Pediatric Oncology
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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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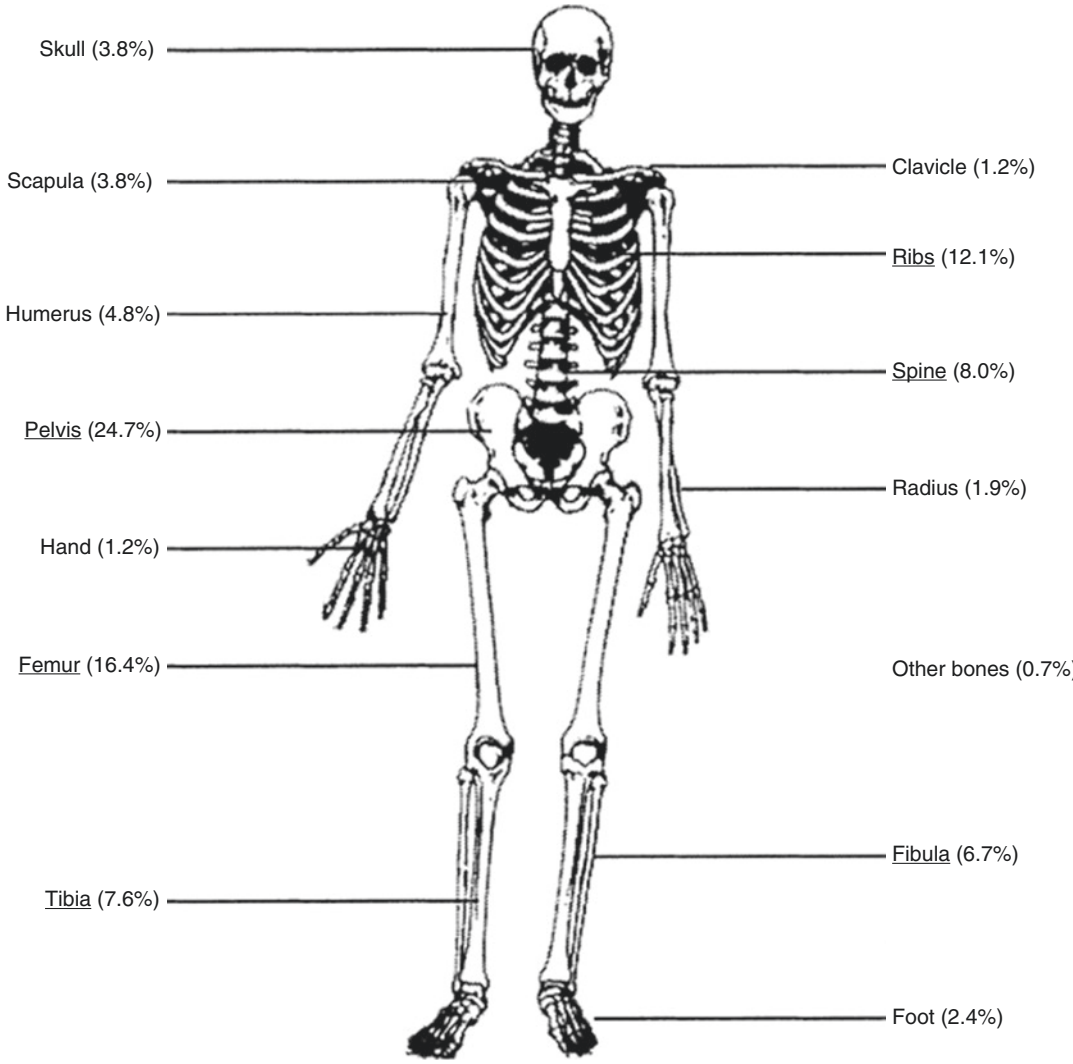

Fig. 2.1 Distribution of primary Ewing sarcoma sites as reported by the European Intergroup Cooperative Ewing's Sarcoma Study Group analysis of 975 patients

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.

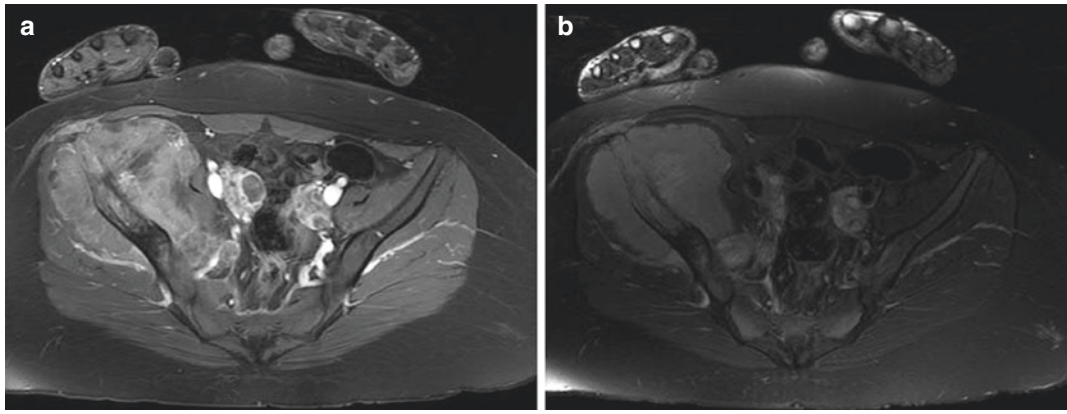

Fig. 2.2 (**a**) Prechemotherapy, post-gadolinium T1 axial MRI of a pelvis Ewing sarcoma. (**b**) Prechemotherapy, T2 axial MRI of a pelvis Ewing sarcoma

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

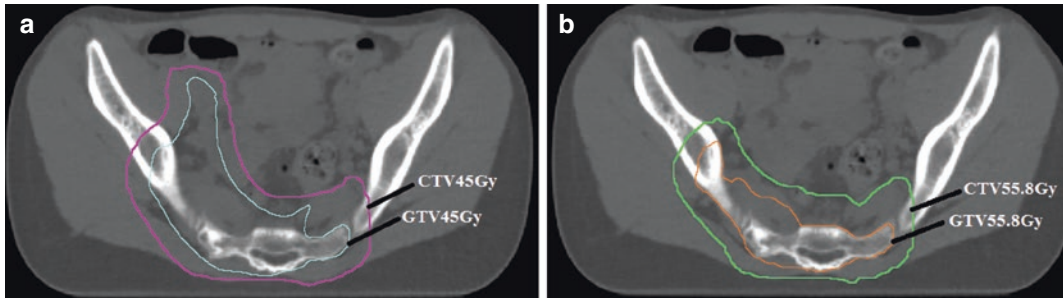

Fig. 2.3 (**a**) Depiction of the GTV45 Gy and CTV45 Gy volumes for a pelvis Ewing sarcoma. (**b**) Depiction of the GTV55.8 Gy and CTV55.8 Gy volumes for a pelvis Ewing sarcoma

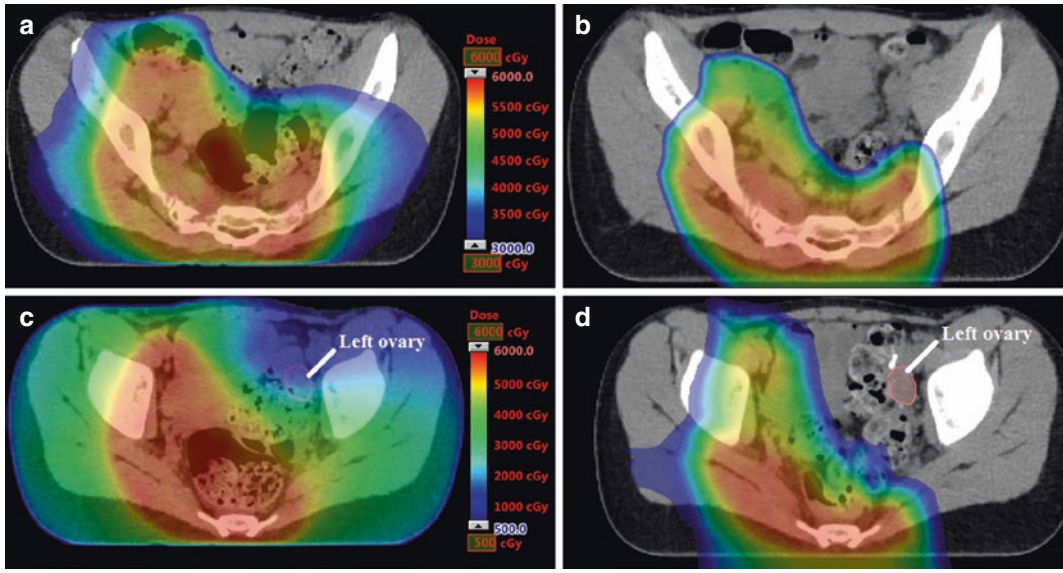

Fig. 2.4 (**a**) Dose distribution resulting from IMRT planning of the pelvis Ewing sarcoma depicted in Fig. 2.3. (**b**) Dose distribution resulting from intensity modulated proton radiotherapy (IMPT) planning of the pelvis Ewing sarcoma depicted in Fig. 2.3. Compared to the IMRT plan, the IMPT plan 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.

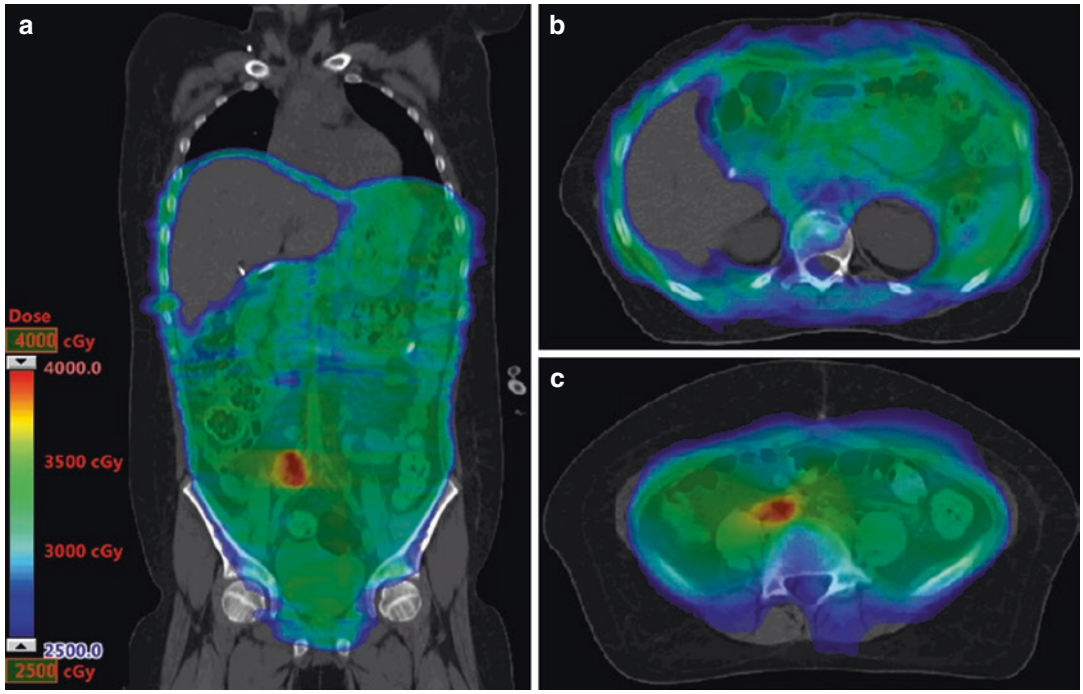

Fig. 2.5 (**a**) Dose distribution resulting from IMRT planning of an intra-abdominal disseminated DSRCT. An area of gross disease was boosted to 3740 cGy. (**b**) IMRT dose distribution at the level of the kidneys and liver. (**c**) IMRT dose distribution at the level of the boost volume

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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