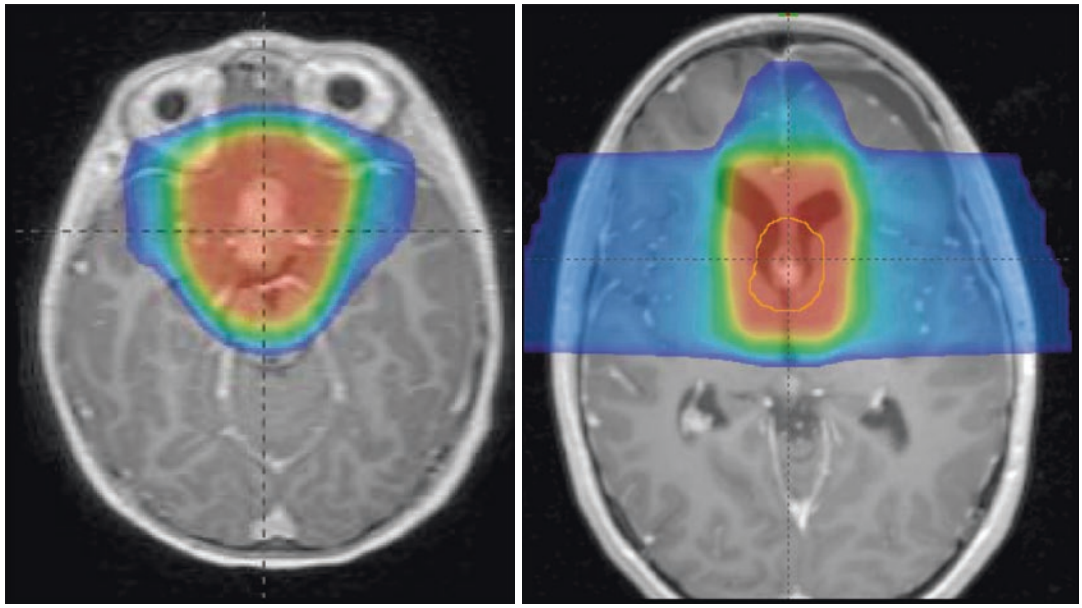

Fig. 17.3 Proton therapy treatment plan for a child with an optic pathway low-grade glioma

54 Gy with 3DCRT from 1997 to 2006. With a median follow-up of 7.4 years, 13 patients experienced disease progression, and the 5- and 10-year event-free survival rates were 87.4% and 74.3%, respectively. The cumulative incidence of local failures at 5 and 10 years were 8.7% and 16.4%, respectively. At 6 years, vasculopathy was observed in 4.8% of patients and was even higher in those <5 years of age at the time of chemoradiation therapy (CRT) (Merchant et al. 2009b).

In a separate report, Merchant et al. reported the late effects of CRT in this series. The effect of age at the time of radiation therapy exceeded the impact of radiation dose, again with patients <5 years old experiencing the greatest decline in cognition. Before CRT, the rates of growth hormone abnormality and precocious puberty were 24% and 12%, respectively. The 10-year cumulative incidence of growth hormone replacement therapy was 49%, thyroid hormone replacement was 64%, glucocorticoid replacement was 19%, and gonadotropin-releasing hormone therapy was 34%. The 10-year rate of hearing loss did not exceed 5.7% at any frequency (Merchant et al. 2009a).

Greenberger et al. reported mature outcomes for 32 patients treated with proton therapy for non-brainstem LGG from 1995 to 2007 (Greenberger et al. 2014). Patients had a median age of 11 years and were treated with a median dose of 52.2 Gy (RBE) (range, 48.6–54 Gy [RBE]). With a median follow-up of 7.6 years, the progression-free survival (PFS) rates at 6- and 8-years were 89.7% and 82.8%, respectively, and the 8-year OS rate was 100%. In all patients who received serial neurocognitive testing, there were no significant declines in IQ ($p = 0.80$) with a median neurocognitive testing interval of 4.5 years from baseline. Subgroup analysis indicated some decline in neurocognitive outcomes in patients <7 years of age and those receiving high doses to the left temporal lobe/hippocampus. Nine patients (31.0%) had a documented endocrinopathy before CRT. The cumulative incidence of any endocrinopathy at 6 years after CRT was 41.4%, comparing favorably to the photon data from Merchant et al.

Patient selection complicates comparisons between published series. As with craniopharyngiomas, tumors involving the hypothalamic-pituitary axis (HPA) frequently cause endocrinopathies and, as a result, patients with tumors involving the optic chiasm or the hypothalamus treated with high-dose radiation therapy will likely see no advantage with reduction in endocrinopathies with proton therapy.

In the series by Greenberger, however, the authors noted that only one endocrinopathy occurred in patients stratified in the low and intermediate endocrine-risk group (i.e., those with tumors that were not intrinsic to the hypothalamus) (Greenberger et al. 2014). If reproducible, proton therapy may enable treatment of peripheral tumors with increased sparing of the HPA and temporal lobes, and thereby improve clinical outcomes.

17.4.3 Ependymoma

Ependymomas comprise 8–10% of pediatric CNS tumors and frequently occur in young patients <3 years of age. The standard of care includes maximal safe resection followed by adjuvant radiation therapy to the tumor bed. In this age group, radiation therapy is historically associated with poor neurocognitive outcomes, and techniques to improve this endpoint are an active area of research.

For context of the modern photon perspective, Merchant et al. reported neurocognitive outcomes in 88 ependymoma patients (66 infratentorial, 20 supratentorial) with a median age of 2.8 years who were treated with 3DCRT for ependymoma to a dose of 54–59.4 Gy (Merchant et al. 2005). IQ testing was performed at baseline and at 6, 12, 24, 36, 48, and 60 months. With a median follow-up was 29.4 months, IQ was associated with age at CRT, the volume of supratentorial brain that received increasing dose, and the time interval since completion of CRT for all patients (Merchant et al. 2005). In a series of 76 patients treated for infratentorial ependymoma from 1997 to 2008, Merchant et al. identified a correlation between mean infratentorial brain dose and IQ scores (Merchant et al. 2014). There was also a significant correlation between mean cerebellar dose and IQ, math, reading, and spelling scores (Merchant et al. 2014). Armstrong et al. found that dose received by the temporal lobes is also correlated with a decline in IQ (Armstrong et al. 2013). Based on the dose-volume effects identified for multiple brain regions on neurocognitive outcomes in patients with ependymoma, who are often at high risk due to young age, minimizing unnecessary radiation exposure using proton therapy may provide clinically relevant advantages in this population (Fig. 17.4).

Macdonald et al. reported the largest clinical experience with proton therapy for ependymoma,

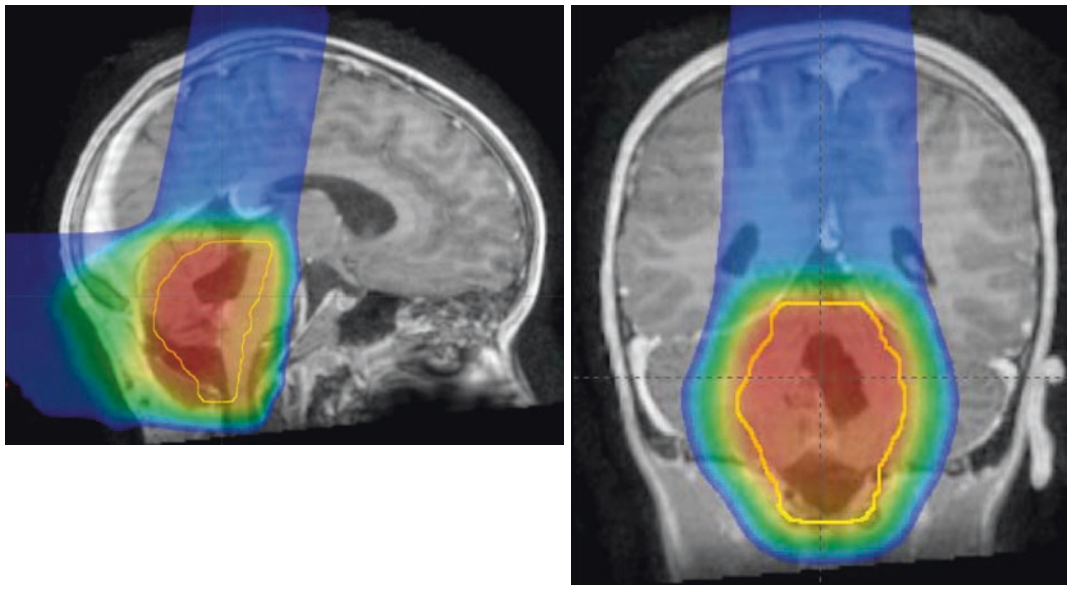

Fig. 17.4 Proton therapy treatment plan for a child with a posterior fossa ependymoma

including 70 patients (median age, 3.2 years; range, 0.25–20 years) treated from 2000 to 2011 (Macdonald et al. 2013). Nineteen (27%) patients had supratentorial and 51 (73%) had infratentorial ependymoma; 66% received a gross total resection and 34% had subtotal resections. At a median follow-up of 3.8 years, the 3-year local control, PFS, and OS rates were 83%, 76%, and 95%, respectively. Patients with subtotal resections had significantly worse PFS and OS (Macdonald et al. 2013).

The authors also reported neurocognitive outcomes in a subset of patients with neurocognitive testing at baseline and after radiation therapy (n = 14) (Macdonald et al. 2013). Mean IQ scores were 108.5 at baseline and 111.3 after a mean follow-up of 2.05 years. In 28 patients with data available, overall adaptive skills were 100.1 at baseline and 100.8 after 2.21 years of follow-up. While this study suggests very favorable early results with proton therapy in this population, longer follow-up and more complete follow-up testing for late treatment effects will be needed to confirm a clinical benefit compared to the best photon literature.

17.4.4 Medulloblastoma and Primitive Neuroectodermal Tumor

Medulloblastoma/primitive neuroectodermal tumor (PNET) is the second-most common intracranial neoplasm in children and comprises 20% of pediatric CNS tumors (Partap et al. 2009). Treatment includes maximal safe resection followed by chemotherapy and craniospinal irradiation (CSI) with a boost to the primary tumor bed. In contrast to the above CNS malignancies that are treated with focal radiation therapy, photon-based CSI delivers the radiation dose to large volumes of uninvolved normal tissues. As a result, patients are at risk of developing numerous systemic adverse effects involving the cardiovascular, pulmonary, neurocognitive, auditory, endocrine, gastrointestinal, hematologic, and reproductive organs along with induction of SMNs.

For historical context, following photon CSI, Christopherson et al. reported late toxicities in a cohort of 53 patients (median age, 7.1 years) treated from 1963 to 2008 (Christopherson et al. 2014). The median follow-up was 15.4 years for all patients and 24 years for surviving patients. The 10-year PFS and OS rates were 71% and 67%, respectively. Sixteen individuals, representing 41% of patients who survived ≥5 years, developed grade 3+ toxicity, 15 of whom received a CSI dose >23.4 Gy. The most common grade 3+ toxicities for long-term survivors included serious hearing impairment in 20.5% and cognitive impairment that prohibited independent living in 18%. Four patients developed secondary (non-skin) cancers in the treatment field, including 3 meningiomas, 1 rhabdomyosarcoma, and 1 glioblastoma multiforme. Three patients (5.6%) died from treatment complications, including radionecrosis, severe cerebral edema, and a fatal secondary malignancy. The authors concluded that ongoing efforts to minimize radiation exposure are justified given the high rate of serious toxicities observed in long-term survivors of medulloblastoma (Christopherson et al. 2014).

Proton therapy has been widely studied in medulloblastoma as a method of reducing normal tissue doses by exploiting the Bragg peak and its lack of an "exit dose" (Fig. 17.5). St. Clair et al. compared conventional 3DCRT, IMRT, and proton therapy treatment plans in patients with medulloblastoma and reported substantial normal-tissue sparing with IMRT and proton therapy (St Clair et al. 2004). The dose to the cochlea delivered during the posterior fossa boost was reduced from 101.2% of the prescription dose with conventional photon therapy to 33.4% with IMRT and 2.4% with protons. The dose delivered to 50% of the heart was also reduced from 72.2% with conventional photons to 29.5% for IMRT and 0.5% for proton therapy (St Clair et al. 2004).

Jimenez et al. reported the long-term outcomes of 15 patients below 5 years of age with medulloblastoma/supratentorial PNET who were treated with surgery and upfront chemotherapy followed by 3D conformal proton therapy (Jimenez et al. 2013). At a median follow-up

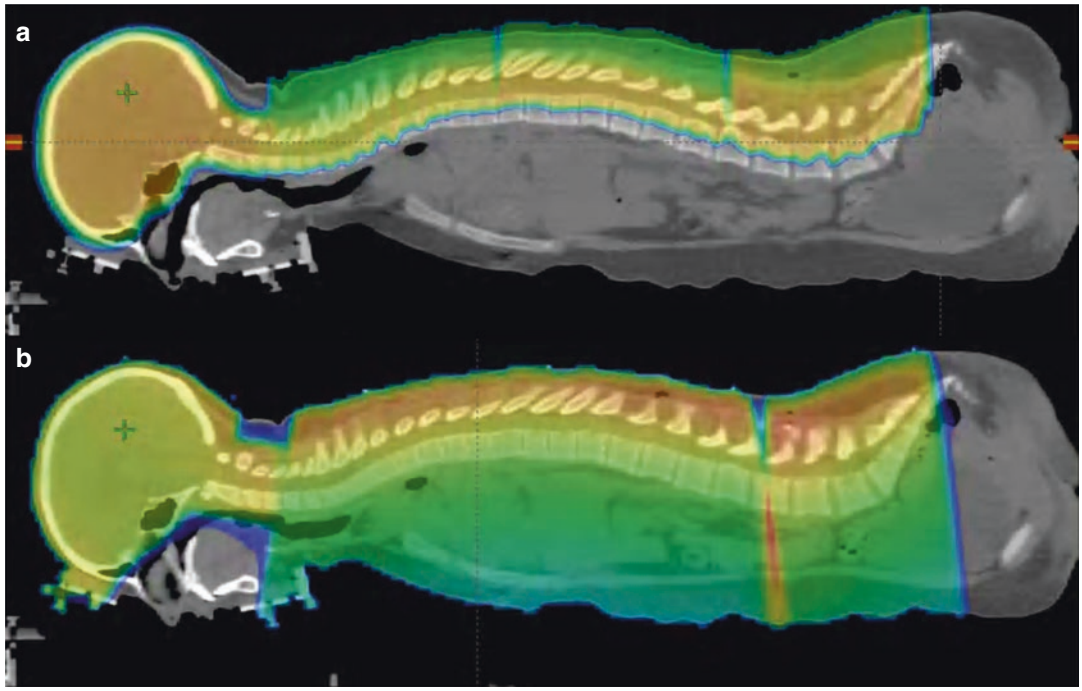

Fig. 17.5 Dose distribution for a pediatric patient. (**a**) Proton and (**b**) photon dose distribution for craniospinal irradiation for a child with a medulloblastoma

of 3.25 years, 13 of 15 patients were alive without evidence of disease. The 3-year local failure and OS rates were 7.7% and 85.6%, respectively. In total, 9 of 13 patients had measurable hearing loss on audiometry with 2 requiring hearing aids; all patients received cisplatin before proton therapy and 5 had bilateral sensorineural hearing loss before starting radiation. Three patients developed endocrinopathies and required hormone replacement therapy. No difference in baseline neurocognition was observed in the 13 surviving patients compared to baseline (Jimenez et al. 2013).

Although large reductions in dose delivered to normal organs can be achieved with proton therapy for medulloblastoma, specifically for CSI, the comparatively low doses administered with contemporary CSI may affect the differences observed compared to historical photon data. The latency required to observe many delayed toxicities from radiation therapy, the most notable being cardiovascular disease and SMNs (Zhang et al. 2014), is generally considered to exceed 5 and even 10 years. Follow-up of this duration is problematic from a cost and logistic standpoint. Although much has been learned from successful longitudinal studies, such as the Childhood Cancer Survivors Group and other cohorts, maintaining follow-up many years after completion of successful treatment remains difficult and will continue to impede progress in measuring therapeutic improvements in the future. Across all modern radiation modalities, longer follow-up with detailed dosimetric correlation is needed to assess long-term outcomes and late toxicity in pediatric patients who have received craniospinal radiation.

17.5 Comparative Quality of Life, Late Toxicities, and Cost Effectiveness

It is estimated that the risk of late toxicities after CSI, including cardiovascular disease, heart failure, blindness, endocrinopathies, hearing loss,

and premature ovarian failure, is lower with proton therapy than with 3DCRT or IMRT (Perez-Andujar et al. 2013; Brodin et al. 2012). Brodin et al. estimated lower rates of cardiac failure, xerostomia, ototoxicity, and hypothyroidism in ten patients receiving CSI with protons rather than photons (Brodin et al. 2011). Compared to photon-based CSI, proton therapy was also found to be associated with significantly fewer life years lost from late treatment-related complications (Brodin et al. 2012).

Investigators argue that the improvements in quality of life and reduced late effects possible with proton therapy make it more cost effective than other techniques in the long-run. At present, the cost of delivering a single fraction of proton therapy is estimated to be 2.4 times that of photon therapy (Goitein and Jermann 2003), but this cost ratio is expected to decline with continued advances in proton therapy. And while the upfront investment in proton therapy is more expensive, in the pediatric patient population for whom there is a high chance of cure and long life expectancy, the long-term cost savings can be realized through the avoidance of late toxicities, such as SMNs.

Mailhot Vega et al. performed a cost analysis using a Monte Carlo simulation to model the risk of developing ten different adverse effects by 18 years of age after treatment for medulloblastoma at 5 years old (Mailhot Vega et al. 2013). Using institutional and Medicare financial data, costs were computed for the initial therapy with photons versus protons and the diagnosis and management of treatment-related sequelae. The authors found that proton therapy was associated with both higher quality-adjusted life years and lower costs compared to photon therapy. Sensitivity analysis suggested that proton therapy remained the favorable strategy across a wide range of cost and efficacy assumptions, proving proton therapy's superiority to photon therapy in terms of lower cost and greater efficacy in 96.4% of simulations (Mailhot Vega et al. 2013). A similar Swedish study demonstrated that proton therapy was associated with €23,600 in savings and provided 0.68 additional quality-adjusted life years per patient (Lundkvist et al. 2005). The most significant cost savings were projected in the reduction of IQ loss and rates of growth hormone deficiency (Lundkvist et al. 2005).

In a more detailed analysis, Mailhot Vega et al. explored the cost-effectiveness of proton therapy using a Markov simulation model to estimate the expected costs and impact of a range of radiation doses delivered to the hypothalamus in pediatric patients (Mailhot Vega et al. 2015). In patients for whom the hypothalamus could be spared, proton therapy would be more cost effective than photons. Conversely, proton therapy may not be cost-effective when the hypothalamus is encompassed by the target volume and subsequent HPA dysfunction is likely.

17.6 Pediatric Extracranial Tumors

Proton therapy has been used to treat a wide variety of extracranial disease sites, although the most extensive experience remains in head and neck and skull base tumors, sarcomas, and increasingly lymphoma. The late effects described for CSI and the risk of SMN induction also apply to solid tumors located near normal tissues. As with primary CNS malignancies, data on treatment efficacy with proton therapy continue to mature. A strong rationale exists to support the use of proton therapy in Hodgkin lymphoma where OS exceeds 90% in most patients and late effects of multimodality treatment are well-recognized. These late effects include cardiovascular morbidity with radiation and doxorubicin-based chemotherapy, pulmonary toxicity with radiation and bleomycin, and second malignancies with radiation and alkylator regimens. Thus, there is great incentive to use proton therapy in this patient population to reduce late treatment-related effects.

Hoppe et al. reported the early clinical outcomes in 15 patients (10 adults and 5 children) with newly diagnosed Hodgkin lymphoma who were treated with involved-node proton therapy

on a prospective phase 2 trial. With a median follow-up of 37 months, the 3-year relapse-free and event-free survival rates were 93% and 87%, respectively (Hoppe et al. 2014), which are comparable to those expected with conventional radiation therapy (Eich et al. 2010; Gordon et al. 2013). No patients developed grade 3 or higher toxicity during follow-up.

In this study, three separate treatment plans were developed prospectively using 3DCRT, IMRT, and proton therapy for all patients enrolled (Hoppe et al. 2012) (Fig. 17.6). The authors reported that patients treated with proton therapy had a statistically significant reduction in total integral radiation dose and dose to critical normal organs, including the heart, lung, and breast (in female patients) (Table 17.2). Specifically, the total integral dose with proton therapy was reduced by 57% compared to 3DCRT and 49% compared to IMRT. Proton therapy reduced the mean heart dose by an average of 7.6 Gy (RBE) compared to 3DCRT, and 3.3 Gy (RBE) compared to IMRT. Similarly, mean lung dose was reduced by 4.5 Gy (RBE) and 2.7 Gy (RBE) compared to with 3DCRT and IMRT, respectively. In women, proton therapy reduced the mean breast dose by 2.1 Gy (RBE) and 1.7 Gy RBE compared to 3DCRT and IMRT, respectively (Hoppe et al. 2014).

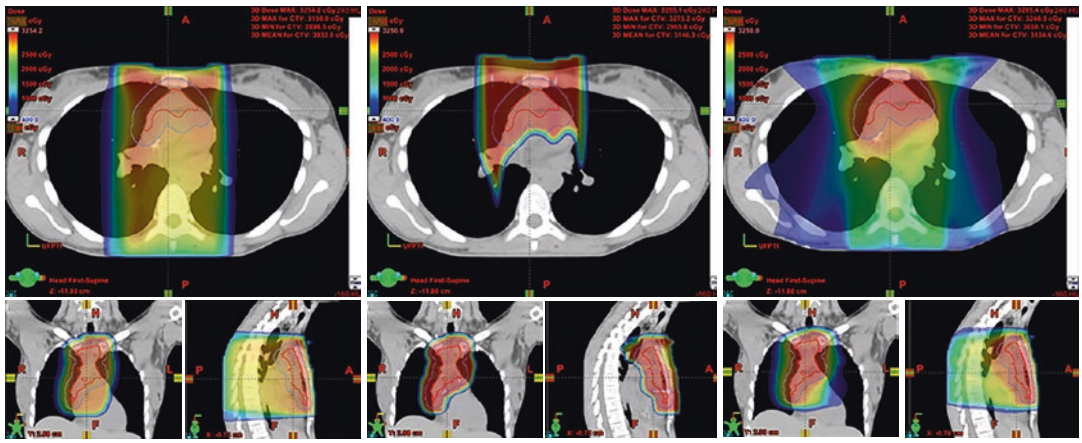

Fig. 17.6 Radiation treatment plans for Hodgkin lymphoma using 3DCRT (*left*), protons (*middle*), and IMRT (*right*). The CTV is contoured in red and the PTV in blue with a color-wash dose distribution

Table 17.2 Average dose to the organs at risk among the different radiotherapy techniques for all patients enrolled in the phase 2 study of involved-node proton therapy for Hodgkin lymphoma

	3DCRT		IMRT		PT	
Structure	Mean	SD	Mean	SD	Mean	SD
Integral dose (joules)	122.9	62.3	103.8	48.6	53.6	32.0
Heart (Gy)	16.5	7.6	12.3	6.2	8.9	5.1
Lung (Gy)	11.6	3.7	9.8	2.8	7.1	2.5
Breast (Gy)	6.3	3.5	6.0	3.4	4.3	3.0
Thyroid (Gy)	19.3	10.1	17.7	9.3	15.8	9.7
Esophagus (Gy)	20.3	4.8	16.4	3.9	13.4	5.6

3DCRT 3-dimensional conformal radiotherapy, *IMRT* intensity-modulated radiotherapy, *PT* proton therapy, *Gy* Gray
Borrowed from Hoppe BS, Flampouri S, Zaiden R, Slayton W, Sandler E, Ozdemir S, et al. Involved-node proton therapy in combined modality therapy for Hodgkin lymphoma: results of a phase 2 study. Int J Radiat Oncol Biol Phys. 2014 Aug 1;89(5):1053–9

17.7 Imaging Changes and Toxicity after Proton Therapy

Surveillance imaging after surgery and radiation for pediatric CNS malignancies can be problematic because of similarities in the appearance of treatment effects, radionecrosis, and tumor recurrence. While the incidence and clinical relevance of asymptomatic imaging changes after radiation therapy are poorly defined, this phenomenon may be affected by radiotherapy modality. Gunther et al. retrospectively reviewed surveillance MRIs performed in 72 patients treated for localized ependymoma with craniotomy followed by adjuvant radiation therapy (proton therapy, n = 37; IMRT, n = 35). Radiation-related changes on MRI were identified in 43% of patients treated with proton therapy compared to 17% treated with IMRT. The median onset of changes was 3.8 months for proton therapy and 5.3 months for IMRT. On multivariate analysis, patients treated with proton therapy were significantly more likely to develop imaging findings (odds ratio, 3.89; 95% confidence interval, 1.20–12.61). Seven patients (proton therapy, n = 4; IMRT, n = 3) were symptomatic and required treatment, most commonly with corticosteroids (Gunther et al. 2015).

Radiation-induced necrosis is a rare but morbid toxicity that can arise after treatment for CNS malignancies, with brainstem damage being particularly morbid and potentially fatal. With modern photon-based techniques, the cumulative incidence of radionecrosis was 2.5% at 7 years in a series of 153 pediatric patients treated for ependymoma between 1997 and 2007 with 54–59.4 Gy (Merchant et al. 2009c), and 3.7% at 5 years in 236 patients treated for medulloblastoma or other CNS embryonal tumors from 1996 to 2009 (Murphy et al. 2012). Assessing rates of radiation-related toxicity in the literature can be challenging because of differences in the definition and characterization of this toxicity, complicating factors like surgical technique and the use of concurrent chemotherapy, and the nature of retrospective analyses. It is nevertheless important to compare proton therapy outcomes to contemporary photon data to measure safety and develop superior predictive models to reduce toxicity.

Indelicato et al. reviewed the rate of brainstem toxicity in 313 patients treated for primary CNS or skull base tumors with proton therapy from 2007 to 2013, who received >50.4 Gy (RBE) to the brainstem. In this series, the three most common tumor histologies were ependymoma, craniopharyngioma, and low-grade glioma. The 2-year cumulative incidence of any brainstem toxicity was 3.8% and the rate of Grade 3+ toxicity was 2.1%. Patients less than 5 years of age, posterior fossa tumor location, and radiation dose volume parameters were associated with an increased risk of toxicity, with one reported death in the cohort due to brainstem toxicity (Indelicato et al. 2014). The reported rates are similar to those expected for photon-based therapy (Murphy et al. 2012; Merchant et al. 2009a, b, c). As with survival outcomes, defining the risk of toxicity is the first step to reducing the rate of treatment-related injury. Children treated for pediatric tumors should be encouraged to enroll on clinical trials, and pediatric radiation oncologists should continue to closely monitor and actively report toxicity outcomes. Radiation modality should be analyzed along with radiation dose, patient age, chemotherapy regimen, pre-existing neurologic toxicity, and other known risk factors for radiation necrosis.

Conclusion

Despite dramatic gains in OS over the past 25 years, pediatric cancer patients remain particularly susceptible to late treatment-related adverse effects that can result in significant distress, impairment, and morbidity. The primary value of proton therapy in childhood cancer lies in its potential to reduce the late effects of radiation exposure. This pursuit represents a logical extension of historical technological advancements in radiation therapy and aligns with the broader goals of the pediatric radiation oncology community. As a result, interest in the application of proton

therapy in pediatric cancer management has grown with the objective to reduce late effects and maintain high cure rates. Such interest is evident in the patterns of care across the United States. Chang et al. reported that the use of proton therapy in patients 18 years of age and younger increased sequentially in the United States from 465 patients in 2010 to 613 patients in 2011 and 694 patients in 2012, representing a 33% increase just 2 years. CNS malignancies were the most common disease site treated; however, the percentage of patients treated for extracranial tumors rose from 28.5% in 2010 to 39.7% in 2012 (Chang et al. 2014). Although widespread utilization of proton therapy in the United States is currently not financially viable, lower hardware costs and economic models that encompass late-effect expenses will expand its availability to children. With the opening of more specialized centers, proton therapy will become more accessible to patients, and valuable outcomes data will continue to accumulate. Finally, it is important to recognize that, unlike the recent advancements in immobilization, localization, or photon radiation delivery, proton therapy involves an inherently different radiation particle. Therefore, clinicians and researchers must remain vigilant for novel and unexpected toxicity.

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18 Helical TomoTherapy in Pediatric-Adolescent Patients

Maurizio Mascarin and Elisa Coassin

18.1 Introduction

Helical TomoTherapy (HT) is a radiation delivery technique, which is able to create highly conformal dose distributions both in terms of dose homogeneity within the target and organs at risk (OARs) sparing. It has been designed as an integrated system for volumetric image guided radiotherapy (IGRT) and intensity modulated radiotherapy (IMRT).

HT is a technology based on the combined principles of linear accelerator and computer tomography (CT). In a HT system, a 6 MV linear accelerator is mounted on a ring gantry that rotates around the patient while advancing slowly through the ring. Opposite to the linear accelerator, an array of Xenon detectors obtains data to reconstruct megavoltage CT (MVCT). This allows daily CT scanning and treatment ("beam-on time") time as well as patient set-up, positioning and image registration to ensure accuracy. During treatment delivery, the radiation fan beam is defined using a pneumatically driven multileaf collimator. Each leaf projects a shadow of 6.25 mm at the isocenter 85 cm away from the target and the fan beam has a maximum width of 5 cm. The alteration of leaf positions as a function of the gantry position while the patient advances slowly through the gantry allows great flexibility in sculpting a sophisticated target dose distribution while sparing critical normal structures. Helical delivery allows the IMRT treatment of extended treatment volumes without the need for field junctioning (Mackie et al. 1993) (Fig. 18.1).

Reproducibility of patient positioning is especially important in highly conformal radiotherapy (RT) techniques. In HT the use of daily pretreatment imaging with MVCT allows to reduce the planning target volume (PTV) margins and thereby to reduce the amount of normal tissues receiving high doses. This potential for setup accuracy may translate to a better local control without increasing complication rates. It also allows monitoring of changes in target volumes (e.g., tumor shrinkage) or patient anatomy (e.g., weight loss) during the treatment course. In addition, the possibility of daily deformable dose registration potentially permits to obtain a true representation of the dose delivered to the patient throughout the course of treatment. HT is then particularly indicated when the target volume has a complex shape or when located close to critical structures. It is also able to deliver radiation to extended volumes without field junctions and to irradiate simultaneously multiple separate lesions. Finally with HT patients can be treated in a supine position, thus resulting in more comfortable treatment, especially for children requiring sedation. On the other hand this

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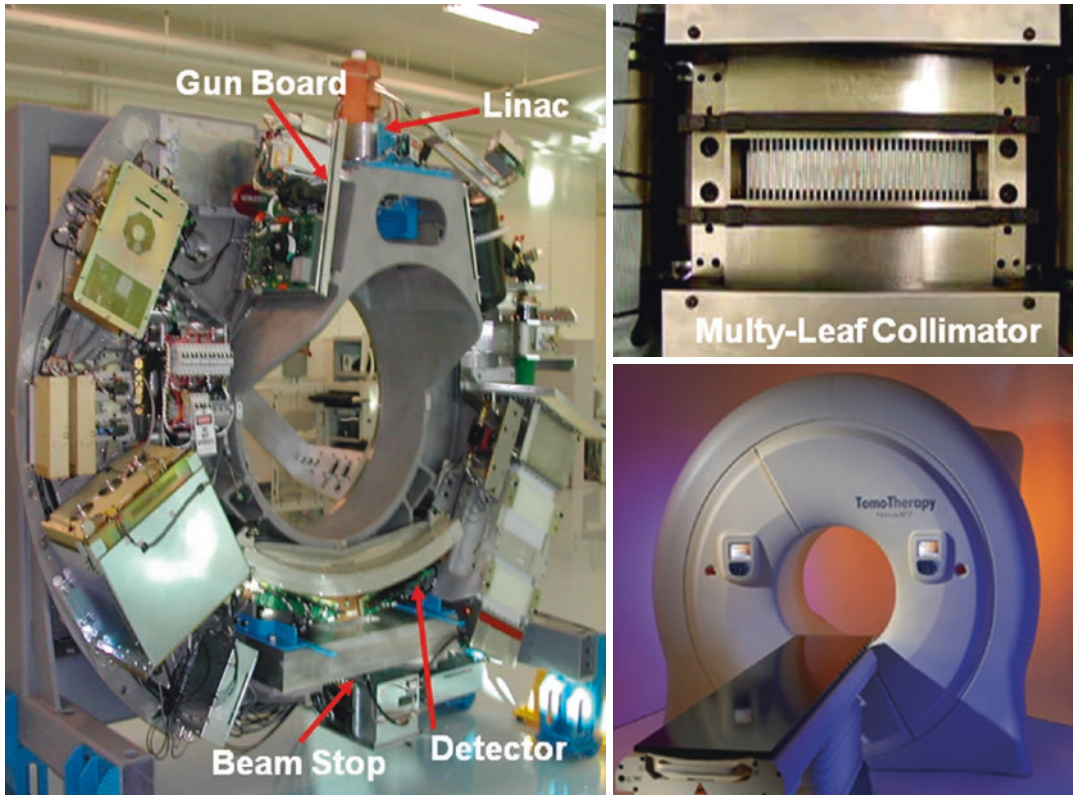

Fig. 18.1 TomoTherapy (TomoTherapy Hi-Art systems; TomoTherapy Inc., Madison, WI) is one of the most sophisticated forms of photon radiotherapy/IMRT machine available. It also includes a megavoltage CT (MVCT) verification (Image Guided system—IGRT) to increase the positional certainty of dose delivery. A 6 MV linear accelerator emits a narrow fan beam (1.0, 2.5 or 5.0 cm) as it travels in a spiral around the treatment couch. The beam may be modified during therapy by a 64 multileaf collimators driven by a pneumatic air system. Leaves are either fully open or fully closed

technique requires more time in the development of different RT steps, when compared to conventional 3D-CRT: target and OARs contouring (if you don't contour it, it doesn't count), planning, delivery and daily verification, quality assurance control. And above all it is mandatory to consider that although HT can be an attractive way to deliver RT to target and limit radiation dose to OARs, this benefit could be achieved at the cost of increasing the volume of normal tissues exposed to lower doses with a potentially augmented risk of secondary malignancies (Mascarin et al. 2011; Mesbah et al. 2011).

We treated 175 pediatric, adolescent and young adult (AYA) patients (median age 13.5 years; range 1–24 years) with HT for various tumor types between 2006 and 2015 at our Institution (IRCCS—CRO Centro di Riferimento Oncologico Aviano). We propose some examples of treatment here. Our experience suggests a greater sparing of critical normal structures and a better PTV homogeneity using HT-based IMRT when compared with conventional 3D-CRT.

18.2 Technique

The main technical differences between HT and conventional RT are presented below.

18.3 Immobilization

With the introduction of HT, children are all treated in the supine position. Immobilization is obtained using several devices and depends on the

treatment site, the patient's age and size, the need to minimize patient movement and setup errors, as well as to maintain the same position during treatment and assure that it could be reproduced accurately each time. Patients are located as comfortably as possible; as many who require RT are very young children and need sedation or anesthesia. Patients with brain tumors or head and neck tumors are immobilized with individual thermoplastic masks, sometimes with an auxiliary bite block. Younger patients with thoracic or abdominal-pelvic tumors are immobilized by using vacuum cradles. Older and taller patients could often be aligned directly on the treatment couch.

18.4 Radiation Imaging: Contouring

One of the fundamental prerequisites for conformal RT and especially for all IMRT techniques is the localization of the target, starting with the gross tumor volume (GTV) and the clinical target volume (CTV), and moving outwards to the PTV. Inverse planning for IMRT-HT requires comprehensive contouring of all OARs. The CT images are acquired from a slice thickness and spacing of 2-5 mm. A 2 mm slice thickness CT is used for brain and head and neck targets. In the broader reported case studies, the volume of interest is generated with a co-registered CT/MRI (magnetic resonance imaging) ± PET (positron emission tomography). Starting with a multimodality diagnostic imaging set, the target and OARs are delineated, to further proceed with treatment planning optimization. Due to the spiral delivery pattern of the machine, some extra structures ("tune structures") could be generated to obtain a better optimization around the target which include e.g., the anterior part of the orbits, the nasal cavity, the jaw-maxillary-dental area, the arms, and the breasts (also in prepubertal girls). Similarly the spinal cord when considered as OAR should be contoured and automatically expanded with a 1 cm margin to create the "spinal cord tuning," which better spares the organ. The expansion of CTV on PTV is not universally attributed and it depends on the tumor site, mobility of the organ involved, age and collaboration of the patient, Center experience, and quality assurance procedures. Generally, we consider an expansion of 5 mm for every CTV, except for patients (fixed with mask ± bite block) with head and neck lesions close to OARs (3 mm). For the definition of PTV brain/head and neck margins we performed an analysis on 42 consecutive children (median age 10 years) treated with HT for different tumoral types for a total of 955 fractions. We found that patients with mask (402 fractions), with mask + bite block (359 fractions), and in sedation with mask (194 fractions) present a median setup error respectively of 4.34, 3.18 and 2.76 mm. The difference was statistically significant when patients with mask + bite block or in sedation with mask were compared to patients with mask only. Displacements >2 mm occurred in 74, 60 and 49% of the fractions of the children with mask, with mask + bite block, and in sedation with mask, respectively. For patients who underwent CSI, different expansions between cranial CTV (4–5 mm) and lumbar-sacral spinal canal CTV (5–7 mm) were used, depending on quality of immobilization (sedation, patient collaboration, etc.) and PTV length, as described later.

18.5 Treatment Planning Parameters

Data sets and structures are transferred to the HT treatment planning system to perform inverse treatment planning. Normally, the planning goal is to deliver the prescription dose to at least 95% of the PTV. The dose constraints for OARs are the standard values used in clinical protocol practice for pediatric tumors, using the priority, importance, and penalty factors. Parameters specified as part of the optimization/dose calculation process are pitch, beam thickness and modulation factor. The typical planning parameters are as follows: field width, 2.5 cm; modulation factor, 2.0–2.5; pitch, 0.287. Different parameters are used in special situations. Briefly, HT system planning uses an interactive inverse treatment planning algorithm based on least squares minimizations of an

objective function, and calculation grid size is selected during the optimization stage (normal 256 × 256, typically used). The coverage of 95% PTV volume with the prescribed dose is set as the minimum optimization objective (high penalty and high importance are set to guarantee the minimum dose to the target).

18.6 Pre-treatment MVCT Acquisition

Image Guided Radiotherapy (IGRT) is of particular importance for HT and IMRT treatments in which there is a highly conformal dose and light variations in patient set-up and organ motion may result in a geometric miss. MVCT acquisitions are performed for all patients to detect set-up deviations and to correct them, usually on a daily basis. The length of scanned area is chosen individually on the basis of anatomy of interest and target. The patient dose is about 1–2 cGy for a scan of 10 cm in length. Generally, particularly sensitive regions like the lens are avoided from the scan. Sometimes multiple scans are needed. The correlation of the MVCT with the planning CT (co-registration) is done automatically with algorithms generally focusing on a mixed "bony and tissue" anatomy. Moreover, a manual correction is often applied, in particular for thoracic and abdominal targets (Fig. 18.2).

18.7 Times

The typical HT process times are relatively long compared with conventional techniques, both for the contouring-planning and for the treatment. In analyzed cases of pediatric malignancies, daily treatment time is composed of time required for patient set-up and anesthesia inside the treatment room, time of MVCT acquisition, time of review/match and applying couch correction inside the treatment room, beam-on radiation delivery time and waiting time of patient recovery (from the end of the irradiation until the patient is awake) from anesthesia. Time of MVCT acquisition and beam-on radiation delivery time are factors that mostly influence time of treatment session. Obviously these parameters strongly depend on the longitudinal extension of irradiated volume (beam-on time ranges from 4–5 min for shorter target volumes to 18–20 min for CSI), as well as on selected MVCT slice thickness.

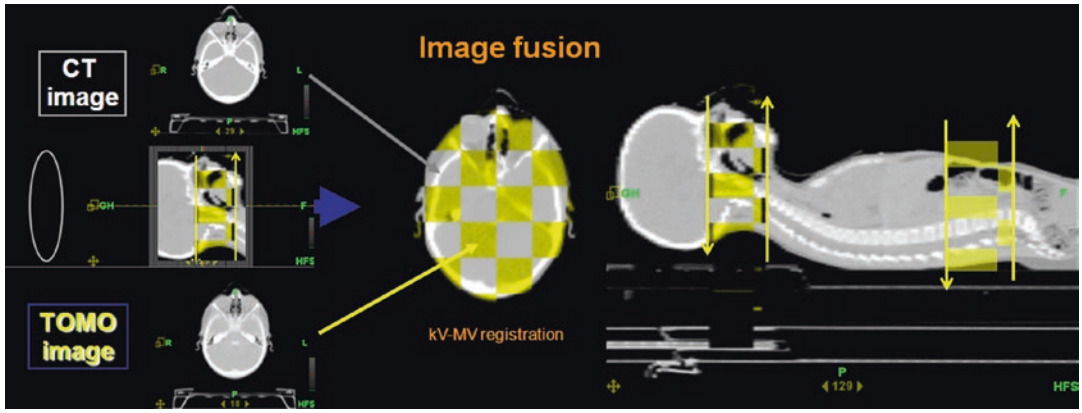

Fig. 18.2 Daily pre-treatment MVCT setup acquisition in a patient who underwent CSI. Daily megavoltage computed tomography (MVCT) scans were performed for setup purposes in a medulloblastoma patient. MVCTs were typically acquired before each fraction allowing a daily patient setup verification and correction. The scan region and length were defined by the radiation oncologist on the first day of treatment and used for all future scans. An image fusion based on a mixed "bony and tissue" anatomy were used to rigidly co-register the MVCT images with those from the planning CT, a feature offered by the Helical TomoTherapy software

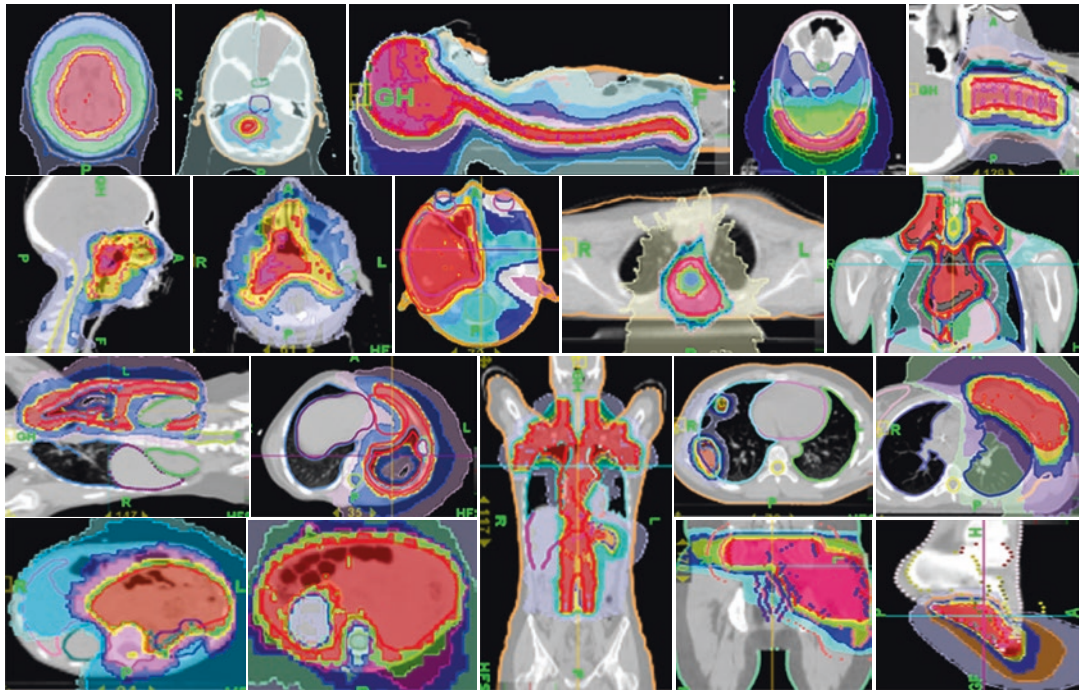

Fig. 18.3 An overview of a "*head-to-foot HT plan*". The dose is very well distributed in about all cases and there are several advantages for the higher doses compared with conventional techniques, but in several plans the resulting low-dose bath is easy visible. On the other hand, there are some plans in which an area is not reproducible with any other photon techniques

18.8 Indications for HT in Pediatric Radiation Therapy

We introduced HT in our Institution in 2006. Through December 2015 we have treated 175 pediatric-adolescent patients using this technique. HT can be used to treat several different volumes and anatomic sites (Fig. 18.3).

18.9 Craniospinal Irradiation

IMRT-HT is increasingly employed in CSI, representing one of the most promising methods of treatment for this indication, especially for reducing the radiation dose to the cochlea and to improve homogeneity of spinal RT (Mascarin et al. 2015). This technique is mainly of interest for CSI because of the possibility to treat the patient in supine position and to deliver an IMRT plan, advancing the patient slowly through the gantry, allowing the dose to be sculpted around a complex target, and avoiding issues of beam matching, junctions, multiple isocenter, and beam gaps that are common in conventional CSI techniques (Myers et al. 2013).

Parker demonstrated that HT plan provides superior sparing of critical structures from high doses (>10 Gy) and excellent target coverage (Parker et al. 2010) and similar results had been obtained before by Penagaricano and Bauman (Penagaricano et al. 2007; Bauman et al. 2005). We have already reported elsewhere our early experience in 15 CSI patients younger than 8 years treated with HT. An inspection of DVH revealed excellent conformal quality both for CTV brain and spinal cord with better sparing of OARs close to the target. In comparison with 3DCRT, HT-CSI resulted able to give a more homogeneous dose and better conformation of the dose to the target, at the price of delivering a low-dose bath to the organs around the PTV and slightly increasing the whole body integral dose, which is inherent to the technique (Mascarin et al. 2010a) (Fig. 18.4).

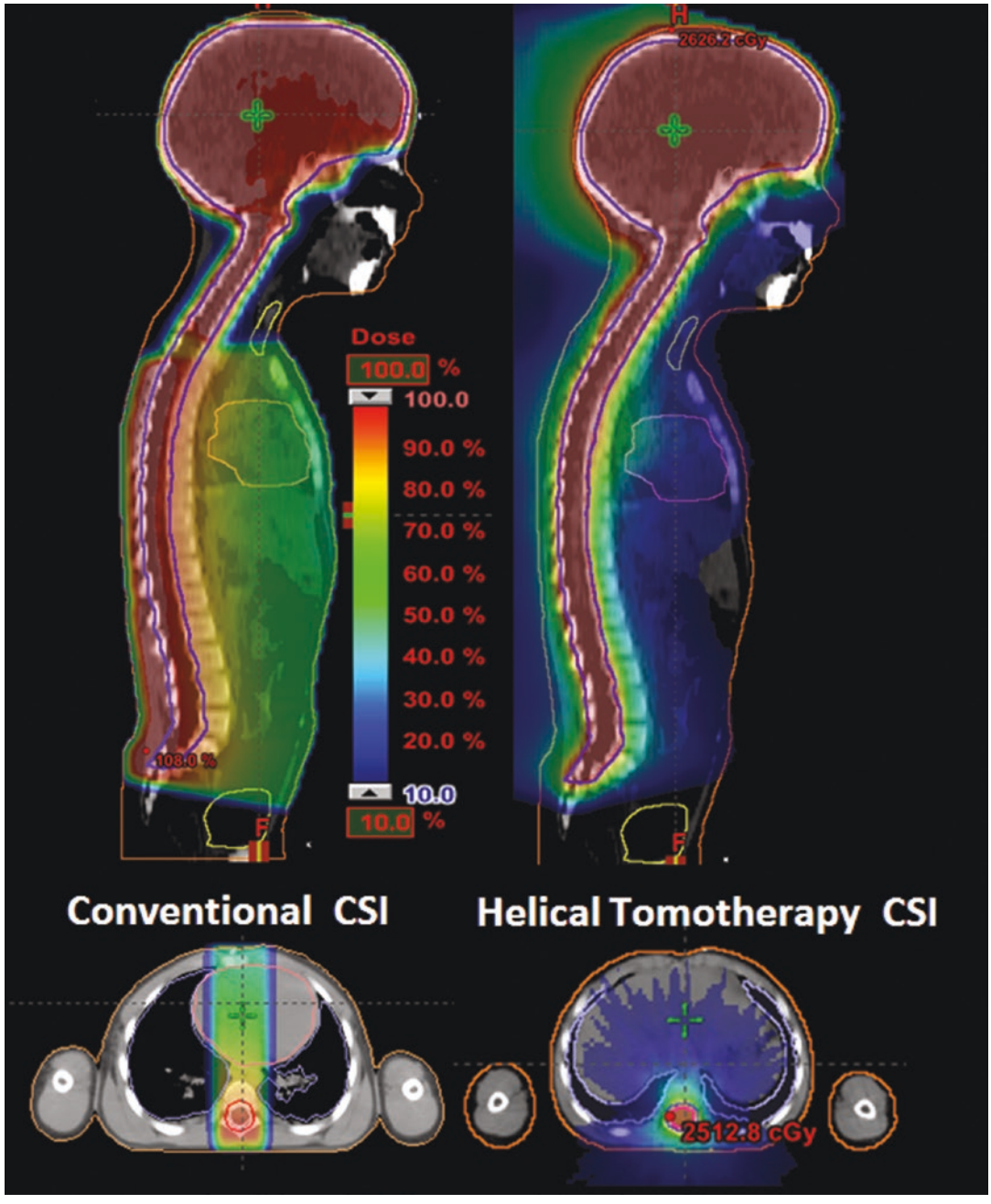

Fig. 18.4 In a 4-year-old medulloblastoma patient, we compared CSI delivered with Helical TomoTherapy (HT) with conventional RT. HT-CSI better conforms the dose to the target. It reduces the extra target high dose irradiation but it increases the low dose bath. It is possible to spare the thyroid and the heart from high doses. The anterior part of the pelvis does not receive the contribute of divergent posterior spinal field typical of conventional CSI. (Conventional CSI calculated by Eclipse Varian®, Palo Alto, USA; HT plan calculated by Hi-Art TomoTherapy Inc.®, Madison, USA). (Courtesy of Drigo A, Med Physics, CRO Aviano, Italy)

As regards target identification, in contouring the whole brain particular attention should be given to include the supraorbital region of the frontal lobes, the bases of the temporal lobes, and the cribriform plate region. The cribriform plate is indeed a possible site of meningeal relapse, but adequate coverage of this structure means that superior orbital tissue is included in the treatment field. In order to achieve good ocular sparing and optimal coverage of this critical site at the same time, it is suggested to build some extra PTV to better control these areas. The volumes of these critical areas are small and their PTV coverage could consequently be underestimated if included in the entire CSI volume (Mascarin et al. 2011). Likewise, the aim of the spinal CTV is to include the entire subarachnoid space with extension along the nerve roots as far as the intervertebral foramina. The width between the intervertebral and the sacral foramina increases no more than 20 mm, as one moves from cranial to caudal regions (Halperin 1996). The lower limit of CTV is the terminal part of the thecal sac, evaluable on a spinal MRI and usually extending inferiorly to at least the lower border of the S2–S3 sacral vertebra (Dunbar et al. 1993). An additional margin, generally 5–10 mm on CTV, should be added for the PTV, according to the center's setup procedures. The largest and most comprehensive report on assessment of set-up errors during HT-CSI was recently published by Gupta et al. In a group of patients of 18 years of median age (range 4–52 years), they demonstrated that mean displacements were least for the brain, slightly more for upper spine, and worst for the lower spine. For this reason, increasing CTV to PVT margins is recommended moving from the brain to the lower spine. In absence of daily image-guidance, minimum margins of 6.5–7.5 mm for brain, 7.0–8.5 mm for upper spine, and 9.5–11.5 mm are suggested (Gupta et al. 2015). We have already published our data on setup errors in HT-CSI with daily IGRT revealing a median 3D displacement vector of 4.1 mm for brain and 5.9 mm for lumbar spine (Mascarin et al. 2015). In our experience we also found a difference in the anterior-posterior axis between the cranial and the lumbar tract, due to the couch flexion depending on the patient weight, particularly relevant issue for such an extended target. However, the corrections to the lumbar tract should be done carefully because any translational movement in this region could have a negative impact on the eye area, putting it in a high dose region. To avoid this, rather than correcting the cranial and lumbar tract with different setup parameters, we decided to apply a different PTV margin expansion between cranial CTV (4–5 mm) and lumbar-sacral spinal CTV (5–7 mm), thus confirming other current approaches. The setup errors in the lumbar spinal region were then preferentially corrected only along the latero-lateral axis, manually adjusting the jaw and keeping the head still (Mascarin et al. 2011).

The optimal protocol for IGRT in HT-CSI is as yet undefined. The Heidelberg group uses a verification protocol for CSI on HT wherein the skull-base is scanned daily and 3D shifts are applied to obtain maximum alignment at the cribriform plate. To allow for co-existing variations and deformations of the spine, increasing PTV margins of 6, 10, and 15 mm are used for cervical, thoracic, and lumbar spinal canal respectively. In addition, the lumbar spine is additionally scanned once weekly and the previously obtained correction shift is applied offline to that region which allows reassessment of adequacy of the applied margins (Stoiber et al. 2011). Daily verification scanning of the entire target volume, as described by the Montreal group, although possible could take as long as 10–15 min. In addition, this would result in unnecessarily increased whole-body doses which are undesirable particularly in younger children (Al-Wassia et al. 2013). Gupta et al. used a novel protocol of scanning a small body segment (5 cm) at three different anatomic levels (skull-base, carina, and lumbo-sacral spine) and co-registering individually at every level for calculating the set-up errors separately for the three levels (Gupta et al. 2015). In our Center we perform a double scan of about 10–15 cm in the cranial-cervical region and in the lumbar region (Mascarin et al. 2011).

The use of delivery systems with a very high degree of freedom, such as HT, could permit to explore the potential of sparing structures and tis-

sues that normally cannot be efficiently spared with more conventional 3D-CRT or IMRT techniques. The following OARs should be routinely outlined: eyes, lenses, optic nerves, pituitary gland, optic chiasm, cochlea, brain, supratentorial brain, brainstem, thyroid gland, heart, lungs, breast, liver, kidneys, bowel, bladder, and gonads (if visible). For any of these organs, a dose-volume histogram (DVH) should be constructed for plan analysis. Dose constraints (maximum dose) for various OARs are as follows: optic chiasm and optic nerves, 55 Gy (Mayo et al. 2010a); brainstem, 54 Gy (Mayo et al. 2010b); spinal cord, 50.4 Gy (Kirkpatrick et al. 2010); lenses, 8 Gy; and cochlea for sensor neural hearing loss, as low as possible (conservatively ≤35 Gy) (Bhandare et al. 2010).

In MB patients HT-IMRT used for PF boost following CSI was able to reduce the cochlear area dose to less than 50%, simultaneously decreasing the higher doses to the temporal lobes and supratentorial brain, although a greater spread of mean doses toward the pituitary region (Mascarin et al. 2015).

With regard to the thyroid in conventional 3D CSI, the upper part of the gland received, with two cranial opposed fields, about 20% of the delivered dose and the lower part, with direct posterior field, between 50 and 70% of the delivered dose. In the HT plans, 90% of the thyroid volume received lower than 23% of the delivered dose (Mascarin et al. 2011) (Fig. 18.4).

The pulmonary toxicity has been studied by Penagaricano et al. They found no acute pulmonary toxicities in 18 patients (age 2.5–21 years) treated with HT-CSI; 11 of them had ≥50% of the lung volume that received ≥10 Gy. The same author reported no high grade acute toxicity profiles: weight loss (14/18 patients, grade 1–2) and nausea (10/18, grade 1–2) were the most common acute toxicities (Penagaricano et al. 2009).

HT-CSI also provides a dosimetric advantage in the exit dose in the pelvic-bladder area when compared to conventional techniques (<5% and ≈10% of dose delivery with HT and with Linac-based conventional CSI, respectively). This is due to the divergent posterior spinal field used with the Linac, being liable for a higher dose in the anterior part of the pelvis. Differently, with HT the helicoidal fields are substantially orthogonal to the spine, and the gonadic region could be the object of OAR planning optimization. This result may be of interest to better spare the ovaries in a female patient treated with CSI, even if the gonads could be difficult to contour (Mascarin et al. 2011) (Fig. 18.4).

Lastly, Kunos reported a decrease of hematological acute toxicity and dose to growing vertebrae with HT (Kunos et al. 2008).

In addition, dosimetric analysis of bowel doses in HT-CSI has been specifically addressed in a case-report of a pediatric medulloblastoma patient with a history of inflammatory bowel disease, comparing three different techniques. A combined 3D 6-MV photons and 18-MeV electrons plan was found to give the lowest dose to the bowel and the lowest nontumor ID when compared to 3D-CRT and HT, while the coverage of the spine PTV was least homogeneous using this technique. The authors concluded that the use of electrons was the best method for reducing the dose to the bowel and the ID, at the expense of compromised spine PTV coverage. As expected, HT was able to achieve the best coverage of the PTVs and better spared the heart, thyroid, and eyes (Harron and Lewis 2012).

Actually, the total body ID slightly increases in comparison to conventional techniques delivered with linear accelerator. Based on our experience, in 15 children younger than 8 years treated with 23, 4 Gy CSI for different brain tumors, the total body ID showed a difference of about 11% in favor of 3D-CRT-CSI when compared to HT-CSI (Mascarin et al. 2010b) (Table 18.1).

However, results for ID in CSI vary in the literature. Shi et al., in a single patient study, showed that the HT plan produces lower non tumor ID when compared to the step-and-shoot IMRT plan and better homogeneity for the spinal PTV (Shi et al. 2008). In a comparison between HT and conventional CSI, Penagaricano et al. found an ID 8% higher in two patients, but 2% lower in another one (Penagaricano et al. 2005).

In 2014 Lopez Guerra JL et al. published the first work showing the clinical outcome of pediatric medulloblastoma patients treated with HT for CSI. In a cohort of 19 children they demonstrated that HT-CSI was well tolerated with low rates of severe acute toxicity, defined and graded

Table 18.1 Total body and "organ at risk" integral dose (ID) calculated in 15 consecutive children (age at time of radiotherapy less than 8 years) treated in our Institute with 23, 4 Gy CSI (C-CSI vs HT-CSI)

	ID $_{(Gy \times Kg)}$	
	C-CSI[a]	HT-CSI
Organ	Mean ± SD[b]	Mean ± SD[b]
Eyes	0.048 ± 0.02	0.050 ± 0.02
Lens	0.002 ± 0.00	0.002 ± 0.00
Teeth	0.130 ± 0.14	0.303 ± 0.18
Thyroid	0.032 ± 0.03	0.027 ± 0.02
Lungs	1.217 ± 0.63	2.101 ± 0.64
Heart	1.793 ± 0.58	1.130 ± 0.43
Kidneys	0.278 ± 0.38	0.709 ± 0.26
Bone	16.966 ± 2.92	18.515 ± 3.38
Body	102.00 ± 14.87	114.93 ± 19.26
Extracranial body	54.79 ± 11.26	65.35 ± 16.37

We compared the ID obtained with Conventional (C-CSI) and Helical TomoTherapy (HT-CSI) Craniospinal Irradiation
[a]Craniospinal Irradiation
[b]Standard Deviation

according to RTOG criteria. The most common acute toxicity was hematological (79%), being grade 2 and grade 3 in 4 (21%) and 11 (58%) cases, respectively. No grade ≥ 2 late toxicities were observed (at a median follow-up for alive patients of 40 months). Two and 3-year overall survival (OS) was 75% and 68%, respectively (Lopez Guerra et al. 2014).

Since the introduction of HT at our Institution, to date, 32 children and AYA received CSI delivered by this technique. The median age at treatment was 7 years (range 2–24). Seven patients (22%) were 5 years old or younger and were irradiated in daily general sedation with propofol. The most prevalent histological type was MB/PNET (81%; of these 50% were HR, 42% SR, and 8% Infants). The prescribed CSI-doses were between 23.4 and 36 Gy (1.8 Gy/fraction). Ninety-five percent of CSI-PTV volume received at least 95% of the prescribed dose.

All patients were examined at least twice a week during RT. Excluding transient alopecia, 34% of patients experienced no acute toxicity. One patient had central acute toxicity with headache and irritability associated with transient edema on CT and four patients (12%) only grade 1 headache. We also registered grade 1 dermatitis in nine patients (28%) and grade 1 oesophagitis in 2 (6%). Between the 21 patients who did not receive concomitant chemotherapy (CT) or however in full haematological recovery after prior CT at the beginning of RT, we recorded 5 cases of grade 3 (24%) and 5 cases of grade 4 (24%) hematological acute toxicity, 14 cases of grade 1 gastrointestinal toxicity—nausea, vomiting without headache—(67%) and 2 cases of grade 1 mucositis.

At a median follow up from RT of 2.3 years (range 0.3–8.2), 48% of evaluable patients (n = 31) died (DOD), 35% in complete remission (NED), and 16% alive with disease (AWD). Between disease-free patients we recorded the following treatment sequelae at a median follow-up of 4.5 years from RT: 1 case of grade 2 sensorineural hearing loss, 1 case of persistent alopecia, and 1 case of central hypothyroidism diagnosed 1 year after RT. Unfortunately we also had a major toxicity represented by a case of ischemic stroke 1.5 years after RT in a girl treated at the age of 6.5 for a diffuse progressive gliomatosis of the craniospinal axis refractory to CT.

We analyzed mean and maximum doses on OAR and expressed them as percentages of prescribed PTV-CSI dose delivered with HT. Mean, median and range of these percentages are listed in Table 18.2 and seem consistent and potentially predictive for acute and late side effects (Coassin et al. 2015).

In the MB group, 2 and 3-year OS was 69 and 55%, respectively.

Table 18.2 Mean and maximum doses on organ at risk (OAR)

	Mean dose (% of prescribed PTV-CSI dose)			Maximum dose (% of prescribed PTV-CSI dose)		
OAR	Mean	Median	Range	Mean	Median	Range
Right optic nerve	82	83	58–97	102	102	95–107
Left optic nerve	83	85	59–99	102	102	95–110
Optic chiasm	102	101	100–106	104	104	101–108
Right ocular globe	37	37	18–56			
Left ocular globe	38	36	18–60			
Right lens	19	20	10–27	26	26	13–38
Left lens	20	19	11–32	28	28	14–45
Right cochlea	98	100	88–104	102	103	92–108
Left cochlea	98	100	86–103	102	103	89–106
Pituitary gland	102	102	100–105			
Teeth	21	22	9–28			
Right parotid gland	58	58	35–80			
Left parotid gland	59	59	41–83			
Thyroid	25	26	13–43			
Trachea	49	45	13–68			
Esophagus	56	54	44–73			
Heart	25	24	18–34			
Right lung	23	23	14–29			
Left lung	21	21	13–27			
Liver	20	20	17–26			
Right kidney	23	23	10–33			
Left kidney	22	21	12–30			
Bladder	6	4	2–17			
Rectum	11	5	2–26			
Male gonads	1	1	0–1	1	1	1–1
Female gonads	3	2	2–6	10	3	2–31
Right breast	12	11	9–16			
Left breast	12	11	9–16			
Skin	39	21	27–75			

The values are expressed as percentages of prescribed PTV-CSI dose delivered with Helical TomoTherapy (HT). The analysis has been conducted in 32 consecutive pediatric and adolescent patients treated with HT in our Institute

An unusual condition in which HT could play a specific role is the re-irradiation of the craniospinal axis. We employed this technique in a 10-year-old male with diffuse meningeal spread of disease, 24 months after the first-line CSI for a standard risk MB, proved to be refractory to salvage chemotherapy. He received 23.4 Gy in 13 fractions to the craniospinal axis, with a reduced dose to posterior fossa of 18 Gy. HT allowed us to adequately re-treat the entire axis, while giving a safe dose to the posterior fossa, previously treated by the full dose (55.8 Gy) (Coassin and Mascarin 2014).

18.10 Whole Ventricular Irradiation

HT offers also an advantage for selected patients such as those who require a whole ventricular irradiation (WVI). A dosimetrical study was conducted by Chen et al., comparing 3D conformal radiotherapy (3D-CRT), IMRT, and HT techniques, for 6 pediatric patients. In this study, a good PTV coverage was achieved in all patients regardless of treatment technique. HT significantly reduced mean dose to the temporal lobes,

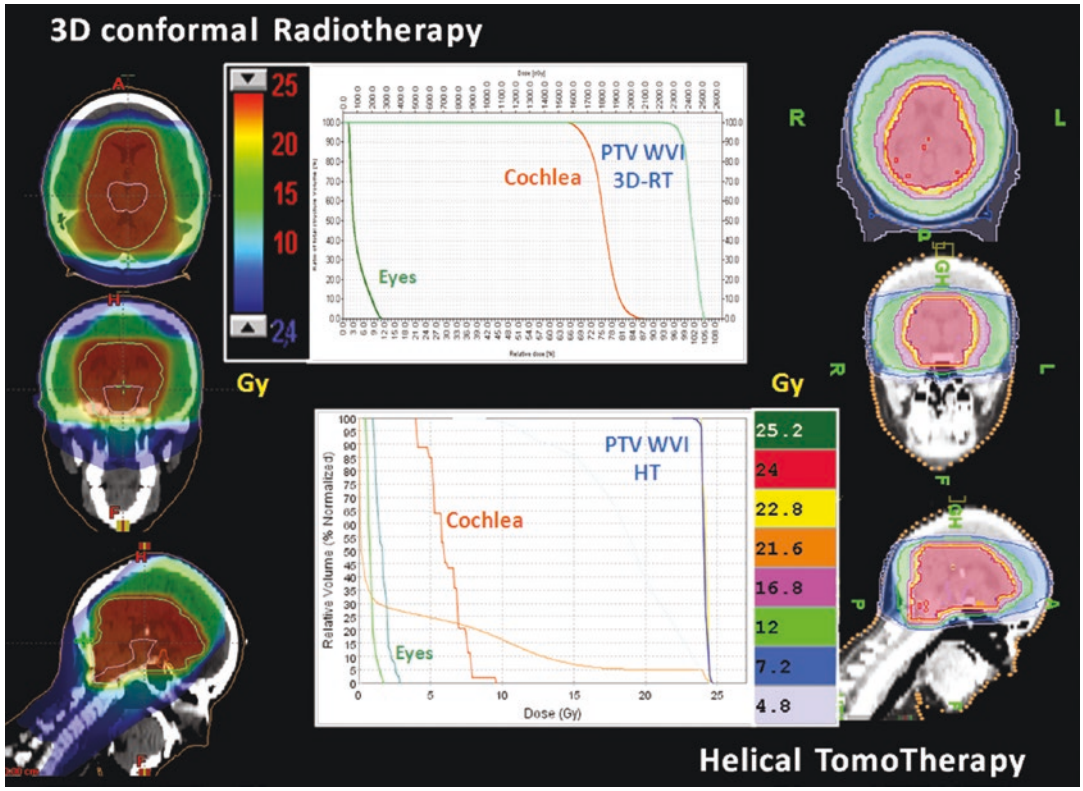

Fig. 18.5 Whole Ventricular Irradiation (WVI) delivered with Helical TomoTherapy (HT) compared with 3D conformal (3D-RT) plan (five no-coplanar fields). A case of an adolescent male with localized central nervous system germ cell tumor who underwent WVI delivered by HT (24 Gy, fractionated), with a sequential tumor bed boost to the primary lesion (16 Gy, fractionated). Although WVI-HT is associated with low dose bath to peripheral areas of the brain, it can spare better the cochlea and delivered a more homogeneous dose to PTV (3D-RT plan calculated by Eclipse Varian®, Palo Alto, USA; HT plan calculated by Hi-Art TomoTherapy Inc.®, Madison, USA) (Courtesy of Sartor G, Med Physics, CRO Aviano, Italy)

pituitary gland and chiasm, but not to the brainstem (Chen et al. 2010).

Only three patients in our series received WVI delivered by HT for localized germinomas at the dose of 24 Gy in 15 fractions. They experienced no acute toxicity. Up to 5 years after RT we recorded no side effects (Fig. 18.5).

18.11 Focal Brain Irradiation

Structures contoured as OARs for brain focal treatments should be at least both parotids, teeth, the mandible (including temporo-mandibular joint), the spinal cord, optical structures (optical nerves, chiasm, eyes, lens), the brain, the supratentorial brain, the brainstem, the pituitary gland, temporal lobes, the cochlea, and the thyroid gland.

Much importance is always given to the prevention of hearing loss as it could compromise the quality of life of these young and very young patients, especially in the future of their workplace and during social relationship. Despite its small size (mean volume 0.14 cm^3), the cochlea is easily identified on CT planning with 2–3 mm cut. The anatomic cochlea contour should be slightly expanded as an OAR to facilitate its preservation from excessive radiation because of its small size. In fact, the value of data resulting from HT planning optimization is not so accurate for OARs whose volumes are lower than 2 cm^3.

Another priority is to limit dose to the hypophysis. Neuroendocrine disturbances in anterior

pituitary hormone secretion are common following radiation damage, the severity and frequency of which correlate with the total radiation dose delivered to the hypothalamus-pituitary axis and the time that has elapsed since treatment. Classically, growth hormone (GH) is the most sensitive of the anterior pituitary hormones to irradiation, followed by gonadotrophins, adrenocorticotrophic hormone (ACTH) and thyroid-stimulating hormone (TSH). We analyzed 44 children (31 males and 13 females) who received cranial RT once daily under the age of 16 years from 2004 to 2013 at our Institution. Patients with germ cell tumors, craniopharyngiomas, and tumors involving the hypothalamic/chiasmatic region were excluded. The growth failure was measured as a growth rate below the appropriate growth velocity for age of more than two standard deviations at a follow up of at least 1 year from RT. Growth failure occurred in 60% of children. The median average dose to the hypothalamus-pituitary axis was double in patients presenting growth failure when compared to the others. When the analysis was limited to 12 patients focally irradiated with HT only for brain tumors, the ability of this technique to spare the hypothalamus-pituitary axis and consequently reduce secondary growth failure was demonstrated. In this subgroup, only 25% of patients had deficits. The median average dose to the hypothalamus-pituitary axis was 21.6 Gy and 15 Gy, in children who presented or not growth failure respectively (final analysis in progress, data not yet published).

Unfavorable neuropsychological and cognitive outcomes have been reported in 20–60% of the long term survivors of pediatric brain tumors. In childhood the most relevant factors are dose received by some critical structures and correlation between high doses and large volumes of irradiation (Mulhern et al. 2004). Studies on correlation between the dose to specific brain regions and the subsequent cognitive impairment, showed the strongest association between temporal lobe irradiation and memory dysfunction, with a dose-dependent effect (Armstrong et al. 2010). This seems to be mediated by a reduction in hippocampal neurogenesis, caused by RT in a dose-dependent manner (Monje 2008). Therefore, radiation-induced damage to the hippocampus plays a considerable role in the neurocognitive decline, providing rational for conformal avoidance of this structure. Gondi et al. demonstrated the capability of HT to conformably spare the hippocampus during cranial irradiation (Gondi et al. 2010), but to do so without compromising local control poses important challenges given the central location and its unique anatomic shape. A study by Kothavade et al. on ten children and AYA (median age 14 years) with benign/low-grade brain tumors compared target coverage, plan homogeneity, and hippocampal doses between HT, linear accelerator-based IMRT, and forward planning SCRT. HT and IMRT achieved significantly better PTV coverage than SCRT. HT as compared to SCRT and IMRT plans showed trend towards significant avoidance of the contralateral hippocampus, in eccentrically located tumors (Kothavade et al. 2015). Hippocampus contouring was done as per guidelines by RTOG0933 (Gondi et al. n.d.).

Many predictive models have been proposed in order to understand the children who are at great risk of developing cognitive impairment after cranial RT, progressively concentrating attention on the role of treatment volumes. Merchant et al. first demonstrated that the volume reduction allowed by CRT could lead to a containment of long term side effects without jeopardizing disease local control. Further studies confirmed the possibility of modeling conformal dosimetry for specific brain subvolumes to predict the effects of RT on neuropsychological outcome (Conklin et al. 2008; Merchant et al. 2004, 2005, 2006a, b, 2008, 2009, 2014; Netson et al. 2013). Other authors proposed NTCP models able to predict cognitive modification after RT based on doses and treatment volumes (Fuss et al. 2000).

Relying on all these experiences, we are building and validating a model based on equivalent uniform dose (EUD), which takes in account dose distribution, irradiated volumes, and tissue response to radiation. As expected, calculated model parameters showed that pediatric brain response to radiation depends on both dose and volume. This finding is consistent with the notion that different brain structures contribute to the

cognitive functions, and some of these are particularly critical. Data are still under definitive analysis, but they seem to confirm that highly focused CRT could afford some protection. There will be a focus on a comparison between different CRT/IMRT techniques. At present, there are no studies specifically investigating the role of HT.

To date, in total 44 patients received focal cranial RT with HT at our Institution. The median age at HT treatment was 13 years (range 1–21.5). Nine patients (20%) were 5 years old or younger and were irradiated in daily general sedation with propofol. The most prevalent histological types were ependymoma (16%), high grade glioma (16%), optic pathway and hypothalamic/chiasmatic low grade glioma (11%), craniopharyngioma (11%), and brainstem glioma (9%). All except one patient were treated with curative intent, including those who had recurrent disease (55%). Four patients who had previously received RT, underwent re-irradiation for local recurrences of ependymoma (two patients), medulloblastoma (one patient), and low grade glioma (one patient). The median administered dose was 54 Gy (range 40–67.4).

Excluding transient alopecia, 84% of patients experienced no acute toxicity. Four patients had grade 1 headache and three patients grade 1 dermatitis. Between the 29 patients free from CT, we had only 1 case of grade 3 haematological toxicity, 1 case of grade 1 asthenia and 1 case of grade 1 anorexia.

At a median follow up from RT of 2.6 years (range 0.1–8.9 years), 44% of evaluable patients (n = 39) were NED, 33% were DOD, and 23% were AWD. Between disease-free patients we recorded the following treatment sequelae at a median follow-up of 3.7 years from RT: 2 cases of grade 1 ototoxicity and 1 case of persistent alopecia. We also had a major subacute-late effect represented by a case of moya-moya syndrome (Wang et al. 2014) diagnosed 10 months after RT in a child treated at the age of 4 to the dose of 54 Gy for a progressive hypothalamic/chiasmatic low grade glioma (unaffected of neurofibromatosis-1). Three patients (18%) presented nonspecific white matter changes on MRI arising 1–4 years after treatment.

18.12 Spinal and Paraspinal Irradiation

In focal spinal irradiation, highly conformal planning and accurate delivery of such plans are imperative for successful treatment without catastrophic adverse events. In an end-to-end testing on HT, Vero, TrueBeam, and CyberKnife treatments for high-dose single-fraction spine stereotactic RT, it has been shown that all platforms were able to meet all dose constraints required and produce exceptional agreement between calculated and measured doses. There were differences in the plan characteristics and significant differences in the beam-on delivery time. Thus, clinical judgment is required for each particular case to determine most appropriate treatment planning/delivery platform (Gallo et al. 2015). There are several published experiences on safety and effectiveness of various IMRT techniques in the treatment of spinal tumors, especially of chordomas (Yamada et al. 2013). The French Society of Radiation Oncology specifically evaluated the feasibility of HT for the treatment of axial and paraspinal tumors. The two AYA patients in their report on 14 consecutive adult patients were respectively treated at the age of 18 and 20 years with an adjuvant intent after incomplete surgery for T6–T7 and L5 Ewing sarcoma to the dose of 56 and 59.4 Gy. In the first case, where the tumor was located close to the spinal cord, D2 (dose received by 2% of the OAR in Gy) was 40.2 Gy. In the second one, where the lesion was situated close to the cauda, D2 was 46 Gy. Considering the entire cohort, the treatment was well tolerated. There were no cases of acute myelopathy/radiculopathy, nor any digestive toxicity. Only 8 cases of acute dermatitis were reported (grade 3 max, n = 2). Particularly concerning the good tolerance of HT for this delicate indication, it could represent a safe option, presently more available than proton therapy (Haddad et al. 2011).

On these grounds, four patients in our series received RT to the spinal cord delivered by HT. Actually, they were treated for CNS tumors (high grade glioma, n = 2; ependymoma, n = 1; recurrent germinoma, n = 1) using conventional fractionation. The median age at treatment was

15.5 years (range 4–20 years). The median administered dose was 48.95 Gy (range 32.4–55.8 years). The two patients treated for spinal HGG experienced no acute toxicity. A 16-year-old girl re-irradiated to the whole spinal axis for a relapsed germinoma 5 years after previous 3D-CRT-CSI had instead multiple acute side effects: grade 3 pancytopenia, grade 1 oesophagitis, grade 2 anorexia, and grade 1 diarrhea. The last patient was treated for a spinal ependymoma and only had grade 1 thrombocytopenia. Unfortunately, no patients were evaluable at long-term follow-up.

Three additional patients received focal RT to the vertebral and paravertebral thoracic region for sarcoma at our Institution. The age at treatment was 9, 13 and 18 years. The administered dose was 54 Gy to D9, 66 Gy to C7–D4 (with the simultaneous integrated boost technique, so that the paravertebral region was treated to the full dose, the perimedullary region to 56 Gy, and the spinal cord to 50 Gy), and 54 Gy to D3–D6, respectively. The only acute toxicity was grade 2 dermatitis in two patients. The younger patient died of disease 9 months after RT. The other two patients were alive in complete remission more than 5 years after treatment and had no sequelae.

18.13 Lymphoma

HT may potentially improve irradiation in Hodgkin's disease (HD). Vlachaki et al. compared the dosimetry of 3D-CRT with HT in pediatric patients with advanced HD. HT decreased mean normal tissue dose by 22% and 20% for right and left breasts respectively, 20% for lung, 31% for heart and 23% for the thyroid gland. Integral dose also decreased with HT by 47% (Vlachaki and Kumar 2010). Based on our early experience, HT allows a greater dose homogeneity in the PTV and has dosimetric advantages compared to the conventional technique in several OARs. In a stage IIIA Hodgkin Lymphoma treated to 25.2 Gy in 14 fractions at the end of chemotherapy, with a volume including mantle field + lumbar-aortic and spleen field, the most striking results have been obtained for the left breast (10.82 Gy and 7.9 Gy mean dose for 3D-CRT and HT, respectively), the right breast (10.13 Gy and 8.73 Gy mean dose for 3D-CRT and HT, respectively), the heart (19.89 Gy and 17.1 Gy mean dose for 3D-CRT and HT, respectively), and the left kidney (17.9 Gy and 8.9 Gy mean dose for 3D-CRT and HT, respectively). To achieve these results we did not perform a full blocking of the structures. We applied a high importance with a very low dose constraint to the specific OAR. In our cases, this approach allowed us to achieve analogous results to full blocking, but with better optimization of the target (Mascarin et al. 2011) (Fig. 18.6).

Advances in the treatment of HD have resulted in a large number of long-term survivors at risk for the serious late effects of therapy, and of RT in particular. Currently, second cancers are the primary cause of mortality among these patients with breast cancer being the most common solid tumor among women. The largest excesses of breast cancer are observed among women diagnosed with HD at age 30 years or younger, a pattern that is consistent with the known radio-sensitivity of the breast at young ages (Travis et al. 2005). The incidence of breast cancer has been reported to increase by a factor of 4.3 (95% CI: 2.0–8.4) for patients treated with mantle irradiation (Zellmer et al. 1991). While the dose response for radiation above 10 Gy remains uncertain, carcinogenesis after radiation is exacerbated by the large dose gradient across the breast and treatment field position. Although HT might significantly decrease high doses delivered to the breast, it increases the volume that receives lower doses, which has also been implicated in the carcinogenesis process (Hodgson et al. 2007).

Thirty-two patients received RT including mediastinal region delivered by HT for lymphoma (HD, 84%) at our Institution. The median age at treatment was 15.5 years (range 6.5–23 years). All patients were irradiated during front-line therapy with curative intent. The median administered dose was 25.2 Gy (range 14.4–50).

Thirty-nine percent of patients experienced no acute toxicity. Approximately one-third of

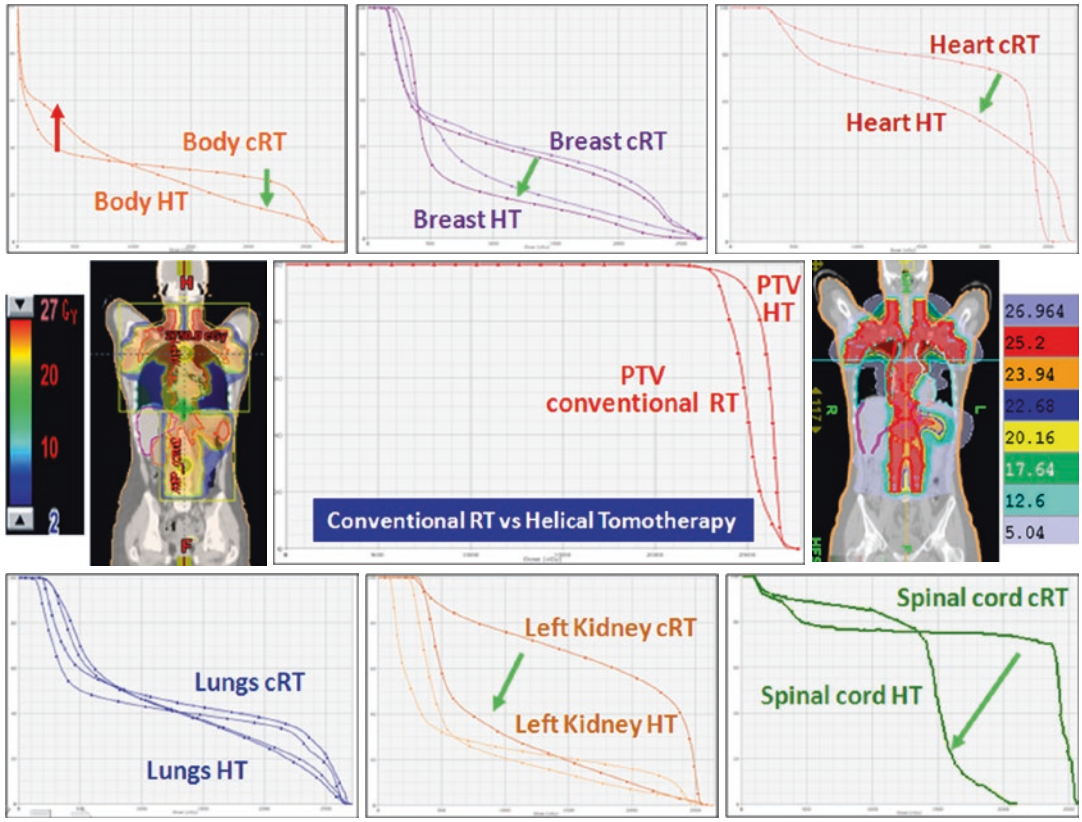

Fig. 18.6 20-year-old female, Stage IIIA HL, treated with 25.2 Gy/14 fractions at the end of chemotherapy. HT plan has dosimetric advantages compared to the conventional RT technique (cRT) delivered with anterior-posterior fields. Several OARs (breast, heart, left kidney, spinal cord) are better spared, whereas whole body HT results in a disadvantage at lower doses and an advantage at higher doses. The PTV coverage result more homogeneous in HT plan

patients had some degree of dermatitis (grade 1, n = 6; grade 2, n = 4) or oesophagitis (grade 1, n = 7; grade 2, n = 3; grade 3, n = 1). Between the 29 patients free from CT, despite sometimes very large volumes of treatment, only 14% of them showed hematological toxicity (grade 1, n = 2; grade 2, n = 1; grade 3, n = 1).

At a median follow up from RT of 2.9 years (range 0.2–7.2 years), 85% of evaluable patients (n = 27) were NED, 11% were DOD, and 4% were AWD. No chronic toxicity to report. A female patient treated at the age of 17.5 years for HD on supraclavicular, mediastinal, and axillary nodes to the dose of 14.4 Gy developed soft tissue recurrent fibromatosis in the breast region within the irradiated area 5 years after RT.

18.14 Head and Neck

The conventional treatment technique for head and neck tumors is composed of two phases. Phase I consists of two lateral opposed fields for the primary tumor and enlarged neck nodes, together with a lower anterior field for the lower cervical nodes. Phase II is used after 40 Gy to shield the spinal cord; usually in this phase the posterior neck nodes are treated with electron fields. The use of HT, as an alternative to 3D-CRT, could be chosen to avoid multiple fields, different energies and junctions, and to spare unavoidably higher dose to critical structures.

In this setting, HT-delivered IMRT may provide superior dose homogeneity and dose conformality when compared to earlier technologies,

such as 3D-CRT or conventional RT, leading to efficient sparing of the spinal cord, the parotids, the teeth and the mandible. In addition, the sparing of pharyngeal mucosal structures and other tissues and organs, such as larynx, thyroid, inner ear and cerebellum is under investigation. This is done to reduce the potentially dose-limiting toxicities. Special attention should be paid to mucosal-sparing techniques to prevent malnutrition and treatment breaks (Mascarin et al. 2011). Indeed, some authors suggested that in pediatric nasopharyngeal carcinoma the use of IMRT resulted in a significant reduction in the incidence of high grade toxicity, and delayed the onset of moderate toxicity, resulting in a reduction in the total time required to deliver RT when compared to CRT (Laskar et al. 2008).

Another important point in favor of IMRT is the possibility to efficiently and easily deliver different doses at different volumes, either through a sequential boost or a simultaneous integrated boost (SIB). SIB-IMRT reaches lower doses than IMRT with a sequential boost in tissue surrounding the high dose PTV, so that it appears to lead to promising outcomes and moderate toxicity (Orlandi et al. 2010). In a recent comparison between different IMRT techniques, it was demonstrated that HT achieves clinically acceptable results in SIB plans for bilateral and unilateral neck irradiation for head-and-neck cancers, with better homogeneity and sparing of spinal cord, larynx, and contralateral parotid gland, when compared to RapidArc. On the other hand RapidArc provided better conformity to elective PTV (Stromberger et al. 2015). The choice between IMRT delivered with Linac or with HT is random for head and neck tumors in our department. Based on our adult experience, there is no difference between the two IMRT modalities in terms of loco-regional control and development of severe, acute, and late toxicities (Franchin et al. 2011).

Since the introduction of HT at our Institution to date, 19 children and AYA received HT for head and neck tumors. The median age at treatment was 14.5 years (range 4–24.5 years). Two patients (11%) were 5 years old or younger and were irradiated in daily general sedation with propofol. The most prevalent histological types were sarcoma (53%), and nasopharyngeal cancer (26%). All except two patients were treated with curative intent. These patients irradiated for palliation were a 14-year-old male affected by metastatic melanoma and a 23-year-old male affected by metastatic nasopharyngeal cancer. The median administered dose was 54 Gy (range 45–68).

We had the following acute toxicities: dermatitis grade 1–2, 64%; dermatitis grade 3, 11%; mucositis grade 1–2, 37%; mucositis grade 4, 5%; oesophagitis grade 1–2, 16%; otitis, conjunctivitis, xerostomia, and haematological toxicity grade 1, 5% each. There was no statistically significant difference between groups (concomitant CT or not) in the risk and profile of acute toxicity.

At a median follow up from RT of 2 years (range 0.4–8.8 years), 60% of evaluable patients (n = 15) were in complete remission, and 40% were DOD (4 of 7 patients affected by sarcoma and 2 patients treated with palliative intent). Between surviving patients we diagnosed a case of cataract 10 months after RT in a young woman irradiated at the age of 24 for Ewing sarcoma arising from the omolateral orbital floor, who underwent lens replacement surgery 3 years later (Dmean to the lens 30 Gy). Another female patient treated at the age of 17 for nasopharyngeal cancer developed hypothyroidism.

18.15 Total Pleural Irradiation

Irradiation of the pleural cavity represents a special challenge for radiotherapists because every conventional technique determines the risk of delivering high doses to the involved lung. Even though this treatment is mostly applied in the adult population with mesothelioma, sometimes also pediatric age cases of soft tissue tumors can involve the entire pleura (Mascarin et al. 2011).

We performed for the first time total pleural irradiation (TPI) with HT in an adolescent patient affected by Ewing/PNET (primitive neuroectodermal tumor) of the right pleural cavity with multiple nodular localizations and, after chemotherapy,

a residual bulky disease along the base of the diaphragm. The patient was simulated in a supine position with arms overhead and fixed with a vacuum bag. The prescription to the right pleural PTV was: first phase, 36 Gy in 20 fractions with a simultaneous integrated boost of 42 Gy in 20 fractions to the post-chemotherapy residual disease and second phase, 10 Gy in 5 fractions (total dose 52 Gy) delivered only to the shrinking residual costal-diaphragmatic tumor. The planning was built with the following constraints: mean total lung dose <20 Gy; V20 Gy total lung <30–35%; left healthy lung, all volume <15 Gy, V5 Gy <5%; heart V20 Gy <20%. A tune structure was built in the central part of the affected lung with a dose constraint of 20 Gy (Miles et al. 2008). The result was quite good both in terms of PTV coverage and sparing of the contra-lateral lung and other OARs. The mean total lung dose and the V5 Gy were 15.9 Gy and 50%, respectively. The mean dose for the affected lung was 29.1 Gy. The maximum dose, the mean dose and the V5 Gy for the healthy lung were 10.5 Gy, 3.4 Gy and 3.8%, respectively. The maximum dose, the mean dose and the V20 Gy for the heart were 38.2 Gy, 15.5 Gy and 22%, respectively. The plan was initially defined on the basis of pre-RT imaging, but this could not accurately reflect the degree of normal lung exposure during all treatment. For this reason, while monitoring tumor shrinkage with daily MVCT, we planned the second treatment phase on the basis of MVCT acquisition, applying an adaptive therapy in order to try to further reduce any exposure to the normal lung. The patient developed a transient radiation pneumonitis in the right lung during the first year, requiring steroid support, and a persistent severe chest deformity with hypoplasia of the right hemithorax. Unfortunately, 7 years later he developed an esophageal cancer in a region previously irradiated to high doses, and considered a second malignancy due to previous RT (Fig. 18.7).

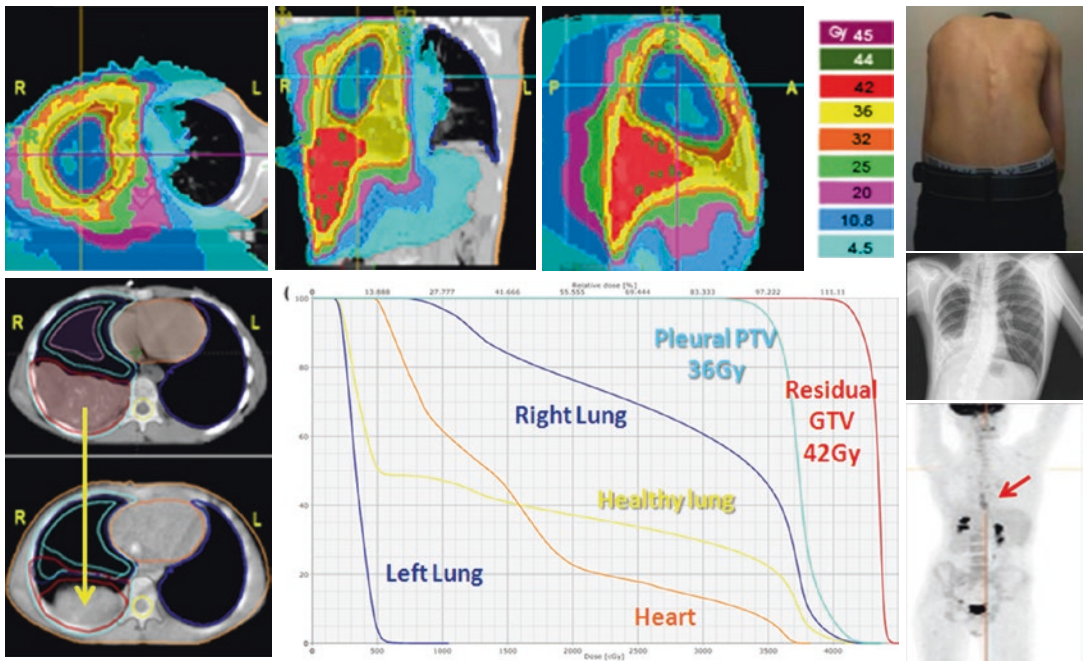

Fig. 18.7 A 15 year old male, affected by right pleural Ewing/PNET. The entire right pleural volume received a dose of 36 Gy plus a simultaneous integrated boost (SIB) of 42 Gy to the residual tumor in the right supradiaphragmatic region. A plan adaptive was adopted during the RT treatment due to tumor reduction. On the right side of the figure we can notice the asymmetry of the rib cage developed 7 years later and the positive FDG-PET on the third inferior portion of esophagus due to secondary cancer araised in a high-dose area

In total, four patients received TPI delivered by HT at our Institution. The median age at treatment was 13.5 years (range 10–17 years). Three patients were treated for pleural sarcoma during first-line therapy and 1 patient for a pleural relapse of Wilms tumor after previous whole lung irradiation. The median administered dose was 47.8 Gy (range 30.6–54).

All patients experienced some degree of acute toxicity, the most serious being grade 3 radiation pneumonitis (n = 2). Other acute side effects were: grade 1 dermatitis, n = 2; grade 2 dermatitis, n = 1; grade 1 oesophagitis, n = 1; grade 2 thrombocytopenia, n = 1.

At a median follow up from RT of 3.4 years (range 0.8–7.7 years), two patients were NED, one was DOD (further pulmonary progression of metastatic Wilms tumor), and one was in complete remission for pleural sarcoma but in treatment for secondary cancer. Apart from this, no significant late effects emerged.

18.16 Whole Lung Irradiation

Whole lung irradiation (WLI) to a dose of 12–15 Gy is widely used in the management of children with pulmonary metastases from Wilms tumor, Ewing sarcoma, and rhabdomyosarcoma, but it results in a higher incidence of cardiac complications. In their report on cardiac-sparing (CS) IMRT in 22 children, Kalapurakal et al. demonstrated the dosimetric advantages of this technique over standard anteroposterior-posteroanterior RT. CS-IMRT resulted in superior cardiac protection, PTV coverage, and dose uniformity in the lungs, with the potential to improve tumor control and reduce cardiac toxicity in children receiving WLI (Kalapurakal et al. 2013).

Only two patients in our series recently received CS-WLI delivered by HT for metastatic Wilms tumor at the dose of 12 Gy in 8 fractions. They were 3.5 and 5 years old at the time of the treatment. They both experienced no acute toxicity (Fig. 18.8).

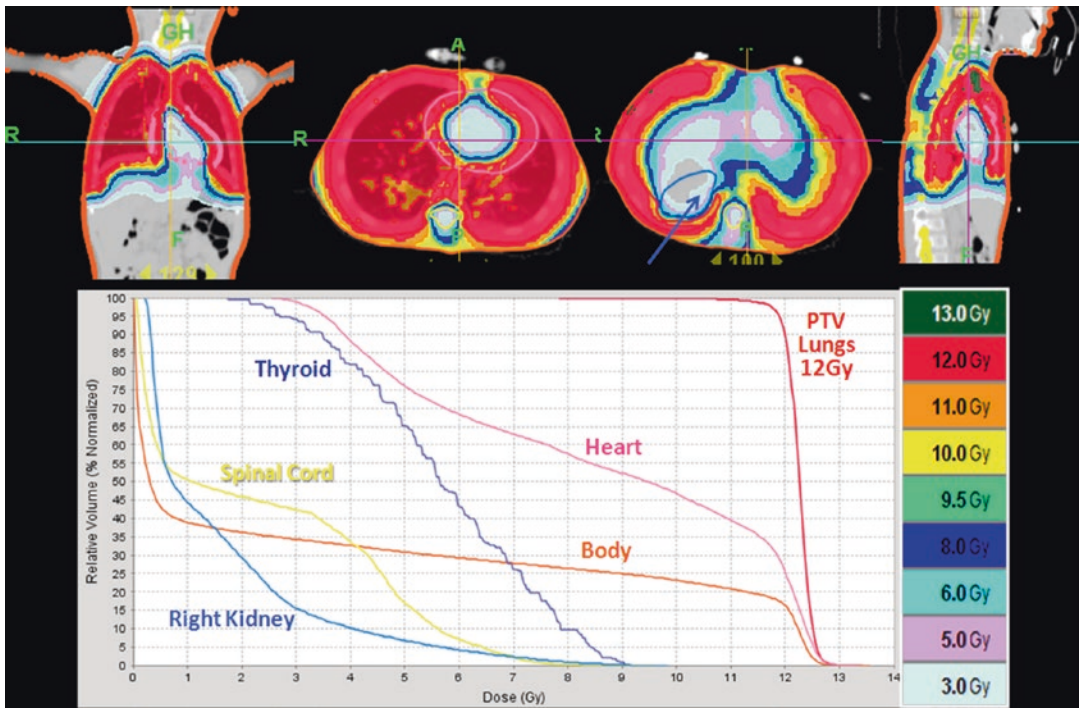

Fig. 18.8 Whole lung irradiation in metastatic Wilms tumor of the left kidney (male, 3.5-years-old). The HT, in comparison with standard technique delivered with two opposite antero-posterior fields, allows to spare part of the central volume of the heart, the vertebral body and the healthy kidney, covering better the costo-diaphragmatic recess

18.17 Lung Stereotactic Radiotherapy

Stereotactic radiation therapy (SRT) is an external beam radiation procedure that has been widely used since the 1990s. SRT allows the delivery of a very high radiation dose to the target volume, while minimizing the dose to the adjacent normal tissues. The reliability of treating "oligometastatic" lung lesions, with a conventional immobilization cast, can be much improved by HT. In our Institution all patients underwent four-dimensional CT (4D-CT) to determine tumor motion for target delineation. After co-registration of the 4D-CT to the simulation, CT an internal target volume (ITV) was created to take into account the fact that the CTV varies in position, shape and size, to finally encompass the maximum intensity projection of the lesion. A 0.5 cm margin is added to the ITV to create a PTV.

Three patients in our series were treated for lung metastases with stereotactic radiotherapy (SRT) delivered by HT; two with metastatic Wilms tumor and one with metastatic soft tissue sarcoma. The last one received a hypofractionated treatment. They all experienced no acute toxicity (Fig. 18.9).

18.18 Thoracic Irradiation

Five patients in our series received focal RT to the chest wall delivered by HT. The median age at treatment was 20 years (range 7.5–22 years). The histological types were sarcoma (n = 3), metastatic neuroblastoma (n = 1), and metastatic lung cancer (9%).

Three of the patients experienced no acute toxicity. The remaining two only had dermatitis (grade 1, n = 1; grade 3, n = 1).

Four of the patients died of disease soon after RT. The only surviving patient was a 20-year-old male treated at the dose of 41.4 Gy in 23 fractions for a localized Ewing sarcoma of the chest wall, in complete remission at 6.4 years from treatment. A year after RT he presented a pathological rib fracture within the irradiated area, but no other late

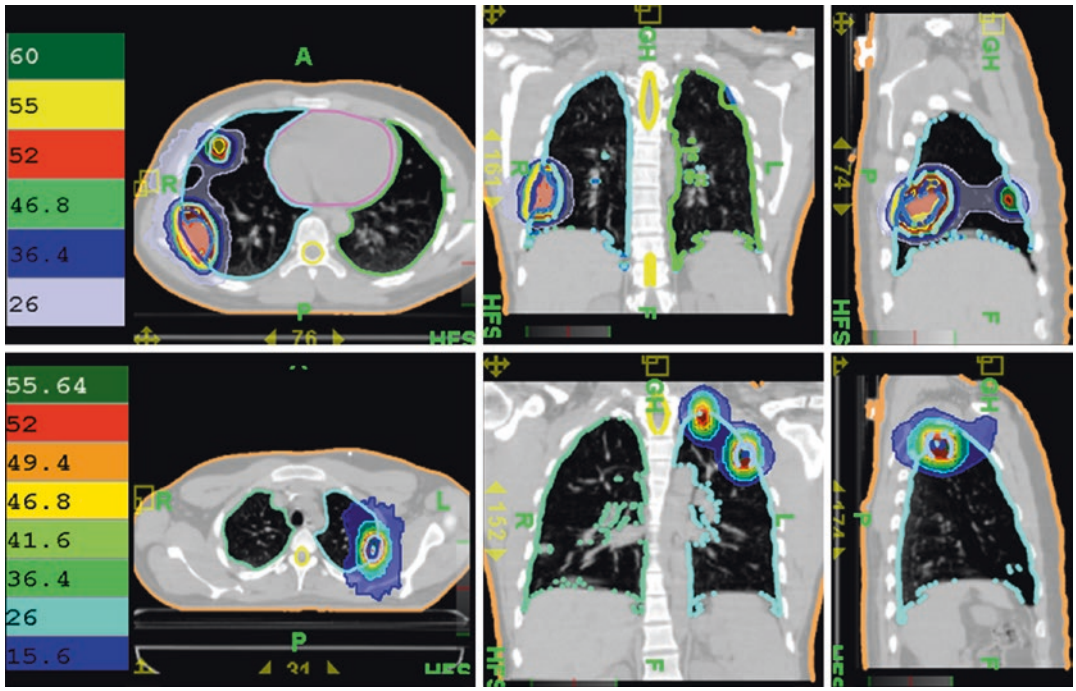

Fig. 18.9 A 17-year-old male with metastatic synovial sarcoma and heart co-morbidity due to the previous chemotherapy was treated with stereotactic lung ablative radiotherapy (SRT). Four bilateral pulmonary metastases were treated to a total dose of 52 Gy in 6 fractions, in 2 weeks

effects occurred. It should be noted that he also had received intraoperative radiation therapy (IORT 9 Gy MeV) on the same site during surgery.

18.19 Whole Abdominal Irradiation

There are several obstacles to treating young patients with whole abdominal and pelvic irradiation. The conventional technique is not only associated with high incidence of toxicity, but also with poor target volume coverage and significant dose heterogeneity because of shielded kidneys and liver as dose limiting organs. For this patient group, contoured organs should be at least the kidneys, the spinal cord, the liver, the spleen, the rectum, and the bladder. HT is feasible and fast for whole abdominal irradiation; this technique provides excellent coverage of the PTV and effective sparing of the OARs. The goal in advanced abdominal disease is to treat the retroperitoneal lymph nodes and the peritoneal surface while reducing the dose to the residual kidney and the bone marrow. Typically, 15 Gy in 10 daily fractions are given to the whole abdomen for patients with Wilms tumor with post-surgical unresectable peritoneal implants or tumor rupture. With conventional techniques the residual healthy kidney is shielded with a block after the first 12 Gy. This results in an under-dosed abdominal area in front of the healthy kidney. Instead with HT, the abdominal cavity is treated uniformly well with a dose to the healthy kidney less than 40% of the prescribed dose, thus allowing a greater homogeneity in whole abdomen irradiation with concomitant sparing of the healthy kidney (Fig. 18.10).

In conclusion, HT provides adequate coverage of the peritoneal cavity while limiting the dose to the residual kidney, spinal cord, liver and bone marrow. It also enables us to further reduce small bowel dose to avoid any serious acute lower gastro-intestinal toxicity, while achieving a very homogenous dose along the vertebral body (Plowman et al. 2008; Rochet et al. 2008).

Another common indication for whole abdominopelvic RT is desmoplastic small round cell

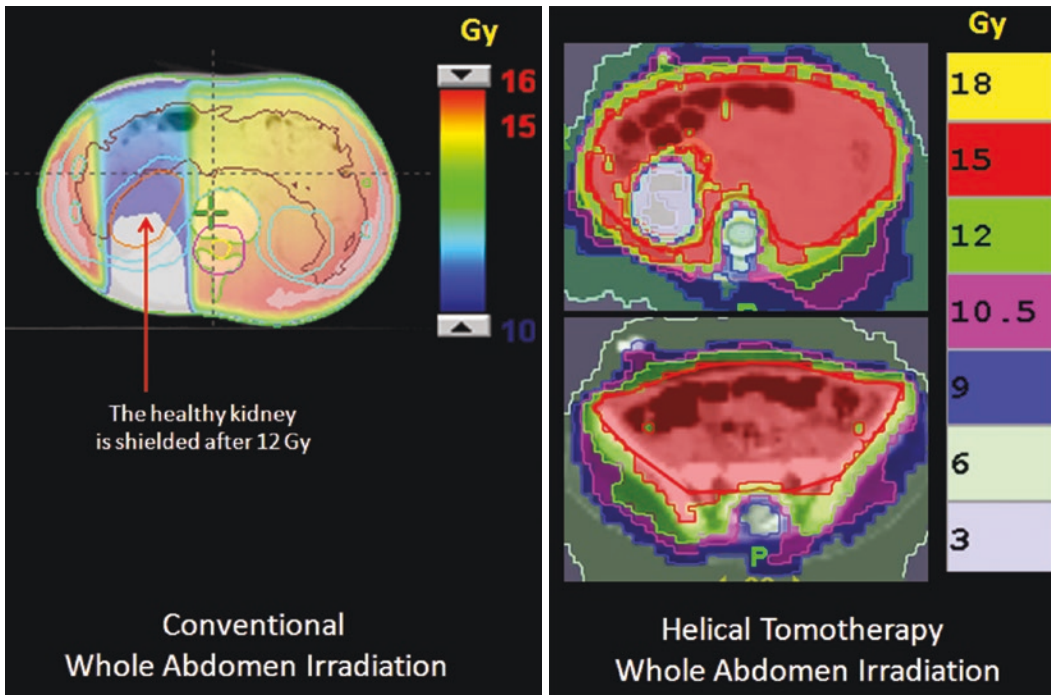

Fig. 18.10 A 2-year-old girl with left kidney Wilms tumor and intraperitoneal diffusion of disease. The whole abdomen is traditionally treated with two opposing fields of radiation and a block to the healthy kidney after 12 Gy. This technique results in an underdosed abdominal area in front of the healthy kidney. Instead, with HT the abdominal cavity is treated uniformly well with a dose to the healthy kidney less than 40% of the prescribed dose

tumor and IMRT appears to be feasible and safe option for these patients too. Dosimetric analysis performed in a study on eight pediatric patients at MD Anderson supported relative sparing of all region of interest with IMRT in comparison to conventional 3D-CRT (Pinnix et al. 2012).

Current Children's Oncology Group guidelines also recommend 24 Gy whole abdominopelvic RT for pediatric patients with other sarcoma types and peritoneal dissemination, malignant ascites, and/or tumor spillage into the peritoneal cavity. In reporting their experience with IMRT, the Memorial Sloan Kettering Cancer Center Group showed excellent rates of tumor control and suggested this approach, despite the high rates of acute and late toxicity (Casey et al. 2014).

18.20 Flank Irradiation

Low radiation doses are typically used to treat the flank in neuroblastoma (21 Gy/14 fractions) and Wilms tumor (14.4 Gy/8 fractions). Even this dose range could be responsible, if delivered to a very young child, for abnormalities in bone growth, especially in vertebral bone with scoliosis as a consequence (Paulino et al. 2000). It has already been described that IMRT can minimize this risk by including adjacent vertebrae into the PTV (Paulino et al. 2006).

Beneyton et al. compared dose distributions with 3D-CRT and IMRT with HT in seven children with neuroblastoma and demonstrated that HT allows a better conformity treatment, a more frequently acceptable PTV-V95% and, concomitantly, a better shielding of the kidneys than 3D-CRT (Beneyton et al. 2012). In this study, the PTV was planned to receive at least 95% of the prescribed dose. The volume of each kidney that received 12 Gy (V12 Gy) was limited to 20% in cases in which both kidneys were preserved and to <15% if only one kidney had been preserved (Dawson et al. 2010). Because of the risk of a lack of homogeneous vertebrae growth if a uniform dose was not delivered to this bone, a uniform dose into all the vertebrae proximal to the targeted volume was required, i.e., at least 80% of each irradiated vertebrae had to receive 80% of the prescribed dose. In all cases, vertebrae were included into CTV as they were in contact with or near the tumor. For the liver, no limit was proposed because a mean dose of 25 Gy into the total organ was considered acceptable (Dawson et al. 2001). In conclusion, to attempt to obtain the best compromise the constraints were organized as following: V12 in the contralateral kidney, coverage of PTV, homogeneity in the vertebrae and V12 in the ipsilateral kidney (Fig. 18.11).

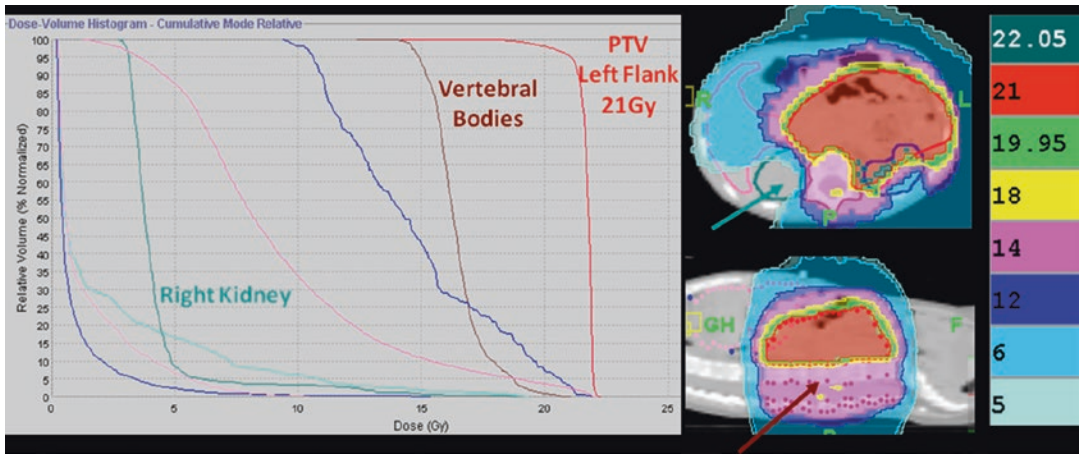

Fig. 18.11 A 3-year-old male with left adrenal gland neuroblastoma treated with HT. The priorities of HT plan were PTV coverage, sparing of healthy kidney and homogeneity of dose in the vertebral body. In this case the goal is not to obtain the lowest dose in the vertebral body, but to maintain a homogeneous dose and reduce the risk of asymmetrical bone growth. A 30% dose gradient was planned between the bone area closest to the target and the other portions of the vertebral body

In total, five children received flank irradiation delivered by HT at our Institution. The median age at treatment was 3.5 years (range 1.5–6 years). Four of them were treated for neuroblastoma and one for Wilms tumor.

Four of the children (80%) experienced some degree of acute toxicity, the most serious being grade 3 leucopenia (n = 1). Other acute side effects: grade 1 dermatitis, n = 1; grade 1 gastrointestinal toxicity, n = 4; grade 2 anemia/neutropenia, n = 1.

At a median follow up from RT of 1.9 years (range 0.3–3.6 years), three patients were DOD, and two were NED and free from significant late effects.

18.21 Pelvic Irradiation

Compared to 3D-CRT, IMRT seems to achieve better results regarding dose conformity and bowel sparing in the treatment of pelvic sarcomas (Mounessi et al. 2013).

In our experience with HT, eight patients were treated for pelvic sarcomas. The median age at treatment was 14.8 years (range 3–17.5 years). They were all males affected by bladder/prostate rhabdomyosarcoma (the youngest) or Ewing sarcoma of the bone (the oldest), with the addition of a rare case of pediatric leiomyosarcoma. The median administered dose was 50.4 Gy (range 41.4–54).

They all received concomitant CT. Sixty-three percent of them experienced some degree of acute toxicity, the most serious being grade 3 dermatitis (n = 1) and proctitis (n = 1). Other acute side effects were: grade 1–2 dermatitis, n = 3; grade 1 constipation, n = 1.

At a median follow up from RT of 2.4 years (range 0.3–7.6 years), four patients were NED, and four were DOD. A 17-year-old patient with metastatic pelvic bones and sacral Ewing sarcoma who was treated with multifocal irradiation delivered by HT including the left femoral head experienced radiation-induced femoral head necrosis. Apart from this, no significant late effects emerged.

18.22 Total Body Irradiation

Increasing attention is paid to the use of HT for total body irradiation (TBI) (Wong et al. 2006; Zeverino et al. 2010). This is also proven by the fact that the only ongoing clinical trials specifically investigating HT in children are about this indication (Rosenthal 2015; Stein 2015a, b).

In a recent study Gruen et al. evaluated HT ability to gain better control over dose distribution, homogeneity, and OARs sparing in a cohort of 10 young patients (age 4–22 years) treated by HT-TBI for high risk acute lymphoblastic leukemia or acute myeloid leukemia (Gruen et al. 2013). Dose prescription to the PTV was 2 Gy single doses delivered twice a day (BID) with an interfraction interval of at least 8 h on 3 consecutive days to a total dose of 12 Gy. Constraints to be fulfilled were the coverage of 95% of the PTV by 95% of the prescribed dose (12 Gy) and the suppression of the lung dose to a mean dose of no more than 10 Gy and a minimum dose of 8 Gy. Planning criteria were the homogenous coverage of the PTV by the prescribed dose and dose to the lungs. Dose peaks (hot spots) were tolerated only if they were located in the bone marrow or musculature. They opted for a minimal lung dose of 8 Gy to prevent underdosing and thus increasing possible relapse rates (Girinsky et al. 1994). To guarantee dose build-up on bony structures lying within close proximity to the skin, they put 1 cm water equivalent flab-material on the hands, sternum and clavicles of the patients.

It could be shown that TBI using HT is feasible and offers advantages over the standard LINAC-based approach. The helical beam-delivery increased both conformality and homogeneity in target-dose distribution. Highly conformal lung sparing could be achieved with mean lung doses of no more than 10 Gy. The TBI treatment have shown limited toxicities, corresponding to only grade 1 side effects, which is in line with the results seen by other groups such as Schultheiss et al. (2007), while grade 3–4 side effects were not observed (Penagaricano et al. 2011). No lung toxicity was observed.

A disadvantage of HT was the limited translation length of the table, allowing irradiable PTV lengths of approximately 145 cm. All patients exceeding 145 cm body length needed a solution concerning the irradiation technique for the lower part of the body. It was chosen to divide the PTV into two parts and to deliver the TBI in two successive sessions: (1) head first from vertex to the cut plane and (2) after repositioning: feet first from toes to the cut plane. Positioning was verified prior to treatment using megavoltage (MV)-CTs either for the pre-defined craniothoracal or the pelvic area (Hui et al. 2012). Additional MV-CTs of the knee area were needed in lower body plans in patients receiving a split-plan treatment. Other groups keep the legs of patients with exceeding body length in a folded position in a vac-loc bag (Hui et al. 2005), others are using ap/pa portals of a Linac for TBI and are applying HT total marrow irradiation only as a boost (Corvo et al. 2011).

18.23 Re-irradiation

HT gives us the opportunity to re-treat areas that have been already treated. The advantages for re-irradiation with HT are the greater conformality of dose distribution and the possibility to respect dose constraints for adjacent, critically sensitive, previously irradiated normal tissues. This opportunity could be of interest both for palliative intent and for patients in which curative treatment could not be obtained with other procedures. HT can be used e.g. for the re-treatment of local relapsed brain tumors and "in field" relapsed Hodgkin lymphomas (Mascarin et al. 2011). While both these situations can adequately be managed by other techniques like Linac-delivered IMRT or stereotactic treatment, an unusual condition in which HT can play a specific role is the re-irradiation of the craniospinal axis (Mascarin et al. 2015).

Conclusions

HT plays a very important part in the history of IMRT and could become a good option for children and young adult patients. In our review, we have proposed some examples of treatment with HT and our experience suggests a greater sparing of critical normal structures and a better PTV homogeneity using HT-based IMRT when compared with 3D-CRT. The dose conformity advantages of HT are sufficient to selectively recommend its use in the pediatric population. We can choose HT when the target/tumor is critical and where the margin of safety (from GTV/CTV to PTV) around the tumor is narrow, when OARs are so near the target they are at higher risk for radiation damage. Moreover, the potential for dose escalation may translate to a better local control without increasing complication rates. The use of daily IGRT requires more time than conventional RT, but it has a major impact on the verification and setup correction. This is true for all patients but especially in the younger ones, in whom treatment compliance is not always adequate. On the contrary, the increase of low doses to normal tissues and the ID demand attention and need to be evaluated with further research.

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19 Localization, Verification, and Anesthesia

Ralph Ermoian, Michael Rossi, Chris Beltran, and Sally Rampersad

19.1 Introduction

Accuracy and precision are essential elements in the quality delivery of pediatric radiation therapy. Accuracy in radiation therapy refers to whether radiation is delivered to volume targeted. Precision refers to the reproducibility of radiation delivery to target volumes over the course of time.

Ideally radiation therapy is delivered with perfect accuracy and precision to clinical targets that are completely still in the exact same location each day. However, in real-world radiation therapy, patients have to be positioned each day with resulting variable patient placement as well as physiologic movement of targets and organs at risk (OARs) (Eldebawy et al. 2011), and beams are precise but still need to be verified. Sometimes the size of target volumes changes over the course of treatment (Laskar et al. 2015). An essential role for the radiation therapy team—radiation oncologists, physicists, dosimetrists, radiation therapists, anesthesiologists, and others—is to create treatment conditions to ensure and verify that radiation is consistently delivered to the smallest possible volume with clinical effectiveness and unquestioned reliability.

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19.2 Consequences of Errors in Radiation Delivery

Radiation planning and delivery has become more conformal and complex. It has changed from two dimensional planning, to three dimensional planning, to now include intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic radiosurgery (SRS), stereotactic body radiation therapy (SBRT), Tomotherapy, and proton therapy. With each step, radiation dose conformality has increased and the margins for error in target localization and treatment verification have decreased (Altunbas et al. 2013).

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Implicit in the need for excellent localization are the consequences of inadequate localization. Errors in clinical radiation have previously been described as relatively rare, but critical when they happen (Huang et al. 2005; Macklis et al. 1998; Marks et al. 2007). Missing the target has two principle consequences: decreased efficacy against the tumor and increased toxicity to OARs. Although more frequently described in tumors typical of adults (Beltran et al. 2012; Goddu et al. 2009; Guckenberger et al. 2012), the consequences of imprecise delivery of radiation therapy may be devastating.

19.3 Localization and Verification

Radiation therapy requires localization of the target volume. Although this takes place with each treatment session, the process begins with the planning for simulation: optimally positioning the patient for treatment. In some respects, this is the most important step in radiation planning. An optimally-positioned patient will tolerate treatment well and radiation will be delivered with accuracy and precision each day with minimal effects on surrounding organs at risk and tissue. A well-immobilized patient allows the radiation oncologist to plan assuming the smallest intrafraction and interfraction target position variability, which translates to the smallest clinically-appropriate clinical target volume (CTV) to planning target volume (PTV) expansion.

19.3.1 Immobilization

Patient positioning and immobilization are tailored to the individual patient and treatment site. In some cases, no immobilization devices are necessary. A wide range of immobilization devices can be employed. They are designed to aid in setup reproducibility while keeping the patient as comfortable as possible. They are designed to have minimal impact on dose buildup and treatment delivery and are typically indexed so therapists place them precisely with each treatment fraction. Some devices include:

- Thermoplastic masks. When treating brain, or head and neck tumors, rigid immobilization with a thermoplastic mask is nearly always required. These sheets of webbed material deform in a hot water bath and then are stretched across the face and neck by the simulation therapist. When the webbed material cools it becomes rigid. The neck and/or occiput is kept in place by either a customized head supporting device such as Moldcare® (Radiation Product Design, Albertville, MD) or standard headrests. The mask is attached to the treatment table and indexed, and CT origin and isocenter can be marked on the mask rather than on the patient's skin. With a thermoplastic mask in combination with daily imaging, intracranial tumors often can be treated with 3 mm CTV to PTV expansions. Figure 19.1 shows an example of a Moldcare® headrest with a thermoplastic mask.
- Similar thermoplastic devices can also be used to immobilized extremities such as feet and hands.
- Vacuum Devices. Vacuum immobilization devices such as Vac-Lok™ (CIVCO Medical Solutions, Orange City, IA) and other devices

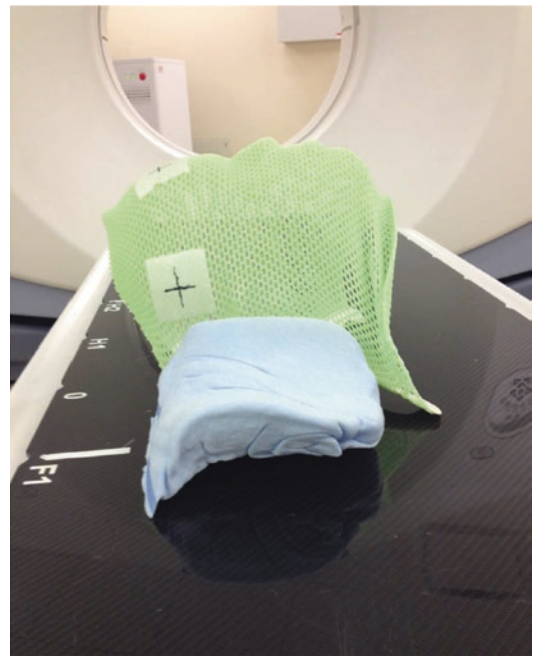

Fig. 19.1 A thermoplastic mask and a customized patient headrest

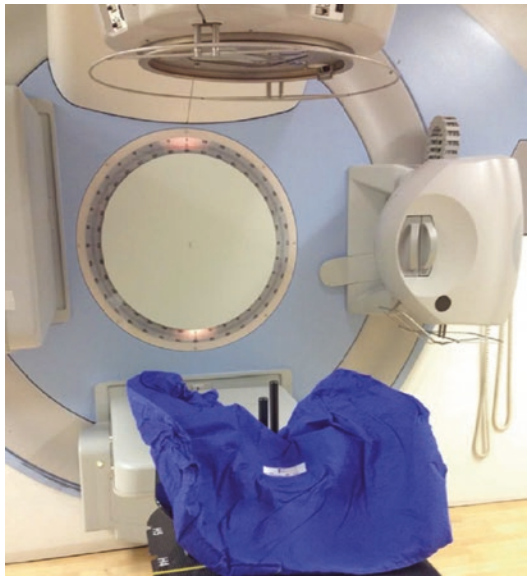

Fig. 19.2 An example of a vacuum immobilization device

are pillow-like objects filled with resin materials that allow a deformable shape while the patient is initially positioned during simulation. Once the patient is in the optimal position, the air is vacuumed from the bag and the resins form a solid structure that maintains its shape until air is re-introduced in the bag. In addition to directly immobilizing the targeted region like an extremity, these immobilization devices can also be used to help align pelvis and abdominal targets by creating an indexed cradle for the lower extremities. They have the advantage that they can be deflated and reused with other patients after the current course is complete and the bags are cleaned. An example is shown in Fig. 19.2.

- Polyurethane foams. These immobilization devices serve a similar function as vacuum devices but are for single patient use. They are similar to vacuum immobilization devices, but can only be used once.
- Custom Stents. A common practice in adult patients with head and neck cancers is to use dental stents that displace non-targeted normal tissue such as the tongue away from target tissues to decrease morbidity of treatment. Although these can be fashioned out of materials stored in the radiation therapy center, recent publications have described stents prepared by dentists in partnership with radiation oncologists (Johnson et al. 2013). These devices have largely been used in adult patients but can be used in older pediatric patients who can tolerate them. Figure 19.3 shows an example of custom dental stent that displaces the tongue to the left.

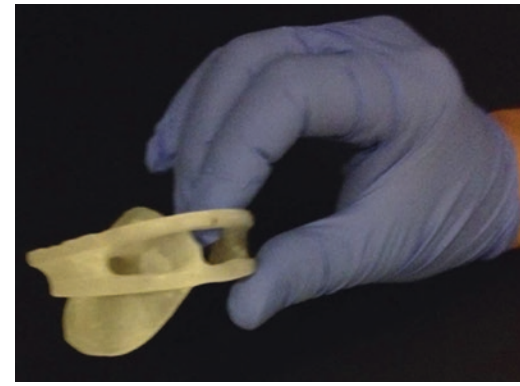

Fig. 19.3 An example of custom dental stent that displaces the tongue to the left

Each device adds some level of complexity to the treatment setup, with associated risks (however small) of errors. Although immobilization devices described below are all considered very reliable, they all can fail in one way or another during treatment courses. For example, though unlikely, a vacuum immobilization device can leak and deflate. Therefore, although the use of immobilization devices are common and should be considered with each patient, the radiation oncologist should choose the minimum number of devices necessary to achieve optimal therapy.

19.3.2 Ensuring Precise and Accurate Therapy from Simulation to Treatment Delivery

The process from consultation to treatment delivery is complex. Ford, et al. identified 90 steps in that process, many of which involved transfer of data essential to treatment localization (Ford et al. 2012). Ultimately the patient is treated by therapists who verify the patient's identity, and

localize treatment based on external marks of CT origin and or isocenters, other external markers, and imaging to confirm isocenter and target volume locations. For patients receiving some of the most advanced-planned treatments such as IMRT and VMAT, this process includes quality assurance by trialing the treatment on a phantom prior to commencement of therapy.

19.3.2.1 On-Treatment Imaging to Localize and Verify

Prior to starting treatment, the patient will undergo a final verification simulation in which treatment delivery is verified on the patient. The radiation oncologist checks that isocenter and beam portals correspond with the treatment plan and encompass the appropriate target structures.

Beam light fields—the shape of the beam projected from the linear accelerator onto the patient—can provide a useful verification of treatment fields. Although not as technologically-advanced as the image verification methods that follow, the light field can show targets apparent by visual inspection or physical examination are in the field, or some critical normal structures/organs at risk are out of the beam. For example, when treating the lower extremity in which there is some difficulty positioning the contralateral lower extremity out of the exit of the beam, the light field might provide daily verification that only the affected limb is in the field.

Several types of imaging can be employed at the verification simulation and throughout the treatment course to ensure radiation is delivered as intended within tolerances prescribed by the physician or the center in which she practices. Some of the types of imaging are listed below.

Two dimensional imaging. These are typically checked using kilovoltage (KV) or megavoltage (MV) radiographs compared to corresponding imaging created by the radiation planning software from planning imaging. MV imaging, in addition to being associated with higher radiation dose compared to KV imaging (Walter et al. 2007), has poorer resolution because increase Compton scattering effect. Increasingly the imaging employed has shifted from physical film to Electronic Portal Imaging Devices (EPID) which allow for better comparison to digitally reconstructed radiographs, quantifying imaging shifts, and verifying treatment delivered dose. An example of electronic portal imaging is shown in Fig. 19.4.

Cone Beam Computerized Tomography (CBCT) are limited view CT scans of the region to be treated and surrounding tissues including critical organs at risk. The images are co-registered

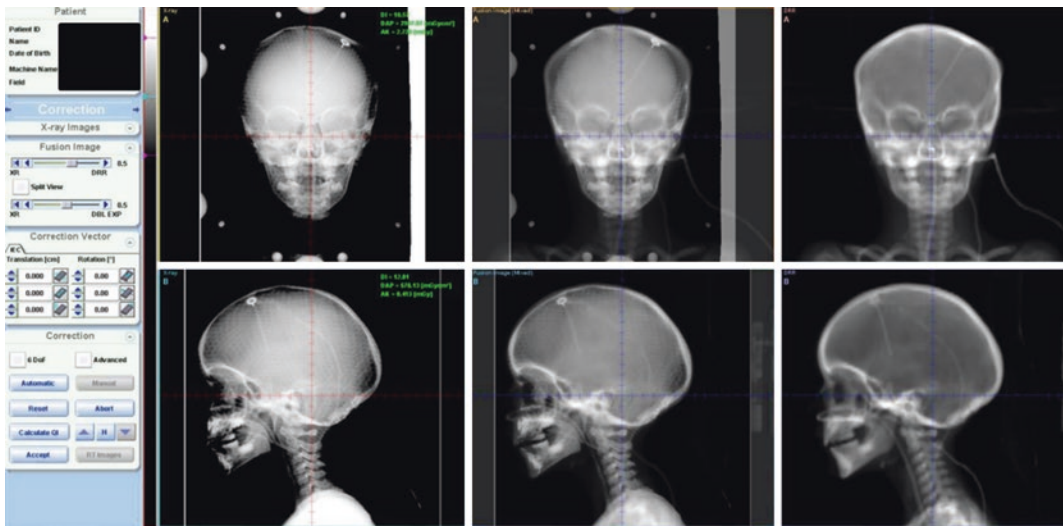

Fig. 19.4 An example of electronic imaging portals. The daily portal is shown on the left, the digitally reconstructed radiograph is on the right, and the blended imaging is in the middle

with imaging from the planning CT to make fine adjustments to bring the patient in alignment with positioning at simulation. The CBCT can be obtained either with the patient on the treatment couch awaiting treatment at the linear accelerator or while on the treatment couch that can be moved from a stand-alone CT scanner to the linear accelerator without moving the patient.

Four dimensional (4D) CBCT. If the radiation oncologist wants to assess intrafraction motion of either the tumor or organs at risk, a 4D CBCT can be obtained. This is uncommonly ordered in part because of the additional time on the treatment machine for the patient, the increased dose associated with the scan, and the information is usually captured in the planning scan during which a 4D computerized tomography (4D CT) can be obtained. Rather, this on treatment imaging is reserved for verifying tissue motion. Alternatively the patient can be re-simulated with a 4D CT and the resulting CT study can be used for replanning.

Other Modalities of localization include ultrasound verification such as of bladder size when treating in the pelvis.

19.3.2.2 Frequency of Imaging

As radiation exposure from verification imaging has decreased and planning techniques have advanced to produce more conformal radiation plans, the frequency of verification imaging has increased. Weekly imaging is necessary for some three dimensional conformal plans. A recent study of 7 pediatric radiation therapy centers found daily imaging guidance (mostly with CBCT) was used in 45% of cases (Alcorn et al. 2014).

Proton therapy is becoming more readily available and pediatric cancers are a key indication for proton therapy. Due to the precision and sensitivity to setup errors of proton therapy, daily imaging of pediatric patients usually is required. This is particularly true for intensity modulated proton therapy (IMPT).

19.3.2.3 In Vivo Dosimetry

In addition to localizing and verifying the position of the patient, delivered dose can be confirmed by physical measurements. In the modern age of intensity modulated radiation therapy, volumetric modulated arc radiotherapy, and Tomotherapy, dose delivery is often confirmed with phantoms prior to delivery of the first fraction of radiation. However, for 3D conformal radiation therapy, delivered radiation therapy can be measured with thermoluscent dosimeters (TLDs) or electronic diodes. An example of diodes is shown in Fig. 19.5. Such devices can be employed either on a regular basis for quality assurance or when unexpected clinical effects are observed during a treatment course.

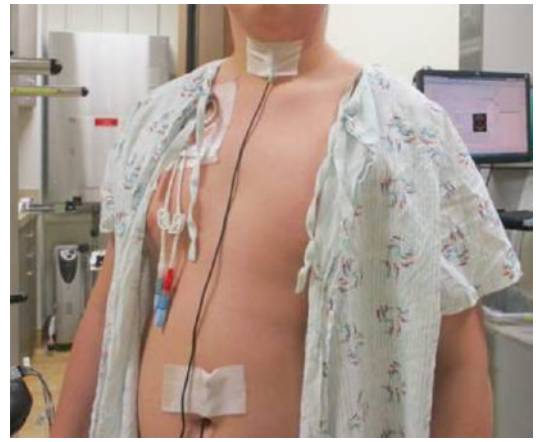

Fig. 19.5 An adolescent patient undergoing total body irradiation with diodes on his neck and abdomen

19.3.2.4 Physics Chart Checks

In most practices, medical physicists take the lead in verifying radiation is delivered as planned. Although not commonly thought of as a verification step, the medical physics weekly review of the treatments delivered can uncover errors to be corrected before the treatment course is complete. In an analysis of a near-miss event incident reporting system at an academic radiation oncology department, Novak and colleagues found that the vast majority of near-misses were discovered in the treatment planning, plan review, and treatment delivery stage. However, although only 12% of events were discovered at the "on-treatment quality management" stage, those events were potentially the most severe (Novak et al. 2016).

19.3.2.5 Physician On-Treatment Visits

Another form of verification is the on-treatment visit, the weekly clinic visit for the patient with his or her radiation oncologist. Unusual findings include unexpected side effects, a lack of side effects when they were anticipated, and more severe side effects than anticipated. These should prompt the radiation oncologist to revisit the radiation plan with the rest of the radiation team and consider further steps including diode measurements.

Other important providers who may provide similar impetus for further investigation include nurses observing the treatment course, radiation therapists, and anesthesiologists who may be helping to care for pediatric patients and who are seeing the patient on a daily basis. The entire team of providers can be sources of input to prompt further steps to ensure patients' safety and effective treatment.

19.4 Anesthesia

19.4.1 Introduction

Safe delivery of radiation requires patients to stay completely still sometimes just for a few minutes but sometimes up to an hour or longer. Despite efforts to prepare pediatric patients for radiation therapy or for proton beam therapy (1), treatment in an awake child may only be possible in older, developmentally typical children (Mcmullen et al. 2015). Thus many younger and developmentally delayed children will present for anesthesia for radiation or proton beam therapy. A typical treatment course may be daily (Monday through Friday) for up to 7 weeks.

Photon therapy remains the most common form of radiation that pediatric patients receive, but proton radiation therapy with its putative ability to reduce effects to surrounding normal tissue is becoming more commonly used. Treatment sessions with proton therapy are generally longer than with standard radiation therapy and this may be important to consider when one is planning a treatment course for a child.

At some centers the standard anesthesia care is a general anesthetic (GA) with inhaled sevoflurane and a laryngeal mask airway (LMA) in place (Buchsbaum et al. 2013). Other centers (Mcfadyen et al. 2011; Owusu-Agyemang et al. 2014, 2016) utilize a total intravenous technique (TIVA), with a natural airway.

While the follow discussion outlines the complexity of providing anesthesia care for patients receiving radiation therapy, single institution studies show the rates of complications are low and comparable to pediatric anesthesia provided in other settings (Owusu-Agyemang et al. 2014; Verma et al. 2016).

19.4.2 Planning, Staffing and Policies

Some radiation therapy facilities are within a hospital but some are stand-alone centers. The location of the center affects the protocols that must be set up for emergency response. If the center is within a hospital, then emergency response may be the hospital's code team, but if the center is stand alone, then there may need to be initial response protocols in place, in order to stabilize the patient while waiting for an external emergency response. If the center is not within a pediatric hospital, then consideration should be given as to which responders are capable of managing a pediatric emergency and how the patient will be transported to a pediatric hospital for admission, or to a pediatric critical care center, if necessary. At many centers the nursing staff are required to maintain Pediatric Advanced Life Support (PALS) certification, so that they can assist in the initial stabilization of the patient.

Practical drills of common expected situations, such as laryngospasm, or airway obstruction are important so that staff feel confident in their abilities to manage these situations. It is also vital to simulate the less common but more serious events, such as anaphylaxis, cardiac arrest and malignant hyperthermia. Cognitive aids such as the PALS algorithms, ASA difficult airway algorithm, MH algorithm and the Critical Event Checklists (Society of Pediatric Anesthesia. 2015) published by the Society for Pediatric Anesthesia, should be readily available. It may be helpful to have a pediatric code cart based upon the Broselow® color coding system, so that the correct equipment can be easily retrieved in an emergency.

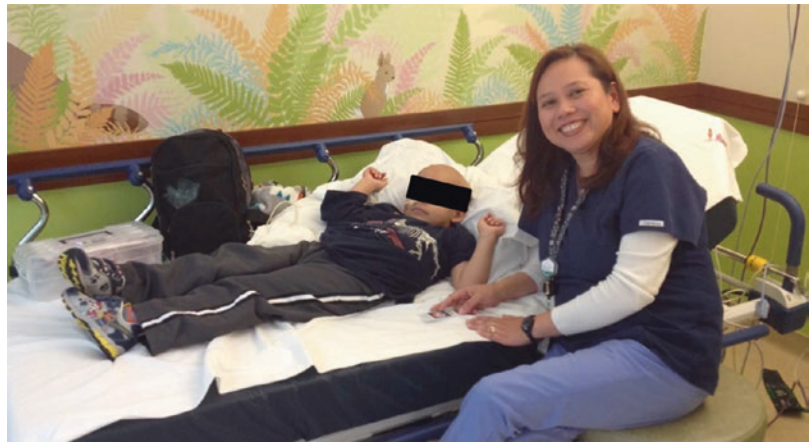

Fig. 19.6 A nurse caring for a patient recovering from anesthesia

Although there may not be a large number of pediatric patients at any one radiation center, anesthesia for such a patient is no less hazardous than it would be if it took place within a major children's hospital. The full range of pediatric anesthesia equipment must be available, including difficult airway equipment. Someone to assist the anesthesiologist is vital. This could be a trained nurse (RN, Fig. 19.6), anesthesia technician, or other type of assistant, or another anesthesia provider. In any remote location where a child is receiving anesthesia and other pediatric anesthesia providers are not in the immediate vicinity it is important that help can be obtained quickly.

An adequate stock of Dantrolene is needed for response to malignant hyperthermia.

19.4.3 Medical "Home" for Out of State and Out of Country Patients

Children presenting for radiation therapy may be sick. They will already have a radiation oncologist at the radiation center to which they were referred. However, they may be in the midst of other ongoing treatments, such as chemotherapy, or they may develop organ dysfunction related to the radiation therapy, or related to the underlying tumor. A fairly common occurrence is the child, on treatment, who develops an upper respiratory infection or febrile illness. Generally the decision is made to try to continue their daily radiation therapy under anesthesia, but the risks/benefits of continuing versus delaying treatment must be carefully considered by the radiation oncologist, anesthesiologist and medical oncologist.

Patients may be referred from out of state, or even out of the country. This is particularly true at proton therapy centers. The treatment course may span seven weeks and so the patients will need to establish care with a local oncologist in order to ensure that other aspects of their oncology care may be managed safely while they are away from home. It may be necessary to make financial or other business arrangements between hospitals and between countries, so that the patients can get the comprehensive medical care and payment can be made for the care that they receive. Medical records, including anesthesia records, must be obtained and reviewed.

Patients and their families also need a place to stay in, food, and travel to the radiation center and to other appointments. For some families, interpreters, either in person or by phone or video link, will be needed frequently in order to get informed consent and to get daily updated information from the patient and family.

19.4.4 Day to Day Communication

At some centers, only a small group of anesthesiologists (from the nearby pediatric center) provide the anesthesia care for patients at the radiation or proton center. Other centers may not have a small group who are dedicated to the radiation or

proton center but may utilize the anesthesiologists from their entire practice. Whatever the model, it may be necessary to communicate daily changes and nuances in management. Knowing the little things such as that a patient likes to sit on a parent's lap for induction, or that he always brings in his favorite toy car, may make the difference between things going smoothly, or not.

Some groups may utilize a secure group email, or may keep a written log in the anesthesia work room at the center. At many centers the patient will have an assigned RN who is with them every day for treatment and who assists the anesthesiologist and does post-anesthesia recovery. This RN is a consistent presence in the patient's life and he/she will be able to communicate with the different anesthesiologists who are providing anesthesia each day.

Agreeing to a standard protocol for anesthesia for these patients is essential. If treatment is planned with a natural airway and the neck slightly extended, then all of the treatments need to be carried out that way. One rogue anesthesiologist cannot decide to use an LMA instead of a natural airway one day, because the target area for treatment may be moved by the change of airway or the mandible position would shift so that the thermoplastic mask would not fit.

Daily communication with the radiation oncologist may be needed too, especially if a patient is not tolerating treatment well, or seems to be developing new and worrying symptoms. Most centers will schedule at least a weekly on treatment visit with the radiation oncologist and a daily check in with a nurse while on treatment. It is important for the anesthesia team to have ready access to the radiation oncologist, so that they may share their observations and concerns.

19.4.5 Simulation

The first step in radiation therapy is the simulation, and it may be the most important element in the patient's treatment, both from the perspective of the radiation oncologist planning the radiation therapy and the anesthesiologist who needs to ensure the treatment position does not compromise anesthesia care. Simulation involves taking measurements and CT scanning, in order to plan the treatment course. For optimal outcomes, the anesthesiologist and radiation oncology should discuss and agree upon treatment positions prior to the simulation. Sometimes this will also require input from radiation therapists, dosimetrists, and medical physicists.

As described earlier in this chapter, a thermoplastic mask is often made during this time and other immobilizers for other body parts may be fashioned during simulation too. The mask starts as a sheet of thermoplastic material that is dipped into hot water in order to make it pliable. The mask is then closely applied over the face and it hardens into its final shape as it cools. The anesthesiologist must be present at this time in order to determine that the head and neck position will allow for a clear airway when the mask is completed. If an endotracheal tube (ETT) or LMA will be used for treatment then that airway device must be in place for simulation, so that the mask can be made around it and measurements made will reflect the presence of an airway device. If a natural airway is planned then as the mask hardens into shape, two holes for the nostrils should be made to allow the application of a nasal cannula external to the mask. A pen is a useful tool for making the nostril holes.

Sometimes it will be necessary to mark the patient with tattoos for future lining up of treatment beams. This is painful, so a short acting analgesic or bolus of propofol may be needed for tattooing.

19.4.6 Anesthesia Techniques

There is not one anesthesia technique that will suit every center and every case. Important considerations are:

1. The airway: natural versus LMA or ETT.
2. Induction and maintenance of anesthesia: inhalational agents versus total intravenous techniques, with propofol or other agents such as dexmedetomidine.

Many cases can be managed with a natural airway and propofol infusion, with nasal cannula oxygen, but there may be cases, where the airway has to be controlled e.g., brain stem dysfunction.

The need to intubate may be present initially and then the dysfunction may resolve, so that a natural airway would be safe. A new simulation, or re-planning may need to occur if the choice of airway changes mid-treatment.

Intra-venous access is an important consideration too, with many centers opting to have some sort of central access placed for the duration of treatment, such as a peripheral inserted central catheter (PICC) line, Hickman or Broviac line, or Port. Care of the line must be meticulous, with strict adherence to protocols for cleaning and accessing the line. A catheter associated blood stream infection can be very serious in these patients and may derail the timing of their treatment.

The administration of radiation therapy does not cause acute pain but there may be patients, with painful conditions who are being treated, so an analgesic may need to be part of the anesthetic regimen. Patients may experience pain from radiation-associated dermatitis, esophagitis, and proctitis. An antiemetic such as ondansetron is included in many anesthetic regimens for radiation because nausea can be a side effect of treatment. Therapies for post-emergence agitation may be needed and the occasional child may need pre-medication prior to entering the treatment room.

An example of a patient receiving craniospinal irradiation under anesthesia in a treatment vault is shown in Fig. 19.7.

Fig. 19.7 A patient undergoing craniospinal irradiation under anesthesia in a treatment vault

19.4.7 Child Life

At many radiation centers there are child life specialists who work with the children, training them to know what to expect and how to cooperate with treatment. In some cases, particularly with older children, a child life specialist may be able to provide sufficient coping and distraction techniques that the anesthesiologist is not needed at all; the child is able to do their treatment awake. A therapeutic plan has been shown to be effective during courses of radiation therapy (Tsai et al. 2013). However, even for those children who do get anesthesia, child life specialists can help to ease that process, providing distraction and rewards for difficult or painful procedures, such as Port access.

19.4.8 Conclusion

Just as surgery is a collaboration between the surgical team and the anesthesiologist, radiation or proton therapy under anesthesia requires teamwork between the anesthesiologist, the radiation oncologist, and the rest of the team caring for the patient. Excellent communication is needed from the initial referral, during simulation, while planning and throughout the course of treatment.

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20 Palliative Radiotherapy and Management of the Pediatric Oncology Patient

Tamara Vern-Gross and Karen Marcus

20.1 Introduction

It is estimated that there are currently over 388,500 childhood cancer survivors living in the United States alone (American Cancer Society 2014). It is estimated that 10,270 new cases will be diagnosed and 1,190 new cancer deaths will occur among children aged 0-14 in 2017 (American Cancer Society 2017). The combined 5-year survival for all childhood cancers has improved from 63% in mid-1970s to 83% today (Howlander et al. 2016). Despite triumphs and advances, approximately 17% of children diagnosed with cancer will die of their disease or treatment-related complications, making cancer the leading cause of non-accidental death in children (Howlander et al. 2016). The intent to cure often remains a priority, and children may receive aggressive treatment until the end-of-life. Extension of life may be overemphasized and promotion of comfort and support can be overlooked during the course of a child's illness (Himelstein et al. 2004). The care of children with advanced cancer requires an interdisciplinary approach; they are at risk of suffering at the end-of life because their social needs, spiritual concerns, and symptoms are not adequately addressed (Contro et al. 2002; Hechler et al. 2008; Wolfe et al. 2000a).

20.2 Palliative Care for Children with Cancer

Children and adolescents diagnosed with cancer experience significant physical and emotional suffering, impacting quality of life, and can have long term consequences on the surviving children and their families (Wolfe et al. 2000a). The diagnosis of cancer is often associated with a fear of death, disruption in life-order, and often followed by a long and demanding treatment course. The care of children diagnosed with malignancies requires a comprehensive team approach from the time of diagnosis throughout the trajectory of their disease, and addresses potential physical, psychosocial, and spiritual needs of the patient and family. Pediatric Palliative Care (PPC) has gained distinction in the care of children and adolescents facing life-limiting or life-threatening disease, and is an interdisciplinary collaboration

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of specialists who strive to find meaning, improve quality of life, minimize suffering, enhance function, and provide opportunities for spiritual, psychosocial, and personal growth (Friebert 2015). According to the World Health Organization (WHO), Pediatric Palliative Care (PPC) is "the active total care of the child's body, mind, and spirit, and also involves giving support to the family. PPC begins when "illness is diagnosed and continues regardless of whether or not a child receives treatment directed at the disease" (Fig. 20.1). It includes individualized integration of palliative care principles to manage expectations of life extension, while at the same time fulfilling goals of comfort and sustaining optimal quality of life (http://www.who.int/cancer/palliative/definition/en/) (Table 20.1). In the setting of advanced illness, when end-of-life care is necessary, more emphasize should be placed on comfort, even in the hope of a miracle. Researchers and clinicians have demonstrated that earlier integration of palliative care, systematic symptom management, and earlier end-of-life conversations facilitate improved quality of life (Liben et al. 2008; Waldman and Wolfe 2013).

20.3 The Role of Palliative Radiotherapy in Pediatric Malignancies

Palliative radiotherapy (RT) is a valuable treatment modality included within this interdisciplinary approach, and is considered for symptomatic relief of progressive or metastatic pediatric malignancies, more often than at the time of initial diagnosis. Similar to adults, children may develop a wide array of symptoms depending on tumor location and potential impact on the surrounding organs or structures involved (Table 20.2). In children at high risk of developing a fracture, cord compression, or airway obstruction, which could negatively impact function and quality of life, a more preventative approach of "preventative palliation" is often initiated. Chemotherapy and radiation have proven

Table 20.1 World Health Organization defining characteristics of palliative care

• Provides relief from pain and other distressing symptoms
• Affirms life and regards dying as a normal process
• Intends neither to hasten or postpone death
• Integrates the psychological and spiritual aspects of patient care
• Offers a support system to help patients live as actively as possible until death
• Offers a support system to help the family cope during the patient's illness and in their own bereavement
• Uses a team approach to address the needs of patients and their families, including
• bereavement counseling, if indicated
• Enhances quality of life, and may also positively influence the course of illness
• Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications (WHO 2008)

Adapted from World Health Organization (2017)

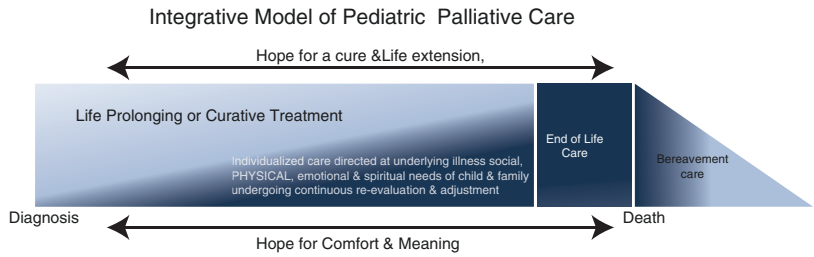

Fig. 20.1 The integrative model of pediatric palliative care. Demonstrates early integration of palliative care at the time of diagnosis, supporting curative therapies, comfort, and meaning throughout the course of the disease (*Adapted from the Institute of Medicine, World Health Organization 2017, and Liben 2008*)

Table 20.2 Indications for palliative radiotherapy

• Bone and soft tissue metastases resulting in pain from pathologic fracture, soft tissue or nerve root infiltration, or compression
• Bleeding involving the pulmonary, gastrointestinal, and genitourinary origin
• Hepatic metastases causing pain from capsular stretch
• Airway Obstruction resulting in dyspnea
• Superior Vena Cava Syndrome or Superior Mediastinal Syndrome
• Obstruction of the pulmonary, gastrointestinal, and genitourinary tracts
• Esophageal obstruction, gastric outlet obstruction
• Spinal cord compression
• Cranial nerve palsies
• Neurologic dysfunction secondary to increased intracranial pressure from brain or leptomeningeal metastases

Adapted from Vern-Gross (2013)

to be effective for the treatment of various pediatric malignancies; however, treatment is guided in order to minimize the risks of both acute and late toxicities (Holgersen et al. 1983; Kozlowski et al. 1984; Lyding et al. 1987; Oviatt et al. 1982; Ortega et al. 1991). Pediatric patients who require emergent symptomatic relief at presentation, especially when a diagnosis has not been established, may be candidates for palliative RT. However, systemic therapy would be the optimal first-line therapy, even for management of spinal cord tumors in the absence of neurologic impairment in patients who present with chemotherapy-sensitive tumors, such as neuroblastoma, Ewing's sarcoma, and lymphoma (Hayes et al. 1984).

Current numbers of children and adolescents treated with RT with palliative intent are underestimated. A subset of patients exists within a grey zone of treatment where definitive doses are delivered for symptomatic relief with an objective for durable control, even when the prospects of cure are unlikely. For example, despite being presented with a grave prognosis, patients diagnosed with diffuse infiltrative pontine glioma (DIPG) are frequently offered definitive courses of RT with the hope of symptom palliation and life prolongation.

In order to achieve the therapeutic goal, many radiobiological principles are less pertinent in the setting of palliative RT. Treatment dose will vary and decisions should be individualized depending on a child's primary diagnosis, child/family goals of care, reason for treatment, prognosis, and anesthesia requirements.

It is challenging to predict survival in children and adolescent, because some may outlive their initial prognosis. Lower treatment doses diminish acute treatment-related toxicities (e.g., radiation dermatitis, esophagitis) and fewer days of sedation for those children who require it during treatment. When long term survival after completion of palliative radiotherapy remains a possibility, (especially because of the unpredictable nature of childhood malignancies), potential implications of the long term toxicities should always be taken into consideration and discussed (Paulino 2003). Furthermore, when a radiation-induced toxicity, such a bone-marrow suppression, could hinder subsequent enrollment on a phase I clinical trial, those side effects should be considered and communicated to the involved Pediatric Oncologist. Compared to adults, research has demonstrated lower mortality rates in pediatric patients while enrolled on hospice and children were more likely than adults to dis-enroll from hospice services (Dingfield et al. 2015).

20.3.1 Differences in Palliative Radiotherapy Between Pediatric and Adult Populations

Several differences exist between adult and pediatric patients who are considered for palliative radiotherapy, including the primary cancer, prognostic implications, presenting symptoms, treatment options, and response to therapy. Oncologic emergencies, including Superior Vena Cava Syndrome (SVCS) and Spinal Cord Compression (SCC) tend to be observed earlier at diagnosis or at presentation in children and adolescents compared to adults (Ingram et al. 1990; Raffel et al. 1991). For examples, SCC in adults is often caused by metastatic lesions from primary breast,

lung, or prostate (Bruckman and Bloomer 1978; Pizzo et al. 1993). In contrast, a child may have been diagnosed with a primary sarcoma involving the spine with subsequent spinal cord involvement in approximately 43–65% of SCC (Ch'ien et al. 1982; Raffel et al. 1991). In addition, the central nervous system (CNS) tends to be more tolerant of injury in children compared to adults. Approximately 50% of children diagnosed with SCC, who present with paraplegia, become ambulatory with initiation of appropriate therapy (Klein et al. 1991; Lewis et al. 1986; Lange et al. 1993). Adults who are non-ambulatory rarely regain ambulatory function (Gilbert et al. 1978; Rodriguez and Dinapoli 1980).

When a child presents with compressive symptoms without a pathologic diagnosis, tissue diagnosis should be attempted to help guide communication, treatment, and symptom management. Because many pediatric tumors are more chemo-sensitive compared to adult tumors, which is also why palliative RT is not commonly first-line therapy in children who present with symptomatic disease at diagnosis, including those with a large mediastinal mass or spinal tumor. This further decreases treatment-related toxicities, especially in the setting of potentially curable disease.

Spinal cord compression or superior vena cava compression from an anterior mediastinal mass in a child can be the initial presenting sign of the malignancy in a child. The use of radiotherapy in such cases is not palliative but rather an attempt to treat a life-threatening problem. The oncology team must be involved as radiotherapy would be used only if absolutely necessary with carefully chosen doses.

20.4 Symptoms and Suffering in Pediatric Cancer

Children diagnosed with cancer experience substantial suffering from the time of diagnosis as they navigate through their disease course due to tumor burden, various diagnostic procedures, and treatment-related toxicities. The low incidence of cancer in children and adolescents prohibits prospective research that investigates the incidence of these symptoms, use of innovative interventions, and the optimal management strategies in order to improve quality-of-life. Symptoms and suffering should be distinguished from those that occur during cancer-directed therapy from those which occur at the end-of-life. Several studies utilize self-reported outcomes from the perspective of both children and adults, describing the prevalence, intensity, duration, and severity of a child's cancer or treatment-related symptoms, the most common ones being pain, fatigue, loss of appetite, psychological distress, and nausea (Collins et al. 2000, 2002; Hechler et al. 2008; Poder et al. 2010). Comparing perspectives of both parents and children, Dupuis et al. (2010) noted that parents found mood swings (85%), fatigue (80%), and disappointment at missing activities with friends and peers (74%) as the most bothersome and severe during treatment. Children expressed disappointment in missing activities with friends and peers (46%); were worried about receiving treatment, procedures or side effects (40%); and found symptoms such as painful, aching, stiff muscles, or joints (36%) as most disappointing (Dupuis et al. 2010).

Parent and provider perception of their children's cancer-related symptoms may depend on the child's emotional and physical developmental stage, cultural and religious values and beliefs, response to disease, and treatment-related factors. For this reason, age-appropriate communication, care, and assessment tools are necessary throughout the child's or adolescent's illness (Cohen et al. 2008; Stinson et al. 2013; Wolfe et al. 2015). Pain is one of the best studied, most prevalent and distressing symptoms; however, it is not always controlled (Collins et al. 2000, 2002; Heden et al. 2013; Poder et al. 2010). Modifying factors should be incorporated into the treatment plan in order to alleviate suffering and lessen the pain response (Fig. 20.2). Frequently, parental ratings of their children's symptoms or degree of symptom burden have been directly linked to their own post-traumatic stress symptom (PTSS) report or any previous history of post-traumatic stress disorder (PTSD) (Poder et al. 2010). In addition,

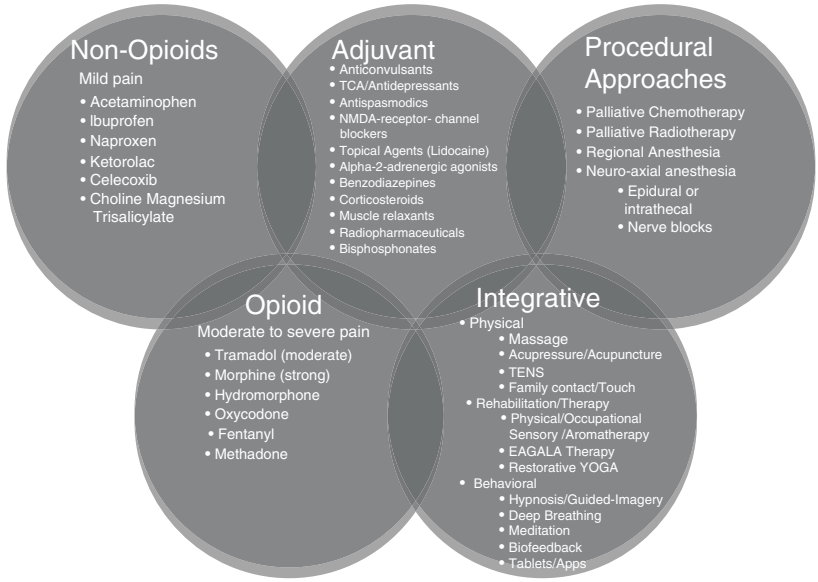

Fig. 20.2 Pain modifiers. *TCA* tricyclic antidepressants, *TENS* transcutaneous electrical nerve stimulation, *NMDA* N-methyl-D-aspartate receptor-channel blockers, *EAGALA* Equestrian Assisted Growth and Learning Association

parents of adolescents tend to report a greater symptom burden for their adolescent compared to parents of the youngest children (Poder et al. 2010). This suggests a distinction in expression between developmental stages rather than actual symptom burden; a better understanding of the relationship between age and symptom burden is warranted through innovative and validated tools. Incorporation of innovative technologies, including web and digital applications to prospective data collection, symptom incidence, and identifying improvement of symptom management in pediatric malignancies is warranted (Bleyer 2007; Cohen et al. 2008; Poder et al. 2010; Stinson et al. 2013).

Symptom management continues to be a major challenge at the end-of-life. At Boston Children's Hospital and the Dana Farber Cancer Institute, of 103 parents whose children died of cancer, a survey of symptom management perception at the end-of-life demonstrated that 89% of the children experienced substantial suffering from at least one symptom, with fatigue, pain, and dyspnea as most common. Parents perceived attempts to control symptoms as unsuccessful, with only 27% expressing relief (Wolfe et al. 2000a). A recent series evaluated symptoms at end-of-life in 57 children diagnosed with advanced solid tumor malignancies, and identified pain (100%), nausea/vomiting (63%), constipation (57%), and anxiety (56%) as the most common (Vern-Gross et al. 2015). Fifty-one patients (94%) suffered from three or more symptoms, whereas 41 (76%) suffered from five or more at the end-of life (Vern-Gross et al. 2015). Insight from bereaved parents has demonstrated that psychological symptoms, such as anxiety and distress are rarely effectively treated (Hechler et al. 2008). Providers are encouraged to implement a comprehensive approach when supporting children and families who are affected by the physical and emotional symptomatic burden of disease. This finding requires that the physicians and staff should provide information on expected treatment-related toxicities, interventional considerations, and other sources of concern.

20.5 Communication

Effective and compassionate communication with the patient and family diagnosed with a pediatric malignancy is critical, beginning with the first interaction. Although radiation oncologists may

feel reserved in the scope of their conversation, especially in the setting of being the referral physician, it remains critical to identify a patient's and/or family's goals of care, concerns, understanding of the child's illness, impact on quality of life, risk/benefit, and limitations of the treatment that you are recommending. Research has demonstrated that although the first conversation is often remembered, approximately one half of those involved recollect noteworthy information, with the exception of diagnosis or milestones in the illness such as recurrent or progressive disease (Bona et al. 2011; Knapp et al. 2012). This communication includes prognostication, which evolves throughout the course of the child's illness; revisiting conversations multiple times is necessary to build rapport, identify areas of needs and support, opportunities for education, and to provide high-quality care (Table 20.3). Identifying the patient's and family's understanding of the diagnosis, indication for RT, and preparing the child and family members for the treatment planning process will provide them with comfort and control within their personal context and environment. Access to educational resources, including video, interactive applications, demonstrations, or games, should be available for education and guidance. Specific to radiation planning, the specific needs of a child should always be addressed based on age, anesthesia requirements, and symptom management in order to minimize movement, enhance compliance, safety, and optimize patient experience. This includes utilization of appropriate support services, including child-life therapy, social work, interpreter services, and additional resources in order to ensure accurate transfer of information and address the needs of the patient and family, especially in a socioeconomically, culturally, and developmentally diverse population.

20.5.1 Prognostication

Because no one can predict future disease and treatment progression, patients and parents value and appreciate clinical skill and caring communication when discussing prognostic information. In a time of uncertainty, most parents wish to be well informed about their child's diagnosis, the acute and long-term consequences and complications associated with treatment, chances of cure, and the potential impact on quality of life and future (Boman et al. 2003; Kilicarslan-Toruner and Akgun-Citak 2013; Mack et al. 2006; Ringner et al. 2011; Trask et al. 2009). Parents' perception of their child's disease and chance of cure depend on their understanding of the disease process and the effectiveness of communication by the primary care team (Lamont and Christakis 2003; Mack et al. 2007; Mulhern et al. 1981; Weeks et al. 1998; Wolfe et al. 2000b). Parents tend to be overly optimistic about cure when the physician lacks confidence about his or her knowledge of likelihood of cure (Mack et al. 2007). This can ultimately impact decisions pertaining to medical care and quality of life (Lamont and Christakis 2003, Mack et al. 2007, Mulhern et al. 1981, Weeks et al. 1998, Wolfe et al. 2000b). The quality of prognostic information is often considered high quality when communication is effective as noted in a study from Boston Children's Hospital and Dana Farber Cancer Institute (Kaye and Pauly 2013).

Doctor-patient communication has been identified as the primary determinant of delivery of high-quality care (Mack et al. 2005). Parents often prefer to pursue cancer-directed therapy (surgery, chemotherapy, biologic agents, radiotherapy, clinical trials) rather than pursuing more palliative treatments for their children, even when given the diagnosis of an incurable malignancy (Mack et al. 2008). Cancer-directed therapy is often continued with the goal of life extension or symptom palliation (Hinds et al. 1997; Slevin et al. 1990). Boston Children's Hospital/Dana-Farber Cancer Institute and Children's Hospitals and Clinics of Minneapolis reported on the perspectives of bereaved parents of 135 children who pursued cancer-directed therapy, even though there was no real expectation of cure (Mack et al. 2008). Only 38% of parents recommended opting for standard chemotherapy in the setting of incurable disease, 61% felt their child experienced at least some suffering from cancer-directed therapy and 57% felt their child received

Table 20.3 Approaching goals of care conversations in children and caregivers when faced with advanced malignancies

Time interval	Goal of conversation	Examples of conversations
Diagnosis	• Connect with the patient and family with an honest, open, and clear conversation • Ask the family what their understanding of their child's illness is	**Discussion with the children** • "Can you tell me how this experience has been for you so far?" "What is your understanding of your child's disease at this point?" "What do you understand about the treatment options available?" **Discussion with the children** • "Can you tell me how this time has been for you so far, going to doctor appointments? Do you know why you are going to the doctor and what's going on with your body?" "What do you understand about the treatment to get rid of the disease for you?" • "What do you want to know about the disease for me to tell you?" • "Do you want me to talk more about your illness and how to get rid of it with your parents?" • "Are there things that you would like to talk with me by yourself?" • "How do you feel about my talking with your parents without you present?"
Goals of care	• Once prognostic information is communicated with patient and family, establishing goals of care is essential • Focus on open-ended questions	**Discussion with the caregiver** • "As we think about your child's illness, what are your hopes? • "What are your greatest worries" • "What keeps you up at night?" • "What are your greatest concerns about your child's illness?" **Discussion with the children** • "What do you like to do the most? What do you miss since you've been in the hospital?...or since you started treatment?" • "Is there anything that worries you or makes you feel afraid?"
Initiation of treatment	• Discuss the possibility cure is unlikely • Introduce Advanced Care Planning (ACP) • Important to include adolescents and young adults in these conversations • This is the time to encourage conversations between the child and parent	**Discussion with the adolescent/young adult** • "Although we are hopeful that your treatment will be successful, we have learned from other families that it is also important to think about some difficult issues early on. For example, if you became very ill or had a complication from a medical procedure, who would you designate to make medical decisions for you?" **Discussion with both children and caregiver** • "If you have strong religious or cultural beliefs about your medical care, pain management or interventions such as life support, that is always helpful to let us know so that we can honor your wishes and be supportive as we begin to work together throughout treatment"

(continued)

Table 20.3 (continued)

Time interval	Goal of conversation	Examples of conversations
Recurrence or disease progression	• This discussion may require multiple conversations; exploring goals of care, teaching parents how to talk to their child, and respond appropriately to their questions	**Discussion with the parent** • "I am hopeful that we will be able to control the disease, but I worry that we will not be successful this time" **Discussion with the children** • "Recently, there have been new things happening with your illness. Would you like me to talk to you about those changes?" • "Are there things you would rather we talk to your parents about first, or would you like to meet with me by yourself first?" • "Do you remember our talk before, as to what we should think about if the treatments do not work as well as we had hoped? Although you have several other ways available to get rid of the disease, I want to make sure we are doing what you want and what is most important to you. Have you had any of these talks with your family members or friends? Can you tell me a little more about what is most important to you?"
Refractory disease to therapy	• Determine from patient or parent how aggressive they would want to be treated if cure would not be possible • Address family dynamics, concerns, and communication	**Discussion with the caregiver** • "Although I am hopeful that your child improves, very rarely have I seen children just like you improve unexpectedly, even if we start cancer-directed therapy for controlling the disease" **Discussion with adolescent/young adult** • "We are at a place where cure, or getting rid of the disease is no longer possible" • "If we didn't do anything now, you are at continued risk for, e.g., disease progression, spinal cord compression, etc.). How would you like us to continue? Would you like to receive palliative radiotherapy in order to prevent or get rid of your symptoms, in order to help you feel better, and let you to continue to do the things that you do day to day?" • "It is important to keep in mind that there is no right or wrong decision here"

(continued)

Table 20.3 (continued)

Time interval	Goal of conversation	Examples of conversations
End-of-life	• For children, they begin to understand death as concrete, real and permanent. Although it may be viewed as a feared event, help support the child's need for control • For adolescents, death may be viewed as a failure, or as giving up. A teenager or young adult needs a sounding board for his or her emotions	**Discussion with the caregiver** • "Although I hope that we can control your child's disease as long as possible, I am hopeful that she or he can feel as good as possible each day" **Discussion with the child and adolescent** • "We will all work closely with you to make sure you are comfortable. It is very important that you let us know how you are feeling and if you need anything. We will be with you so that you do not feel afraid" • "I can only try to imagine how you must be feeling. It is important for you to know, that despite all of this, that you are doing an amazing job working with us to get rid of the disease and the problems it is causing. I'd like to hear more about what worries you the most, and what you are hoping for"

Adapted from Wiener et al. (2013), Mack et al. (2011), Davies (2001), Block 2001, and Hurwitz et al. (2004)

no benefit despite initial goals of therapy. Providing clear information about what to expect during the end-of-life period, communicating with sensitivity, speaking directly with the child, and preparing the parents for potential scenarios surrounding a child's death were associated with high quality care (Mack et al. 2005).

Once prognostic information is conveyed, the focus of care should be transitioned to identifying the various goals of care unique to the child and family. Involving children in conversations and decision making can be challenging depending on several factors: parental preference (Young et al. 2011); the comfort level of the provider, and variability of developmental stages between age groups which requires different language and understanding (Himelstein et al. 2004; Wiener et al. 2013). By age 14 years, many children have an adult-level understanding of their condition. Studies have demonstrated that children by the age of 3 years have awareness of their prognosis (Bluebond-Lagner 1978; Hinds et al. 2005). On the part of the physician or staff, there is often a desire to protect the patient and the family by not stripping away hope, especially in the face of disease progression (De Vries et al. 2010; Kreicbergs et al. 2004). Clinicians and healthcare providers should encourage open and honest conversations in most encounters.

Opportunities for improved communication and confidence when facilitating discussions are enhanced by prior physician awareness of parental concerns. Helpful guidelines when communicating prognostic information at the time of diagnosis and during the course of a child's illness includes: identify goals of care, ask parents what they understand and what they would like to know, inquire what a child or parents' greatest concern(s) are, offer information that is clear, reassess their understanding, respond to emotion, and be present during the conversation (Baile et al. 2000; Garwick et al. 1995; Makoul 2003; Masera et al. 1997).

20.5.2 Identifying the Goals of Care

Access to clinical trials and better salvage therapies have allowed children with advanced malignancies to survive longer, increasing the risks of treatment-related toxicities. Palliative RT may be introduced at various intervals throughout the child's illness as an adjunct to relieve suffering, improve function and quality of life. Because each patient and family has unique experiences, values, and preferences, the decision to pursue treatment is often a thoughtful process, individualized to their needs, beliefs, and goals of care (Hinds et al. 1997; Kane and Hilden 2007). Not establishing rapport and observing the needs of the child and family places the treating team at risk of mistrust and suboptimal care for the patient and family. Identifying goals of care for both the child and/or parents will provide a guide in the decision-making process, identify necessary supports, and optimize outcomes (Table 20.4). In her book, The Private Worlds of Dying Children, the anthropologist, Myra Bluebond-Langner recommended that in talking with children: "Tell them only what they want to know, what they are asking about, and on their own terms." It is also sometimes helpful to begin the conversation by asking the child and family what they are asking about to better understand how to respond (Bluebond-Lagner 1978).

20.5.3 Advanced Care Discussions

Historically, advanced care discussions (ACD) often occur late in the course of the child's illness; end-of-life decisions such as resuscitation orders, and preferences for place of death are made near the time of death (Baker et al. 2010; Vern-Gross et al. 2015; Widger et al. 2007). A survey evaluating clinician perception of barriers to ACD among 107 physician and 159 nurses indicated that unrealistic parental expectations, differences between clinician and patient/parent understanding of prognosis, and lack of parent readiness to have the discussion were the most common barriers (Durall et al. 2012). Nurses identified lack of importance to hold ACD and various technical considerations as hindrances; physicians considered insecurity in not knowing what to say to the patient and family as a greater obstacle (Durall et al. 2012). A majority of providers (71%) agreed that ACDs occurred too late in the patient's clinical course (Durall et al. 2012).

Within a country that is diverse with multiple ethnicities, cultures, and religions, appropriate baseline knowledge and multilingual interpreters are essential to communicate with patients and families. This will help avoid some of the reported barriers to treatment, improve communication at end-of-life, strengthen patient-physician rapport, and eliminate cultural misunderstandings (Periyakoil et al. 2015).

Table 20.4 Identifying goals of care

• Who is your child (as a person)?
• What is your understanding of your child's illness? What does the illness mean to you and your family?
• In light of your understanding, what is most important regarding your child's care?
• What are your hopes for your child? What are your fears regarding your child? What are your greatest concerns?
• Where do you find support and strength?

Adapted from Waldman and Wolfe (2013)

20.6 Clinical Indications for Pediatric Palliative Radiotherapy

The prognosis of children suffering from metastatic disease remains guarded, and palliative interventions are both underutilized and limited (Little 1999). Depending on the primary malignancy, palliative RT may tackle oncologic emergencies or assist in improving quality of life. Radiation planning should always be addressed based on the specific needs of a child (age, anesthesia requirements, and symptom management) in order to minimize movement, enhance compliance, safety, and optimize patient experience.

Although most of the radiotherapeutic techniques are often extrapolated from adult series, select literature including a limited number of

single-institution published series have demonstrated the effectiveness of palliative RT for symptomatic bone and soft-tissue, mediastinal, brain, and liver sites in pediatric patients. The University of Pennsylvania published one of the largest pediatric series, including 104 children referred for urgent palliative intervention (Bertsch et al. 1998). Forty-five of the treated problems treated resulted in a primary cancer diagnosis, while the remaining 70 were relapses of previously established disease (Bertsch et al. 1998). Overall treatment doses ranged from 1.5 to 4.0 Gy per fraction and treated to total doses that ranged from 3.0 to 55.8 Gy; treatment of hematologic malignancies ranged to total doses of 2.2–22.5 Gy (Bertsch et al. 1998). Treatment outcomes are described in Table 20.5.

20.6.1 Superior Vena Cava Syndrome and Superior Mediastinal Syndrome

Superior Vena Cava Syndrome (SVCS) is a rare clinical diagnosis which describes a mediastinal mass causing major vessel or airway compromise, presenting in approximately 12% of children and adolescents diagnosed with mediastinal tumors (Arya et al. 2002; King et al. 1982). Because of their more compressible trachea, children are at increased risk of developing "superior mediastinal syndrome" (SMS) (Ferrari and Bedford 1990; Loeffler et al. 1986). Presenting symptoms include tracheal edema, chest pain, cough, hoarseness, headache, respiratory difficulty, swelling of the face, neck, arms, and hands, or dizziness (Ferrari and Bedford 1990). Although Non-Hodgkin's Lymphoma (NHL) is the leading cause in children, it only comprises 6% of primary diagnoses in this population (Rheingold and Lange 2002). NHL and T-Cell acute lymphoblastic leukemia are the most common causes of SVCS in pediatrics, unlike lung cancer which is most common cause in adults (D'angio et al. 1965). This distinction is critical; the vast majority of children presenting with SCVS have lymphoma or leukemia which is curable and sensitive to systemic therapy. The diagnosis can be made from pleural fluid if effusion is present or peripheral blood in the case of leukemia. The use of radiotherapy in this setting in children has diminished and should not be considered palliative in the case of a new diagnosis.

Obtaining a tissue diagnosis is critical when a child presents with SVCS or SMS, since an anterior mediastinal mass could be a benign or malignant process, requiring different treatment courses. Because of the risk for respiratory compromise in these patients, attempts should be made to obtain a biopsy when a tissue diagnosis cannot be established because of anesthesia risk, absence of peripheral lymphadenopathy, or lack of marrow involvement, systemic chemotherapy is often attempted as an initial therapy to stabilize the mass and resolve any clinical compromise. The initiation of systemic chemotherapy often results in accurate treatment of the primary disease (Kumari et al. 2006). Pre-biopsy radiation therapy may impede the ability of obtaining an accurate diagnosis (Loeffler et al. 1986).

A St. Jude Children's Research Hospital study reported 24 children who presented with SVCS; NHL was the most frequent malignancy followed by Acute Lymphoblastic Leukemia (ALL), Hodgkin's disease (HD), neuroblastoma and yolk sac tumor (Ingram et al. 1990). Eight patients developed SVCS late during their treatment course: five patients presented with recurrences of their initial mass (Ingram et al. 1990). Of these patients, three developed a thrombus secondary to treatment-associated factors and/or tumor hypercoagulable state. Median time to development of SVCS from initial diagnosis with recurrent solid tumors was 10 months (range, 2–15 months); median survival time was 92 months (range 5–164 months) (Ingram et al. 1990). Regardless of aggressive salvage therapies in patients with recurrent disease, survival was significantly decreased and ranged from 2 to 20 weeks (Ingram et al. 1990).

Radiotherapy can play a valuable role in dyspnea secondary to malignant chest disease causing obstruction of the major airways or vessels, especially in the setting of relapsed disease refractory to systemic therapies. Although data is limited and often extrapolated from

Table 20.5 Patterns of pediatric palliative radiotherapy

Author	No. of patients and sites	Pathology	Most common symptoms at presentation	Radiation dose	Treatment outcomes
Bertsch et al. (1998)	*104 patients* *115 sites*	**Group I-SCC** **(N = 33)** PNET (10), Ewing (4), rhabdomyosarcoma (3), leukemia (3), lymphoma (2), Wilm's (2), astrocytoma (2), MFH (1), LCH (1), ependymoma (1), osteogenic sarcoma (2)	**Group I** Weakness or paralysis (n = 20) Severe pain (n = 13) Bowel/bladder dysfunctions (n = 4)	**Solid tumors:** 1.5–4 Gy fx to a total dose 3–55.8 Gy	**Group I** 85% response rate −55% improvement of symptoms −30% stabilization of symptoms
		Group II-Respiratory (N = 37) Neuroblastoma (6), Wilm's (4), NHL (3), ALL (1), Ewing (1), rhabdomyosarcoma (1), endodermal sinus tumor (1), hemangioma (1)	**Group II** Thoracic disease causing respiratory difficulty (n = 14) Abdominal tumor causing respiratory compromise (n = 5)	**Leukemia/lymphoma** 1.5–4 Gy fx to a total dose 2.2–22.5 Gy	**Group II** 72% response rate
		Group III-Abdominal (N = 8) Neuroblastoma (5); ALL (2); nasopharynx (1)	**Group III** Renal dysfunction (n = 1), inferior vena cava compression from hepatomegaly (n = 1) gastrointestinal obstruction (n = 1) extra splenomegaly (n = 1) pain from peritoneal seeding (n = 1) ureteral obstruction		**Group III** 66% response rate
		Group IV-Intracranial **(N = 16)** Glioma (6); PNET (4), leukemia (2), craniopharyngioma (1), germinoma (1), nasopharynx (1), neuroblastoma (1)	**Group IV** Cranial nerve palsies (n = 10) Respiratory failure/obtunded (n = 5)		**Group IV** 63% response rate 19% stable disease
		Group V = Pain **(N = 15)** Neuroblastoma (7), sarcoma (3), hemangioma (1), nasopharynx (1), retinoblastoma (1), leukemia (1), lymphoma (1)	**Group V** Pain from bone (n = 10) Pain from lymph nodes (n = 4)		**Group V** 93% response rate (Complete and partial)

Abbreviations: *SCC* spinal cord compression, *No* number, *fx* fraction, *Gy* gray, *LCH* langerhans cell histiocytosis, *MFH* malignant fibrous histiocytoma, *NHL* non Hodgkin lymphoma, *ALL* acute lymphoblastic leukemia

adult literature, SVCS and SMS can be addressed with standard fractionation or hypofractionated 3D conformal radiotherapy regimen. In cases of refractory malignancy causing SVCS, a balance between shorter treatment times and fewer fractions in order to decrease acute treatment-related toxicities and anesthesia time will enable the child and family to achieve their goals of care.

20.6.2 Bone and Soft Tissue Metastases

Bone and soft tissue metastases often result in pain as a result of obstruction, infiltration, and discomfort, resulting in discomfort and pain from inflammation, ischemia, and destruction of surround normal tissue (Foley 1987, 2004). Palliative RT in is effective in alleviating associated symptoms of pain by reducing the size of the progressive tumor or metastatic invasive lesion progression. Shorter fractionation schemes are favored of 1–5 fractions for convenience of the child and family. Single fraction treatments of 800 cGy × 1 fraction are especially valuable when treating a child who requires anesthesia for immobilization or pain management and treatment comfort. The few or lack of treatment-related toxicities, including radiation dermatitis, is also favorable because of the goal of minimizing adverse outcomes on quality of life.

Symptomatic relief from prior palliative RT usually indicates radiotherapy treatment as an option should the need arise, in order to address intractable pain from metastatic or progressive disease (Grier et al. 2003). The benefits of palliative RT have been demonstrated in Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and osteosarcoma (Koontz et al. 2006; Bertsch et al. 1998; Deutsch and Tersak 2004; Paulino 2003) (Table 20.6). Utilization of age-appropriate assessment tools and baseline parental assessments are key when evaluating these patients; an older child may express discomfort, pain, and dissatisfaction, but a younger child may guard, become reserved, and withdraw from active play (Cohen et al. 2008). An optimal fractionation scheme is yet to be established in the pediatric population, and most data continues to be reported from single institutions. Currently, most pediatric radiation oncologists extrapolate from the adult literature, and notable studies including the Dutch Bone Metastasis Study, The Bone Pain Trial Working Party Study, and the Radiation Therapy and Oncology Group have inspired current palliative RT practiced in the pediatric populations (Hartsell et al. 2005; Steenland et al. 1999; Bone Pain Trial Working Party 1999). The University of Pittsburgh authors reported outcomes in children who received palliative RT for symptomatic bone metastases from non-hematologic primary tumors (Deutsch and Tersak 2004). The most common fractionation schedule was a single dose of 300–1000 cGy (43 courses), followed by 2 and 5 fractions (22 and 23 courses, respectively) (Deutsch and Tersak 2004). Younger children were more likely to receive shorter treatment courses if immobilization was challenging, they had discomfort maintaining daily visits, or were demonstrating disease progression and rapid clinical decline (Deutsch and Tersak 2004). Children with predicted survival outcomes of several months were treated to schedules of 10 fractions (Table 20.6).

Bone and soft tissue metastases are traditionally treated utilizing 3D conformal radiotherapy. For widely metastatic disease involving multiple painful sites, sequential hemibody irradiation has been effective, although no longer favored in the pediatric population (Jenkin and Berry 1983). More common and innovative techniques include intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT) (Brown et al. 2014), stereotactic radiosurgery (SRS) (Nanda et al. 2014), radiofrequency ablation (RFA) (Botsa et al. 2014), and radioisotopes (Anderson et al. 2002). Because of the variability in patient preference, tumor location, treatment response, and previous radiotherapy, advanced techniques and approaches continue to be developed and utilized in order to address painful bone and soft tissue metastases.

Table 20.6 Pediatric palliative radiotherapy for bone and soft tissue metastases

Author	No. of patients and sites	Pathology	Most common symptoms at presentation	Radiation dose	Treatment outcomes
Caussa (2011)	*34 patients*	**Neuroblastoma**	**Group I-Soft tissue** (N = 10)	**Group I** Median 20 Gy (range 8–36 Gy in 8–20 fx)	**Group I** Response rate—84.5% • ≥ 15 Gy-RR 100% • < 15 Gy-RR 57%
			Group II-Bone (N = 38)	**Group II** Median 16.5 Gy (range 6–40 Gy in 2–20 fx)	**Group II** Response rate—63.2% • ≥ 20 Gy-RR 81.2% • < 20 Gy-RR 50%
			Group III-CNS (N = 9)	**Group III** Median 15 Gy (range, 1.6–36 Gy in 1–17 fx)	**Group III** Response rate—44%
			Group IV-Liver (N = 3)	**Group IV** Median 5 Gy (range, 1.5–9 Gy in 3 fx)	**Group IV** Response rate—N/A
Deutsch and Tersak 2004	*37 patients*	Neuroblastoma (18) Ewing (5) Osteosarcoma (5) (SCC) of the lung (2) Wilm's tumor (1) Retinoblastoma (1) Medulloblastoma (1) Angiosarcoma (1) Rectal adenocarcinoma (1) Nasopharyngeal (1) Esthesioneuroblastoma (1)	**Bone** • Skull (40.5%) • Spine (43.2%) • Hip/femurs (43.2%) • Humerus/shoulder (32.4%) • Pelvis (29.7%)	**130 Courses:** 3–10 Gy × 2–5 fx **43 Courses:** 3–10 Gy × 1 fx	**Overall response** 93% pain relief (55/59 evaluable courses) **MS**: 1–52 Months 22 pt (29%) >12 months 3 pt (8.1%) >2 years

Author	No. of patients and sites	Pathology	Most common symptoms at presentation	Radiation dose	Treatment outcomes
Koontz (2006)	*21 patients* *63 sites*	**Ewing sarcoma**	**Group I-Primary site** (N = 21) **Bone** • Chestwall/sternum/ribs (2) • Femur/tibia/fibula/knee (6) • Shoulder/scapula/clavicle (4) • Humerus (2) • Pelvis/hips (4) **Soft Tissue** • Lung (1) • Eye (1) • Axillary lymph node (1)	**Group I-Primary site:** N/A	**Overall response-(84%)** • 35 sites (55%)—CR • 18 sites (29%)—PR • 9 sites (14%)—NR **Median overall treatment response:** • 81 days (range 0–1760 days) **Median portion of remaining lifespan spent in palliative treatment after diagnosis of metastases:** • 10% (range 0.5–25) months, days?
			Group II-Metastatic sites (N = 63) **Bone** • Chestwall/sternum/ribs (6) • Femur/tibia/fibula/knee (7) • Shoulder/scapula/clavicle (2) • Humerus (5) • Pelvis/hips (10) • Spine (11) • Orbit (1) • Hemibody (2) **Soft Tissue** • Lung (8) • Brain (5) • Parotid (1) • Cervical lymph node (3)	**Group II-Metastatic sites:** 30 Gy (range 4.5–68.5 Gy)	**Group II-Bone** Complete response 7 sites (11%) Partial response 5 sites (8%) No response 3 sites (5%) **Group II-Soft Tissue** Complete response 28 sites (44%) Partial response 13 sites (21%) No response 7 sites (11%) **MS after diagnosis of metastases:** • 1 year after metastatic diagnosis (range 17 days to 6.8 years)

(continued)

Table 20.6 (continued)

Author	No. of patients and sites	Pathology	Most common symptoms at presentation	Radiation dose	Treatment outcomes
Paulino (2003)	*29 patients* *53 sites*	**Neuroblastoma**	**Group I-Soft tissue** (N = 26)	**Group I** Median 2000 cGy	**MS following palliative RT** • 2.5 months **Duration of response until death** • 90–93% **Group I** • CR-1 (4%) • PR-19 (73%)
			Group II-Bone (N = 19)	**Group II** Median 2000 cGy	**Group II** • CR-8 (42%) • PR-7 (37%)
			Group III-Brain (N = 5)	**Group III** Median 2400 cGy	**Group III** • Neurologic improvement—4 (80%)
			Group IV-Liver (N = 3)	**Group IV** Median 450 cGy	**Group IV** • Respiratory improvement—2 (66%)

CR complete response, *PR* partial response, *NR* no response, *RR* response rate, *NHL* non-Hodgkin lymphoma, *SCC* squamous cell carcinoma, *ALL* acute lymphoblastic leukemia, *DOD* dead of disease, *F/U* follow-up, *CTX* chemotherapy, *RT* radiotherapy, *VCR* vincristine, *N/A* not available, *MS* median survival

20.6.3 Spinal Cord Compression

Although uncommon in children, spinal cord compression (SCC) is the most frequent cause of symptomatic spinal cord disease in children diagnosed with childhood malignancies (Baten and Vannucci 1977). Common causes of pediatric SCC have included primitive neuroectodermal tumors (PNET), Ewing's sarcoma, soft tissue sarcoma, and neuroblastoma (Pollono et al. 2003). Children may present with motor or sensory deficits, back or radicular pain, gait abnormalities, or sphincter dysfunction. While SCC often presents towards the end-of-life, it may also be a presenting symptom at initial diagnosis (Punt et al. 1980). A tissue diagnosis is essential to identify the primary disease, so that the child benefits from more definitive treatment. Such cases are not palliative and strategic management must involve a multidisciplinary approach based on histologic diagnosis, extent of neurologic deficit, and prognosis. It and may entail: a decompressive laminectomy, radiotherapy, and/or chemotherapy (Fig. 20.3). Palliative radiotherapy in cases of relapsed or refractory disease has been used alone and as an adjunct to surgery in order to alleviate symptoms, restore, and maintain function (Baten and Vannucci 1977; Gupta et al. 2009; Pollono et al. 2003; Punt et al. 1980; Shyn et al. 1986; De Bernardi et al. 2001) (Table 20.7).

Neurosurgical consultation is critical in the interdisciplinary approach of spinal disease, especially to obtain a tissue diagnosis in new presentations in order to guide management of care and to restore any neurologic deficits (Tachdjian and Matson 1965). Although a laminectomy may be appropriate in certain clinical scenarios when neurologic function is compromised, surgical intervention is often reserved for children with a poor response to chemotherapy and RT (Fabian et al. 1994). Children with a positive response to chemotherapy and/or RT should delay surgery until a relapse or further progression or neurologic symptoms develop. A laminectomy or additional surgical interventions may be appropriate in situations of neurologic compromise, and often reserved for children with a poor response to chemotherapy or RT. Children who present with significant motor impairment continue to be at risk for significant neurologic impairment, regardless of the initial intervention (Hayes et al. 1984; Simon et al. 2012).

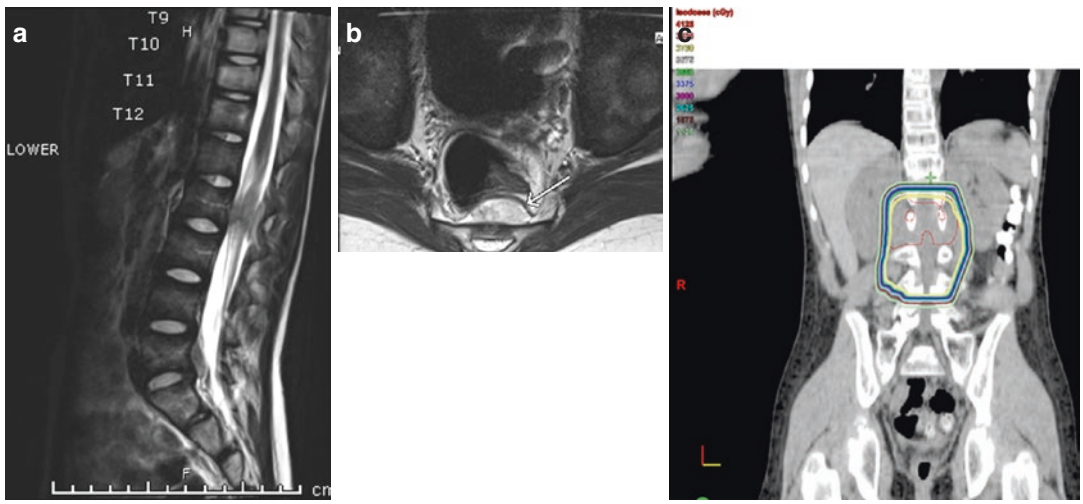

Fig. 20.3 Spinal cord compression. Eight year old child with relapse of alveolar rhabdomyosarcoma (**a**, **b**); she received salvage chemotherapy and conformal radiotherapy (**c**). Conformal radiotherapy was administered to a total dose of 37.5 Gy at 2.5 Gy per daily fraction. She is doing well on salvage chemotherapy without progression 12 months after completion of therapy

Table 20.7 Pediatric palliative radiotherapy for spinal cord compression

Author	No. of patients and pathology	Presenting symptom	Sites treated	Treatment received	Radiation dose	Treatment outcome
De Bernardi et al. (2001)	**N = 76**	**All presented with motor deficits:** Grade 1 in 43 (57%) Grade 2 in 22 (29%) Grade 3 in 10 (13%) **Back and radicular pain** (N = 47) **Sphincteric deficit** (N = 30) **Sensory deficit** (N = 11)	**Thoracic** (N = 34) **Lumbar** (N = 17) **Thoracolumbar** (N = 14) **Other** (N = 11)	**Decompressive SX-most common SX** (N = 32) **Initial RT** (N = 11) • Resectable (N = 2) • Unresectable (N = 9) **CTX** (N = 33)	N/A	**Symptom outcome** • 33-full neurologic recovery • 14 improved • 22 stabilized • 8 worsened (none with severe motor deficit recovered or improved Patients required additional therapy for SCC • 26 of 32 treated with SX • 11 of 11 treated with RT • Only 2 of 33 treated with CTX Patients treated with RT or SX usually required additional therapy **Disease outcome** • Median f/u 139 months (range 4–209 months) • Overall Survival at 5 years was 70% ±5.3

Author	No. of patients and pathology	Presenting symptom	Sites treated	Treatment received	Radiation dose	Treatment outcome
Isome (2011), Mostafavi (2000), Pui (1985), Kataoka (1995), Buyukavci (2003), and Iqbal (2003)	**N = 10** Leukemia	**Back and radicular pain** (N = 4) **Bowel/bladder dysfunction** (N = 5) **Sensory deficit** (N = 9) **Restricted breathing** (N = 1)	**Cervicothoracic** (N = 1) **Thoracic** (N = 6) **Thoracolumbar** (N = 1) **Lumbar** (N = 1) **Cervicothoracic** (N = 1) **Thoracic** (N = 6) **Thoracolumbar** **(N = 1)** **Lumbar** (N = 1) **Thoracolumbosacral** (N = 1)	**CTX/SX/RT** (N = 2) **CTX/RT** (N = 5) **CTX/SX** (N = 1) **CTX Alone** (N = 2)	Median RT dose 10 Gy (Range 3–25 Gy)	**Symptom outcome** • CR (N = 3) • Data N/A (N = 7) **Disease outcomes** • CCR (N = 5) • DOD (N = 3) • Data N/A (N = 2)

(continued)

Table 20.7 (continued)

Author	No. of patients and pathology	Presenting symptom	Sites treated	Treatment received	Radiation dose	Treatment outcome
Pollono (2003)	**N = 70** PNET (N = 18) STS (N = 17) NBL (N = 10) GCT (N = 5) LCH (N = 5) ES (N = 5) OS (N = 3) RTB (N = 2) HL (N = 2) NFB (N = 1) Ad Ca (N = 1) Hm (N = 1)	**Motor dysfunction** (N = 66) **Back or radicular pain** (N = 66) **Sensitive alteration** (N = 39) **Sphincter dysfunction** (N = 6) **Asymptomatic** (N = 2)	**Dorsal** (N = 30) **Cervical** (N = 12) **Lumbosacral** (N = 30)	**Group A (paraplegia)** (N = 35 **21/35-SX** 16/21-CTX 8/21-RT 12/21-Improved **14/35-No SX** 13/14-CTX 8/14-RT 2/14-Improved **Group B (Paresis)** (N = 35) **12/35-SX** 10/12-CTX 8/12-RT 12/12-improved **23/35-No SX** 21/23-CTX 16/23-RT 20/23-improved	600 rads Langerhans 2400 rads STS, GCT, MCNST	**Group A** **SX (N = 21)** • Improved 12 (57%) • Survived 2 (38%) **No SX (N = 14)** • Improved 2 (14%) • Survived 5 (36%) **Group B** **SX (N = 12)** • Improved 12 (100%) • Survived 11 (97%) **No SX (N = 23)** • Improved 20 (87%) • Survived 9 (39%)

Grade 1 mild hyposthenia with walking disability for legs or difficulty in raising hands above head for arms, *Grade 2* moderate hyposthenia with walking disability for legs or difficulty in raising hands above hands above head for arms, *Grade 3* severe hyposthenia with paraplegia, no elicitable tendon reflexes or muscular movements, *STS* soft tissue sarcoma, *GCT* germ cell tumor, *MCNS* metastatic central nervous system tumor, *PNET* primitive neuroectodermal tumor, *CNS* central nervous system, *NFB* nephroblastoma, *HL* Hodgkin lymphoma, *NBL* neuroblastoma, *LCH* langerhans cell histiocytosis, *OS* osteosarcoma, *RTB* retinoblastoma, *ES* Ewing sarcoma, *Ad Ca* adrenal carcinoma, *Hm* hemangioendothelioma, *CTX* chemotherapy, *SX* surgery (laminectomy), *RT* radiotherapy, *CR* complete response, *CCR* continuous complete remission, *DOD* dead of disease, *N/A* not available, *f/u* follow-up

20.6.4 Brain Metastases

The incidence of brain metastases in children and adolescence is much lower compared to adults, reported at approximately 1.5–2.5% in children diagnosed with solid tumors (Allen 1990; Deutsch et al. 1982, 2002; Suki et al. 2014; Vannucci and Baten 1974; Bouffet et al. 1997). Soft tissue sarcoma, melanoma, osteosarcoma, neuroblastoma, Ewing sarcoma, Wilms tumor, germ cell tumor, and retinoblastoma are some of the most common primary tumors with metastatic potential (Suki et al. 2014; Graus et al. 1983; Macrae et al. 2002) (Fig. 20.4). Considering age, systemic disease burden, tumor histology, and potential of long term survival, a more prolonged treatment course of 30–36 Gy in 1.5–2.5 Gy fractions would be acceptable. Although the literature is limited, incorporation of techniques, including stereotactic radiosurgery (SRS) may be a reasonable option for circumstances that require palliation of symptoms, gain of tumor control, and minimization of tissue toxicity, especially in the setting of previously irradiated tissue areas (Keshavarzi et al. 2009; King et al. 2014; Suki et al. 2014) (Fig. 20.5). Non-invasive techniques and decreased fractionation schedules are ideal in order to optimize quality of life.

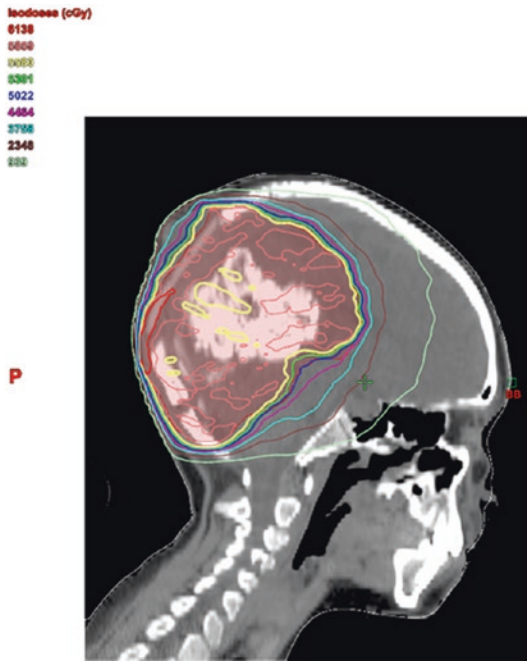

Fig. 20.4 Conformal radiotherapy for brain metastasis. Thirteen year old boy with metastatic osteosarcoma of femur, isolated relapse in the brain 18 months after completion of therapy. Resection was attempted but aborted due to hemorrhage. Conformal radiotherapy administered to a total dose of 59.4 Gy at 1.8 Gy per daily fraction. He is doing well and going to school with no evidence of progression 8 months following radiotherapy

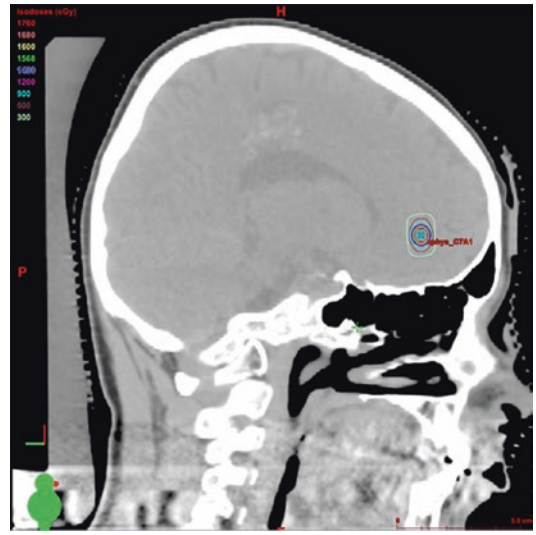

Fig. 20.5 Stereotactic radiosurgery for brain metastasis. Fourteen year old boy with metastatic Ewing sarcoma and brain metastasis. Stereotactic radiosurgery (16 Gy) in a single fraction was administered

20.7 Comprehensive Management of the Pediatric Oncology Patient

Children diagnosed with cancer experience physical and emotional symptoms which can have long term effects. Pediatric research has demonstrated that terminal symptoms and suffering are poorly controlled (Contro et al. 2002; Wolfe et al. 2000a, 2002). Symptom control specialists are needed, yet resources are not always available or utilized (Hilden et al. 2001; Wolfe et al. 2002). When they are available, they are frequently not pediatric-trained (Hilden et al. 2001; Khaneja and Milrod 1998; Liben 1996; Wolfe et al. 2002).

Parents of a child diagnosed with a life-threatening illness or dying from disease require extensive preparation by providers to support the child (Liben 1996; Martinson 1995; Wolfe et al. 2002). Comprehensive Pediatric Care Teams work with the child and family to provide care and support from the time of diagnosis, through palliation of symptoms, and after the child's death.

20.7.1 Early Palliative Care Consultations in Oncology Practice

Optimal care for children diagnosed with high risk for advanced malignancies requires effective communication, comprehensive care, and advanced care planning. A misconception often exists that palliative care is synonymous with limited hospice and/or end-of–life care. Palliative care should not be interpreted as 'giving up' on cure. The goals of palliation, including relief of symptoms and improvement in quality of life need not preclude the goal of long term survival or cure. Pediatric Palliative Care addresses the needs of infants, children, and adolescents with the goal of improving quality of life in the face of life-limiting or life-threatening illness from the time of diagnosis through bereavement (Liben et al. 2008). This aspect of medical care aims to relieve suffering, optimize decision-making by patients, families, and health care providers, and assist with coordination of care as a patient transitions through all dimensions during the trajectory of their disease (Hain et al. 2012; Himelstein et al. 2004; Kang et al. 2005; Liben et al. 2008). When pediatric patients require palliative RT in the face of prognostic uncertainty, the impact of the cancer diagnosis and treatment, and the associated physical and psychosocial suffering can have tremendous implication on clinical outcomes and quality of life. As a result, patients and families require the support of radiation oncologists to be at ease and comfortable with the principles of palliative care (Liben et al. 2008; Waldman and Wolfe 2013; Section on Hospice and Palliative Medicine and Committee on Hospital Care 2013). Although children and families often continue to look to their primary team for management and guidance; integration and partnership with a palliative care team provides added support and specialized expertise, especially when seeking treatments including palliative radiotherapy. If there is an early involvement of palliative care, it is focused on assisting children and families to find meaning in the face of life-threatening malignancies, and live to their maximum potential while navigating through their complex medical condition.

Guidelines from the American Academy of Pediatrics (AAP) recommend routine early consultation of high-quality Pediatric Palliative Care and Pediatric Hospice Care teams in order to optimize prevention and treatment of distressing symptoms, and facilitate complicated decision making, from initial diagnosis when the goals of care are focused on cure (Section on Hospice and Palliative Medicine and Committee on Hospital Care 2013).

Current barriers to providing comprehensive palliative care in children with cancer include the overall low incidence of pediatric malignancies and death, variation in developmental stages, lack of prospective data on the symptom origin, management, and impact on quality of life, limited medical and residency program exposure to palliative education and competencies, and insurance provider reimbursement (Foley and Gelband 2001). Advanced care planning helps facilitate early integration of home services and assures the family that death occurs in their preferred location (Dussel et al. 2009; Vern-Gross et al. 2015). During patient psychosocial and emotional challenges, strained resources including poor reimbursement, few trained staff, and institutional budget cuts can prevent appropriate implementation of specialized palliative care services (Hui et al. 2010).

Developed health care systems with structured palliative care services have demonstrated success, despite the barriers set forth. The Aetna Compassionate Care Program endorses early cure-managed palliative care and advanced care planning in conjunction with traditional therapy, resulting in decreased hospital stay and cost at

end-of-life by 22% (Krakauer et al. 2009; Parikh et al. 2013; Spettell et al. 2009). Furthermore, recent implementation of the Affordable Care Act allocates services for children and adolescents diagnosed with a life-limiting illness who are eligible for Medicaid or Children's Health Insurance Program, providing access to palliative-care or hospice-care services in tandem with other disease-related treatment. Comprehensive services should be reimbursed and supported by Medicare and commercial insurers regardless of intent of treatment and prognosis of the disease. Provider advocacy for these services is essential to ensure that the patient and family goals and care are met.

20.7.2 Perspectives and Utilization of Pediatric Palliative Care

A survey organized through the American Society of Clinical Oncology (ASCO) evaluated oncologists' attitudes and practices regarding palliative and end-of-life care (Hilden et al. 2001). Of the responders, only 10% had formal training in palliative care, whereas most learned through role models and trial and errors. Regardless of the lack of training, approximately 91% of oncologists rated their skills in the management of pain as "competent to very competent"; however, 58% of the physicians felt less confident in the treatment of depression and 68.9% reported significant anxiety when managing difficult symptoms of terminally ill children at the end-of-life (Hilden et al. 2001). Furthermore, pediatric oncologists who believed they were deficient in symptom management confirmed feeling unsuccessful in providing adequate care for their patients (Hilden et al. 2001). Barriers to providing effective comprehensive end-of-life care included the family's unrealistic expectations (47.5% of pediatric oncologists), family denial (35.7%), family conflict (30.3%), the patient's unrealistic expectations (10.1%), and patient denial (7.6%) (Hilden et al. 2001). Insurance reimbursement did not hinder access to palliative chemotherapy, radiation therapy, and parenteral nutrition, the value of clear and effective communication between the provider, patient and family at diagnosis and during the course of illness, especially when addressing prognosis, treatment-related outcomes, and potential for cure (Hilden et al. 2001).

20.7.3 End-of-Life Care and Discussions with the Pediatric Oncology Patient

Advanced care planning and earlier end-of-life discussions facilitate hospice discussions and enrollment and do-not-resuscitate orders, decrease suffering from uncontrolled symptoms, decrease intensive care unit deaths, and facilitate preparations during a child's last month of life (Vern-Gross et al. 2015; Wolfe et al. 2008). Understanding the parental perspectives on decision-making and the characteristics of their child's death is crucial when optimizing end-of-life care and minimizing the risk of complicated bereavement in surviving parents (Houlahan et al. 2006; Kreicbergs et al. 2005). Toward the end-of-life, children are often aware of their imminent status, and can experience fear, loneliness and anxiety. They need honest answers (Hechler et al. 2008). Psychological distress at the end-of-life is rarely recognized by health care providers and therefore not always treated successfully (Theunissen et al. 2007). A child's somnolence and withdrawal from play may also represent unrelenting pain and may be misinterpreted as a disinterest in engaging relation. Addressing parental concerns regarding their child's symptoms provides an avenue for open conversation, an opportunity to redirect misguided fears, and providing high-quality care by tending to the child's needs. Research suggests that most children with advanced malignancies ages 10–20 are capable of participating in end-of-life discussions, engaging the decision-making process, understanding the consequences of their medical decisions, and acknowledging the potential impact of their death on the involved care providers and loved ones (Hinds et al. 2005). Clinician efforts to attend to both parental and

child suffering toward the end-of-life can positively impact coping, improve quality of life, and reduce the risk of complicated bereavement (Kreicbergs et al. 2007).

20.7.4 Sibling Support

Siblings of children diagnosed with cancer require support and opportunities to talk about the illness, along with any fears, goals, and their emotional experience (Gaab et al. 2014). Although they often develop a unique level of elevated maturity and empathy, they face many emotional, academic, social challenges, and often feel a sense of loss and inattention within the family and are (Alderfer et al. 2010; Hamama et al. 2000). A siblings' impending death and a desire to be actively involved in their care are frequently some of the most significant concerns when witnessing a brother or sister face a life-threatening illness (Gaab et al. 2014). Open discussions provide an understanding of the diagnosis and prognosis, facilitate coping and preparation through the various clinical situations, provide appreciation for their sibling, and freedom to enjoy time with one another. Support Groups of siblings and their parents have shown success in addressing the concerns of the children and adolescents, who may feel left out of the family when all the attention is devoted to the sick child (Mu et al. 2015; Nolbris et al. 2010).

20.7.5 Bereavement

The death of a child can be devastating and intense, impacting the emotional and physical well-being of a family (Brown 1989; Martinson et al. 1994; Sloper and While 1996). Bereaved parents are at long-term risk of developing various psychosocial morbidities such as depression, anxiety, diminished quality of life, poor social function, and suicidal ideation, which can endure up to 15 years beyond the death of their child (Dyregrov and Dyregrov 1999, Hendrickson 2009, Rosenberg et al. 2012, Saunders 1979–1980). Bereavement care begins well before a child's death and is often helpful long term. The emotional and psychological adjustment before death can help parents cope with the loss of the child over time (Rando 1985). A loss of communication from the time of the child's diagnosis through bereavement follow-up can greatly impact outcomes. Feelings of dismissal or being patronized, insensitivity in the delivery of bad news, perceived disregard for parents' judgment regarding their child's care, or poor communication of important information are examples of parental interactions leading to long-lasting emotional distress (Contro et al. 2002). It is not uncommon for parents to develop a sense of isolation because others often feel insecure in how best to respond to the bereaved (Decinque et al. 2006; Worden 1991). Parents may find solace in the continuous bond or finding ways to keep their child present (Rubin 1996). The desire to connect with other parents and families with similar experiences is not uncommon (Decinque et al. 2006). Pediatric oncology services and units continue to play a critical role in the delivery of palliation and bereavement support for children, siblings, and parents throughout the trajectory of the illness and death (Decinque et al. 2006).

20.8 Barriers to the Use of Palliative Radiotherapy

Palliative RT in children and adolescents is vital but often underutilized due to misconceptions and unwarranted fear of life disruption and treatment toxicities. A Canadian survey described the knowledge and practices of various indications for palliative RT among 80 pediatric oncologists (Tucker et al. 2010). Almost two-thirds of responders (62%) had prior training in radiation oncology; however, only 28% received formal palliative medicine training. Ninety-two percent of responders had provided palliative care for their patients within the preceding 12 months and 80% had initiated a palliative RT referral (Tucker

et al. 2010). Oncologists with previous palliative care training were more likely to refer children for palliative RT compared to responders without previous training (94% vs. 73%, $p < 0.01$). Although 59% of all respondents believed they had sufficient knowledge to identify indications for palliative RT, nearly 41% responded "no" or "unsure." While survey takers responded that they considered palliative RT adequate for soft-tissue (61%), bone metastases (89%), dyspnea (61%), bleeding (40%), and hemoptysis (22%), most were unsure of palliative RT effectiveness for bleeding (45%) and hemoptysis (64%) (Tucker et al. 2010). Additional barriers associated with underutilization of pediatric palliative RT included patient and family reluctance, short life expectancy of the child, potential treatment-related side effects or lack of improvement and impact on QOL, proximity of cancer center, transportation limitations, and lack of knowledge of potential benefits (Tucker et al. 2010). Shortfalls in clinician education in palliative competencies may prevent proper recommendations and utilization of palliative RT, whenever there actually may be a potential role and/or benefit for the patient and family (Tucker et al. 2010). Addressing parental and provider concerns, active presence and participation in multidisciplinary conferences, and explaining potential risks and benefits associated with fewer treatments and comparatively minor toxicities can often diminish any previous hesitation.

20.9 Future Directions

Radiotherapy is an essential component in the interdisciplinary management of children and adolescents diagnosed with cancer, whether in the setting of curative intent or palliation of symptoms. Advanced radiotherapeutic techniques, stereotactic body radiotherapy (SBRT) (Brown et al. 2014; Dubois et al. 2014), stereotactic radiosurgery (SRS) (Nanda et al. 2014), and other techniques such radiofrequency ablation (RFA) (Botsa et al. 2014), have the potential of delivering highly conformal therapy in order to provide necessary dosage to the tumor for treatment response and symptomatic relief, while lowering radiation dose to uninvolved healthy tissue surrounding the tumor. Although there is a heavy emphasis on the reduction of late toxicities, when quality of life is at the forefront of therapy, there may be some utility in proton beam therapy, especially in order to minimize both acute and late treatment-related toxicities or for treatment in the re-irradiation setting (Bakst et al. 2011; Brown et al. 2013; Padovani et al. 2011). The utilization of these advanced technologies such as proton beam therapy remains controversial, especially in patients with limited life-expectancies who are not expected to benefit from the therapy they receive. Children with advanced malignancies can have unpredictable disease trajectories with prolonged survival. One must not underestimate the risk of late toxicities, even when pursuing non-curative disease-directed therapies.

20.9.1 SBRT

Stereotactic body radiotherapy (SBRT) can be considered as a unique treatment modality, particularly for metastatic and/or recurrent sarcoma. It has been utilized in order to optimize local control in the metastatic setting, or palliate impending or intrusive symptoms, impinging on quality of life (Dubois et al. 2014). SBRT has the potential advantage of delivering a highly conformal therapy, short favorable treatment schedules, while maintaining excellent local control of disease and palliation of symptoms (Brown et al. 2014). Median total palliative SBRT doses of 40 Gy in 5 fractions (range, 16–50 Gy in 1–10 fractions) have been documented to provide successful pain relief for metastatic and recurrent osteosarcoma (Brown et al. 2014). SBRT is a treatment modality that is versatile, used both with curative and palliative treatment courses; however, regardless of the intent, the treatment has been shown to be effective at disease control, palliation of symptoms, it is a treatment modality that should be considered in the re-irradiation setting (Brown et al. 2014).

20.9.2 Education and Training

Currently, the AAP recommends that all physicians be trained in basic approaches to palliative care principles and be able to provide appropriate assessment and management of symptoms, communicate effectively with patients and families, recognize when pediatric palliative care and pediatric hospice care consults are indicated, and ensure that best patient care is consistent with best practices (Section on Hospice and Palliative Medicine and Committee on Hospital Care 2013). Formal education beyond trial and error and role model settings is lacking for medical students, resident, and physicians training and continuing medical education (CME), especially for those who plan to be or are specialized in caring for pediatric patients diagnosed with advanced malignancies. Innovative curriculums such as "Oncotalk" have been designed in graduate medical education programs to enhance communication skills (Back et al. 2007). Validated studies have demonstrated significant improvement in communicating bad news, transitions, and goals of care discussion (Back et al. 2007). Recent data from the Association of American Medical Colleges has demonstrated an increased exposure of palliative care training for students (Sulmasy et al. 2008). Ongoing efforts continue to create curriculums designed to increase clinical exposure to seriously ill patients, in conjunction with structured didactic lectures in order to improve the communication skill base and approaches towards palliative care (Parikh et al. 2013). Comprehensive training opportunities are available to radiation oncologists, primary, and specialty physicians in order to build additional skills of symptom management, coordination of care, communication of decision making and end-of-life, through collaborative conferences and major academic institutions, including Palliative Care Education and Practice (PCEP) and Professional Oncology Educational (POE) series (Poe 2015; PCEP 2015). Palliative care efforts should not be limited to end-of-life care, but should also focus on symptom management, psychosocial support, coordination of care, and effective communication regarding prognostication, and decision-making, and facilitate prospective research for continuous improvement in the understanding and care provided for the patients and families.

Conclusion

The prognosis of pediatric patients diagnosed with refractory or metastatic disease remains poor. Attending to children and adolescents with life threatening malignancies is an intricate process, requiring support from an interdisciplinary team and personalized approach. Palliative RT has demonstrated value as an adjuvant treatment in the relief of symptoms and improvement of quality of life. When evaluating the risks and potential benefits of palliative RT, the long term side effects should be considered, especially in situations when a child may survive for several years or decades depending on diagnosis and treatments received. As the technologies and practices within radiation oncology continue to evolve, efforts to improve the comprehensive approach for the management of children and adolescents diagnosed with malignancies should continue to advance. It should emphasize interdisciplinary collaboration, systematic delivery of palliative RT for relief symptoms, effective communication, and identifying patient and family's goals of care in order to achieve optimal outcomes.

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Pediatric Radiotherapy in Low and Middle Income Countries

21

Natia Esiashvili, Verity Ahern, Jeannette Parkes, Hester Burger, Yavuz Anacak, and Siddhartha Laskar

21.1 Introduction

Communicable diseases are still the leading cause of childhood mortality in third world countries. However, as prevention and treatment of malnutrition and infectious diseases improves, global health challenges are shifting towards combating non-communicable diseases including cancer which has high rates of mortality in children (Wilimas and Ribeiro 2001). More than two-thirds of the world's pediatric cancers are currently diagnosed in low- and middle income countries (LMIC) (Kellie and Howard 2008). The patterns of occurrence of childhood cancer in LMIC compared to high income countries (HIC) and the lack of population-based cancer registries suggest that many patients die from undiagnosed cancer and the burden of childhood cancer is under-estimated. Children diagnosed with cancer in low-income countries (LIC) continue to have a much poorer chance of survival compared to those in HIC (Fig. 21.1).

This inequality gap will only continue to widen due to the rapidly growing young population in third world countries with limited resources (Magrath et al. 2013). Families dealing with childhood cancer are caught in a vicious cycle of poverty, low level of cancer literacy, cancer stigma, lack of access to healthcare, lack of proper diagnostic procedures, late diagnosis, lack of cancer therapy options, inability to manage treatment toxicities, and treatment abandonment (Sala et al. 2004; Israels et al. 2008). As LMICs continue to be confronted with economic challenges and change in population dynamics, it is essential to continue adapting the most

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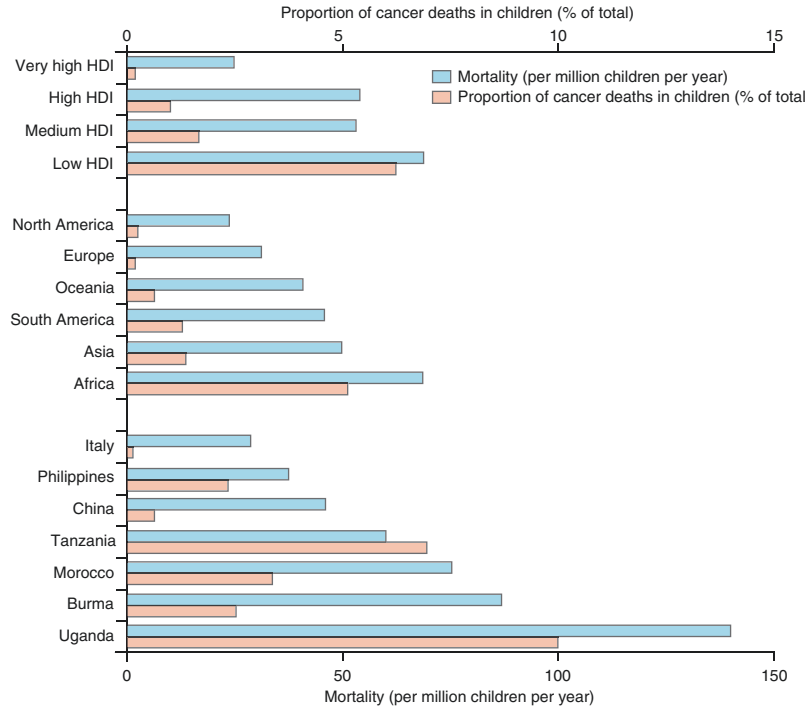

Fig. 21.1 Overall childhood mortality and cancer mortality rates by Haman Development Index, regions and countries. *HDI* Human Development Index (Magrath et al. 2013)

practical and cost-effective healthcare model applicable to a particular region or nation. Beyond setting up a proper infrastructure, advancing knowledge and skills can become the biggest driver of progress in healthcare.

Pediatric radiation therapy is an integral part of cancer treatment and it still faces multiple and unique barriers in countries with limited resources.

21.2 Pediatric Oncology in LMIC

Disparate distribution of resources for cancer care partly stems from very different public health priorities in HIC versus LMIC. It is not surprising that there is direct association between healthcare spending and cancer survival outcomes (Fig. 21.2).

Poor health-care infrastructure in LIC results in only a few special cancer centers with very limited access for families from remote geographic areas. For example, 80% of the African population still has no access to essential cancer care including surgery and radiotherapy (Barton et al. 2006). Comprehensive national policies and programs are needed to overcome this massive problem (Kellie and Howard 2008). Improving pediatric oncology care can only be achieved in the context of a national cancer control program which begins with cancer prevention and screening as well as establishment of cancer registries. Despite resource limitations, several middle-income countries—e.g., Argentina, South Africa, and Iran—have implemented national population-based cancer registration for children, with support from nongovernmental organizations in some cases (Valsecchi and Steliarova-Foucher 2008).

Healthcare systems in LIC are usually very fragmented. Lack of diagnostic tools prohibits timely and accurate cancer diagnosis contributing to the presentation of children with advanced stage tumors. Basic level healthcare infrastructure and insufficient numbers of health-care workers are substantial hurdles for the development of pediatric cancer services. Social factors profoundly impact cancer outcomes. For example, 47% of parents from deprived areas in Indonesia refused or abandoned treatment compared to 2% from affluent areas (Mostert et al. 2006). The same study suggested that strong

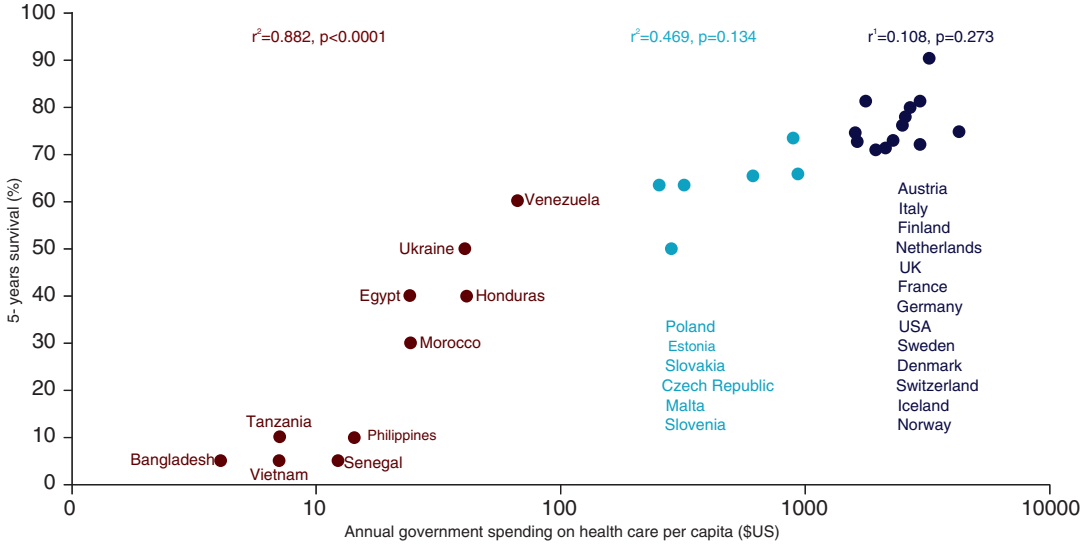

Fig. 21.2 Correlation between country's annual governmental spending on health care per capita with 5-year survival of pediatric cancers. Ribeiro et al. (2008)

social hierarchical structures hindered communication with doctors, and resulted in insufficient parental understanding of the need to continue treatment. Social policies to support families of children with cancer will play a major part in the delivery of treatment and better outcomes. Poverty and malnutrition negatively influence the course of disease. Modern therapies are less accessible or entirely non-existent to children in LMIC. Furthermore, psycho-social and cultural barriers interfere with treatment adherence and treatment abandonment remains a big challenge (Antillon et al. 2008; Usmani 2001).

Africa serves as an example of serious public health challenges (Stefan 2015). Data on the current status of cancer treatment and outcomes from most countries on the African continent is still sparse and unreliable (Ribeiro et al. 2008; Hadley et al. 2012). The current estimate is that over 36,000 new cases of malignant disease in children will be diagnosed in this region each year (GLOBOCAN 2012 Available at: http://globocan.iarc.fr). Fewer than 20% of African children have access to curative treatment and more than 70% of children present with advanced stage disease (Uba and Chirdan 2007). Health budgets throughout sub-Saharan Africa are insufficient, ranging from US$17.00 per person per year in Democratic Republic of Congo to US$819.00 per person in South Africa (Hadley et al. 2012). Compliance with treatment due to psycho-social barriers is still a major challenge for families living in countries with limited resources. In Sudan, only 11% of children with Wilms tumor completed treatment, and 27% received no treatment at all (Abuidris et al. 2008). Survival outcome in children diagnosed with most type of cancers in Africa (with exception of South Africa) rarely exceeds 30–50% (Hadley et al. 2012).

Significant progress has been made in adapting lower cost therapy options in LMIC. For example, in 2004–2005, the total cost per patient with ALL was reported to be US$16,700 in Recife (Brazil) and US$11,000 in Shanghai (China) (Bhakta et al. 2013; Liu et al. 2009). Organizations like SIOP -PODC have adapted treatment recommendations for LMIC (Parkes et al. 2015; Gajjar and Finlay 2015; Israels et al. 2013). Malawi is one of the few sub-Saharan African nations with a pediatric oncology unit and Wilms tumor survival was reported in 2009 as only 40% at 8 months (Israels et al. 2009). Preoperative chemotherapy caused considerable hematological toxicity and treatment-related mortality in malnourished Malawian children (Israels et al. 2012) and reduced dosage treatment may be more feasible for optimal outcome in such setting (Israels et al. 2013).

A multidisciplinary approach is essential from cancer diagnosis to treatment to management of treatment toxicities. Investing in education and training should remain a top priority. Relatively inexpensive communication technology such as the internet can strengthen professional collaboration between distant cancer centers and can be used as an opportunity for advancing medical education, sharing knowledge, stimulating interest in clinical research (e.g., International Atomic Energy Agency project AFRONET, Cure4kids telemedicine from St. Jude Children's Research Hospital).

21.3 Pediatric Radiation Oncology Challenges for LMIC

Data accumulated from clinical trials in HIC has led to significant refinement of the role of radiotherapy in pediatric tumors over the course of past 4 decades. Changes include the development of risk-adapted treatment, elimination of RT in certain low-risk tumor and patient groups and significant radiation dose and volume reduction for higher risk groups through incorporation of intensification of systemic chemotherapy and improvements in surgical techniques. Current pediatric oncology treatment guidelines and protocols may not be applicable to the LMIC environment where there are late cancer stage presentations, a lack of advanced surgical techniques, a limited supply of chemotherapy drugs and an inadequate number of radiotherapy machines. According to the International Atomic Energy Agency Directory of Radiotherapy Centres (IAEA-DIRAC) database, only four LMICs have the requisite number of teletherapy units, and 55 (39.5%) have no radiation therapy facilities at present (Datta et al. 2014) (Fig. 21.3).

It is not only the shortage of equipment that is a concern, but also age and general technological status of the units that are available. In many cases

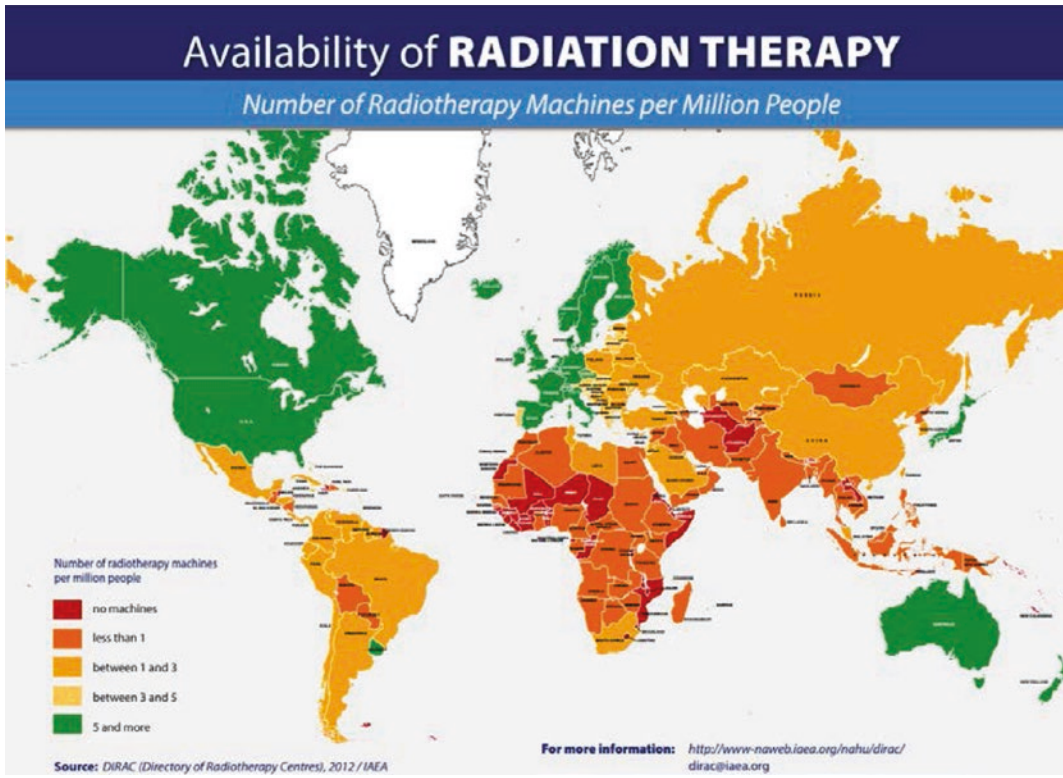

Fig. 21.3 Global Distribution of radiotherapy teletherapy units per million population based on IAEA DIRAC (Directory of Radiotherapy Centers) 2012 data. https://www.iaea.org/sites/default/files/dirac2012.pdf

the equipment is outdated and not ideal for treatments required for curative intent, especially for children. Development and upgrading of radiotherapy facility is technologically very challenging, and costly, and requires a multi-disciplinary team of professionals including medical physicists, radiation therapy technologists, nurses and physicians. Many LMIC will not be equipped with material and human resources to overcome such challenges. Collaboration and assistance from international organizations, societies and institutions can make appreciable difference.

Linear accelerators (linacs) have gradually substituted cobalt-60 units in industrialized countries and made their way to emerging nations over the last three decades. Cobalt-60 units may still provide more cost-effective and practical radiotherapy solutions in LMIC environment than linacs. Cobalt-60 units are preferred in centers where power supply and infrastructure are not reliable or stable (Adams and Warrington 2008; Van der Giessen 2002; Van der Giessen et al. 2004; Page et al. 2014; Ravichandran 2009). Basic Cobalt-60 units may have a lower upfront cost but this may not be the case when upgraded features are added. The production of cobalt-60 sources is increasingly costly due to heightened security concerns. As a result, modern cobalt units are rising in price. While the cost of linacs can be significantly reduced by them with more basic features, costs of maintenance over a typical lifespan of 10–12 years, commissioning, training and complex quality assurance may still exceed the maintenance costs of Cobalt-60 even after taking into account source replacement every 5 years.

Overall, service and maintenance of linac is more likely to be cost-prohibitive for countries with limited resources unless vendors offer a lower cost option for their own service contract or, support the training of local engineers and physicists capable of machine maintenance. Many LMI countries may benefit from the use of a mix of cobalt units and linacs with use based on complexity of treatment.

Another hurdle for LMIC is the acquisition of robust and high quality treatment planning systems. Recent advances in radiation therapy planning and delivery allow improved normal tissue sparing and more conformal delivery of the tumor dose compared to conventional techniques (2D RT). These improvements require precise definition of the target volume, based on registration of diagnostic imaging with treatment planning images. Three-dimensional conformal radiation therapy (3D-CRT) is a logical step towards improving precision and conformity of dose delivery. Dedicated computed tomography (CT) scanning is required to be integrated into treatment planning software. Children with cancers requiring higher doses close to critical structures, would benefit from 3-D planning which can used with both linac and Cobalt-60 treatment units; as dealing with the long term late effects of the wider field radiotherapy of 2-D planning can be problematic in LMIC, due to lack of resources (Parkes et al. 2015). Training programs aiming specifically at transition from 2-D radiotherapy to 3D-CRT has recently been developed through partnerships between academic institutions and industry.

New treatment technologies are rapidly evolving in radiation therapy, fueled by progress made in engineering and computer technology (IAEA-TECDOC-1588). Although these advances improve the ability to perform radiotherapy, they also increase the risk in terms of harm to patients if not implemented correctly, so much so that the use of radiation in healthcare has been listed as one of the top 10 Health Technology Hazards since 2010 (https://www.ecri.org/press/Pages/ECRI-Institute-Announces-Top-10-Health-Technology-Hazards-for-2015.aspx). A systematic and step-by-step approach to implementation, teaching and training is therefore, essential.

The marketplace is the biggest propeller of the spread of radiotherapy technologies in HIC and, more recently, in emerging countries. Static, dynamic and volumetrically intensity modulated radiotherapy, on-board imaging, stereotaxis and other tools require very robust, complex and comprehensive quality assurance programs with independent dosimetry and audits. There are several essential components for quality in any radiotherapy system: (1) adherence to established clinical practice standards; (2) defined clinical workflow; (3) complete information flow; and (4) sound

integration of hardware and software. However, the most important principle is to keep everything as simple and straightforward as possible. Human resources are commonly overlooked when planning for a new radiotherapy center. There are many instances of expensive equipment being left unused in LIC because of infrastructure and the need for staff training and equipment maintenance were not properly anticipated.

Challenges in pediatric radiation oncology (PRO) in LMIC vary in different jurisdictions. A very demanding work-load, need for a large number of well-trained staff, technology capacity, cost-effective care solutions, and adaptability with increasing patient volume are particular challenges for PRO programs established within tertiary centers in populous countries, for example, Tata Memorial Center in Mumbai, India and Children's Cancer Hospital 57,357 in Cairo, Egypt. High-volume pediatric radiation oncology practice also creates the opportunity to gain substantial experience and expertise. Some centers with basic technology capacity and sparse human resources may be organized to treat a primarily adult population. Their challenges include training their staff in pediatric oncology and the use of radiotherapy for pediatric cancers, becoming child and family focused and to establish or link in with a multidisciplinary pediatric oncology team which incorporates the provision of psycho-social support. They must be able to provide immobilization devices suitable for children and sedate children safely, as well as have access to medication for symptom management of children and have a pediatric emergency response system. Where the radiotherapy center is not co-located with a pediatric hospital, safe transportation of children between centers is an additional challenge.

21.4 Training in Pediatric Radiation Oncology in LMIC and International Collaborations

There is a global shortage of radiation oncologists, medical physicists and radiation therapy technologist with experience in PRO and a need for a long-term strategy to produce trainers and educators to increase the supply of adequately trained staff. Training must be adapted to both the working environment and the level of complexity of the available technology; little benefit is derived by a trainee or the trainee's institution when the education addresses a technology not available in his or her own country (Salminen et al. 2009). Training for radiation oncologists must include modules on late toxicities of pediatric radiation therapy due to their impact on quality of life as well as cost of care.

Networking on the national, regional and international levels can play a significant role in supporting educational and research activities in LMIC. Forging partnerships with institutions in HIC can potentially become the first step towards the development of a new pediatric oncology program at LMIC centers. Twinning programs are a partnership between a pediatric cancer unit in a developing country and a group of health care providers in the developed world (Antillon et al. 2005). A partnership should be only sustained if realistic short- and long-term goals are achieved based on mutual agreement. Twinning programs for individual centers, and regional networks of similar centers, provide the forum for international mentoring, development of regional expertise, and generation of common knowledge that will help others who treat children with cancer (Ribeiro et al. 2008). Teams can be productive in designing treatment protocols adapted to local needs and realities (Chantada et al. 2013; Hesseling et al. 2013; Israels et al. 2013; Qaddoumi et al. 2008a, b).

A number of successful collaborative projects have been established between institutions in HIC in Europe, North America, Australia and LMIC in South America, Africa and Asia. For example the Franco-African Group of Pediatric Oncology was founded in 2000 and established pilots units in 12 African countries (Lemerle et al. 2005). This project provided material, logistics and educational support from French stake holders for the sustained training of physicians, nurses and laboratory personnel. It also involved collaborative research in adapting modern treatment protocols in management of selected

malignancy prevalent on African continent. To date, there are more than 50 publications originating from these activities (Moreira et al. 2012). Another successful twinning program is collaboration between Sanderson, United States, Europe and South Africa. This project is supported by World Child Cancer charity in Ghana, Malawi, Mozambique and Cameroon. The international outreach program at St. Jude Children's Research Hospital includes training programs within the hospital, partner sites in 13 countries, a school for Latin American nurses, a distance learning website, and telecommunications programs, which are described in detail. Future programs should be designed to maximize and evaluate impact, report accomplishments and failures, and avoid duplication (Wilimas and Ribeiro 2001).

International collaboration efforts are still fairly sparse and there is a demand on practitioners in HIC to participate in outreach.

21.4.1 Partnering with International Organizations

Several international organizations demonstrated leading role in advancing PRO globally. The International Atomic Energy Agency (IAEA) has provided significant technical assistance to LMIC. The Organization's approach involves strategic long-term planning with its Member States in establishing national cancer care programs, capacity-building and technical assistance (Deatsch-Kratochvil et al. 2013). The projects are typically designed to improve the accessibility, safety and quality of RT applications (Salminen et al. 2005). The number of IAEA projects has increased during recent years, especially in Africa, Latin America, Eastern Europe, and countries of the former Soviet Union (Abdel-Wahab et al. 2013; Fisher et al. 2014).

IAEA programs also encompass an increased awareness of childhood cancers and delivery of current evidence-based best treatment regimens. The Agency launched the first global initiative for optimization of radiotherapy for children, termed the Paediatric Radiation Oncology Network (PRON). The program involves 14 centers in 13 LMIC from Africa, Asia and Latin America with the objective of improving adherence to evidence based protocols, supportive care guidelines and quality assurance guidelines of RT provided for children. Data on RT treatment from PRON will be collected within the Pediatric Oncology Networked Database (POND) with the support of St. Jude Children's Research Hospital's International Outreach Program. The data will inform improvements in practices in pediatric radiation oncology in LMIC and to reduce the disparity in outcomes between HIC and LMIC (Salminen et al. 2005).

Other examples of successful international programs in this field include nongovernmental organizations (NGO) such as the Monza International School of Pediatric Hematology/Oncology (MISPHO), which was founded in an attempt to narrow inequality gap in childhood cancer. Its educational efforts include oncology nursing, supportive care, cancer-specific updates, epidemiology, and clinical research methods. MISPHO Educational efforts are facilitated by educational content and online conferencing via www.cure4kids.org. Identifying preventable causes of abandonment of therapy and documenting the nutritional status of patients treated at MISPHO centers are areas of active research (Howard et al. 2007). In 1998, MISPHO spawned a collaboration of Central American pediatric oncology centers: the Asociación de Hemato-Oncología Pediátrica Centroamericana (AHOPCA) and developed several cooperative protocols that are currently in progress. Twinning programs between MISPHO centers and centers in HIC have proven invaluable to harness the resources of these centers to improve pediatric oncology care in LMIC.

Professional organizations, such are the Program of Developing Countries (PODC) of International Society of Pediatric Oncology (SIOP) and Pediatric Radiation Oncology Society (PROS) are dedicated to employ professional expertise for their members in developing educational and collaborative projects between HIC and LMIC. Other professional societies are making similar strides (Wilimas et al. 2003; Day et al. 2013).

21.5 Future Goals

Around 80% of children with cancer are now expected to be cured by current therapies, although the most important determinant of outcome is where a child with cancer is born. The difference in survival for children diagnosed with cancer between HIC and LIC continues to widen as curative therapies are developed in the former but not implemented in the latter.

The introduction of education and social capital policies in developing countries, and the development of dedicated units for treating children with cancer, will be essential for the delivery of adequate childhood cancer services (Howard et al. 2004). Because local conditions change as new infrastructure and more highly trained personnel become available, the adaptation of treatment regimens to local conditions is a continuous project. Clinical research is needed for progress in LMIC. Clinical trials have an essential role in the development of new treatment strategies children with cancer specifically applicable to each country or region and children who do not enter trials should undergo the same rigor of disease diagnosis, staging and treatment as children enrolled in clinical trials. A system of continuous quality improvement in PRO should become routine practice.

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Future Directions

22

Thomas E. Merchant and Rolf-Dieter Kortmann

The treatment of children and young adults with cancer and conditions that require irradiation is challenging. Tumors in these patients arise in critical locations throughout the body. All treatments result in morbidity. Cure remains elusive for many patients owing to diverse biology, resistance to therapy, and failure to appreciate subclinical disease extent.

Progress in the treatment of childhood cancer using radiation therapy has been continuous and attributed to well-designed clinical trials and advances in treatment planning and delivery methods. Reductions in radiation dose and target volumes, intelligent sequencing, and intensity-modulated photon and proton beams have contributed to make radiation therapy safer and more effective. Whether administered as the primary or adjuvant treatment, radiation therapy takes a definitive and lead role in curative treatment regimens and serves as a benchmark to which other treatments are compared. This includes disease control and complications. Radiation oncologists support the concept of combined modality therapy in appropriately selected patients. They understand the ability of combined modality therapy to reduce radiation-related side effects in vulnerable low-risk patients and the need intensify therapy to achieve durable disease control in high-risk patients. The advent of conformal and intensity-modulated proton therapy has created another opportunity to advance the role of radiation therapy and set new standards in target volume conformity and normal tissue sparing. Regardless of modality, treatment of children with radiation therapy should be undertaken with the latest advances and experienced care teams including anesthesia when required. However, clinicians in low and middle income countries should not withhold irradiation because they are lacking the most advanced methods.

The primary aims for many international clinic trials during the past 20 years have focused on answering important questions about the role of radiation therapy. The systematic use of irradiation has increased the proportion of patients achieving durable disease control with acceptable functional outcomes as measured by objective measures. Clinical, pathologic, and molecular risk stratification should be used to refine treatment regimens for children to reduce the risk of complications associated with radiation therapy and increase the rate of disease control in the setting of com-

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bined modality or more intensive therapy. Future salvage regimens should consider re-irradiation for selected patients given the opportunity associated with tumor progression in the setting of reduced radiation dose and volume regimens. Increasing the number of children enrolled on clinical trials supported by intense quality assurance to address timely questions related to the use irradiation should continue to have priority in single institution and cooperative group studies.

As noted in this work, methods of irradiation undergo a continuous process of optimization and modern technology (e.g., intensity modulated radiotherapy, proton therapy, inclusion of modern imaging in treatment planning and use of imaging to precisely guide treatment delivery) are rapidly becoming essential in the management of children and young adults. New technology provides high precision applications with the aim to improve tumor control and have been pragmatically transferred to the pediatric environment prospectively to assess their value.

These developments include the assessment of changes in tumor volume and its location during the application of radiation therapy and permit a better coverage of the target while preserving surrounding tissue. Current and future developments also include the application of proton therapy. While an improvement in tumor control cannot be expected, the expectations are high that proton therapy will help to reduce the risk for late effects.

The rapid progress in molecular genetic profiling will in the future permit an individualized treatment in childhood cancer. Current research is presently addressing the role of new agents. The impact on pediatric radiation oncology and specifically the selection of dose and volume, remains open and warrants specifically tailored research. The implementation of new agents in pediatric oncology is aimed to improve outcome. They might also be associated with an increased risk for late effects mandating an adequate monitoring for complications.

Developments in radiation oncology technology have become health care standards in high income countries despite their increased cost. By contrast, poor nations struggle with establishing basic levels of irradiation at a more affordable cost. Unfortunately, the gap between western countries and low and middle income countries has widened. The number of children in these countries requiring radiotherapy services will rise at the same time putting high demands on the installation of modern radiotherapy equipment and the necessary education.