Practical Guides in Radiation Oncology
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Radiation Therapy for Sarcomas and Skin Cancers

A Practical Guide on Treatment Techniques

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Practical Guides in Radiation Oncology

The series Practical Guides in Radiation Oncology is designed to assist radiation oncology residents and practicing radiation oncologists in the application of current techniques in radiation oncology and day-to-day management in clinical practice, i.e., treatment planning. Individual volumes offer clear guidance on contouring in different cancers and present treatment recommendations, including with regard to advanced options such as intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT). Each volume addresses one particular area of practice and is edited by experts with an outstanding international reputation. Readers will find the series to be an ideal source of up-to-date information on when to apply the various available technologies and how to perform safe treatment planning.

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Contents

Extremity Soft Tissue Sarcoma

1

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Contents

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1.1 Introduction

Extremity soft tissue sarcomas (eSTS) are the most common type of sarcoma (relative to retroperitoneal or primary bone sarcoma). Median age range of initial presentation is 40–60 years with a slight male prevalence among the 13,190 cases expected in 2022 in the United States, according to the American Cancer Society [1]. Risk factors include genetic predisposition (such as neurofibromatosis 1, hereditary retinoblastoma, Gardner syndrome, Gorlin syndrome, Li-Fraumeni syndrome, Werner syndrome, and tuberous sclerosis), chronic lymphedema (Stewart-Treves syndrome, lymphangiosarcoma, or angiosarcoma), viral infection (HIV and HHV-8 for Kaposi sarcoma), and prior radiation.

eSTS can occur within any organ or any anatomic location within the musculoskeletal system. Specifically, sarcomas arise from mesenchymal tissues such as the muscle, connective tissue, nerves, and vessels. Approximately, 60% of soft tissue sarcomas present in the extremities, which will be the focus on this chapter. Two-thirds of extremity soft tissue sarcomas present in a lower extremity, with the thigh as the most common subsite of origin [2]. Less common sites, in order of decreasing prevalence, are the trunk, upper extremity, retroperitoneum, and head and neck.

In general, the tumor presents as a painless lump of a few weeks' to months' duration, growing by direct spread along the longitudinal axis of the muscle compartment without initially traversing or violating the major fascial planes or bone. Invasion proceeds to the adjacent muscle, skin, nerves, and bone, and tumors of the trunk, head, and neck may invade adjacent structures earlier. Sudden increase in size of a tumor at presentation or afterward is usually due to hematoma formation rather than acute increase in volume of tumor cells.

Ten percent of patients have distant metastases at presentation, with the lung being the most common site of metastatic disease. Hematogenous metastasis is the most common pattern of metastatic spread and occurs more frequently in high-grade tumors and for large (>10 cm) tumors. Meanwhile, lymph node metastases are uncommon (<5% overall) but are an ominous sign when they occur. Histologies such as angiosarcomas, synovial cell sarcomas, clear cell sarcomas, rhabdomyosarcomas, and epithelioid sarcomas have a higher rate of nodal involvement (15–22%) [3, 4]. Skin involvement is seen in approximately 10% of patients.

The most common soft tissue sarcoma is undifferentiated pleomorphic sarcoma (UPS, previously known as malignant fibrous histiocytoma or MFH) which occurs in 30% of cases. Other sarcomas include (in order of most to least common) liposarcoma, leiomyosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor (MPNST), fibrosarcoma, myxoid liposarcoma, rhabdomyosarcoma, and other rare histologies.

1.2 Staging System

Staging of extremity soft tissue sarcomas has changed significantly from AJCC 7 to AJCC 8. While AJCC 7 distinguished whether the primary tumor was smaller or larger

Table 1.1 AJCC eighth edition staging system for extremity soft tissue sarcoma

AJCC eighth (extremity)	T	N	M	Grade
IA	T1	N0	M0	G1
IB	T2, T3, T4	N0	M0	G1
II	T1	N0	M0	G2, G3
IIIA	T2	N0	M0	G2, G3
IIIB	T3, T4	N0	M0	G2, G3
IV	T any	N1Mx	NxM1	G any

than 5 cm, T stage in AJCC 8 delineates tumor size up to 15 cm with the classification as follows: $T1 \leq 5\ cm < T2 \leq 10\ cm < T3 \leq 15\ cm < T4$. Staging for sarcomas originating in the head and neck or retroperitoneal regions has separate staging systems.

The most important change in AJCC 8 is incorporation of tumor grade, which is the most important factor in overall- and disease-free survival. In the absence of nodal or distant metastasis, grade 1 lesions (regardless of T stage) are defined as stage I, while grade 2 or 3 lesions are defined as stage II if they are T1 and stage III if they are larger (T2–T4). Stage IV continues to be defined by nodal and/or distant metastasis (Table 1.1).

Other prognostic factors include age, recurrent disease, positive surgical margins, and the histologic subtypes fibrosarcoma and MPNST [5]. The Memorial Sloan Kettering Cancer Center nomograms for sarcoma-specific death at 12 years [6] and local recurrence after limb-sparing surgery without radiation therapy [7] are useful tools for patient counseling and prognostication.

1.3 Treatment Strategies to Be Discussed in this Chapter

- Stage I: Surgery alone with margins >1.0 cm or +RT if closer margins
- Stage II/stage III: Surgery + RT with consideration of chemotherapy for downstaging of primary or if high-risk factors of distant metastatic disease
- Stage IV: Systemic therapy with consideration of surgery and RT

1.4 Management Principles

1.4.1 Workup

In general, patients with a soft tissue lump or mass that is growing in size should be evaluated by a musculoskeletal oncologist (orthopedic oncologist) or a surgical oncologist who specializes sarcomas. A detailed family history and specific questioning with regard to prior therapeutic irradiation are critical. The physical examination must detail the mass size, mobility, proximity to joints, and any evidence of neurovascular compromise, lymph node involvement, or fixation to the bone. The first step to assess a new soft tissue lump or bump is to obtain radiographs of the entire bone and then MRI with and without contrast of the site of concern. In order to establish diagnosis, a biopsy must be performed. Biopsy is best to be obtained or ordered by the treating surgeon. It is important to plan biopsy in line with the potential definitive resection.

Incisional biopsy was long considered the gold standard for biopsy due to the ability to review frozen specimen intraoperatively and ensure adequate tissue volume to make a diagnosis. Imaging can help identify areas of necrosis, liquefaction, fibrosis, and location of neurovascular structures that are typically avoided in obtaining viable biopsy specimen. Lastly, when considering open biopsy, there are several principles that make it crucial that a trained orthopedic oncologist or surgical oncologist be the one performing the procedure. Planning for the incision must take into account the definitive surgical approach, so the biopsy tract can be excised en bloc during the subsequent procedure. In the extremities, extensile, longitudinal incisions are used to minimize tissue contamination. Drains must also exit in line with the longitudinal incision. It is key to maintain meticulous hemostasis and avoid any associated neurovascular structures.

Core needle biopsies (CNB) have been shown to be a safe alternative to open/incisional biopsy procedures [8]. Accuracy of CNB has made this method of biopsy become more prevalent. They can be done in office or by a trained musculoskeletal radiologist under image guidance. It is overall more cost-effective when comparing the expenses included with open biopsy. Studies show varied results on the accuracy of histologic diagnosis of soft tissue musculoskeletal tumors compared with incisional biopsy, but the complication rate was lower than that of open biopsies [8, 9]. Fine needle aspiration is another less invasive method of biopsy but is less commonly utilized due to the need of more substantial tissue specimen for pathologists to adequately diagnose sarcomas. Excisional biopsy is rarely used for soft tissue masses, except in the case of benign soft tissue lesions, because of the risk of field contamination and how it can affect the definitive surgery. The choice of biopsy technique is typically a decision made by the evaluating orthopedic oncologist, weighing the clinical picture, imaging characteristics, and location (i.e., superficial vs deep).

1.4.2 Staging

After a diagnosis has been made, it is important to complete a staging workup. The staging recommendation for most soft tissue sarcomas remains the CT chest, abdomen, and pelvis, with MRI imaging of the primary site if not already performed. While lymph node metastases from sarcoma are uncommon, certain sarcomas warrant PET/CT evaluation if they have a known propensity for lymph node metastasis. A popular acronym is "SCARE," including synovial sarcoma (14–17% rate of nodal metastasis), clear cell sarcoma (20–28% rate of nodal metastasis), angiosarcoma (14–25% rate of nodal metastasis), rhabdomyosarcoma (14% rate of nodal metastasis), and epithelioid sarcoma (17–22% rate of nodal metastasis). All other sarcomas have nodal metastasis rates <5% [3, 4].

1.4.3 Treatment Planning

Once a tissue diagnosis has been established and staging imaging has been completed, a formal treatment plan can be created with the help of a multidisciplinary

sarcoma team. In general, for localized disease, soft tissue sarcomas are managed with surgery and radiation. Certain high-risk subtypes, such as synovial sarcoma, have improved outcomes with neoadjuvant chemotherapy. Additionally, in the setting of metastatic disease, consideration of chemotherapy would generally be recommended.

Radiation can be utilized in the neoadjuvant or the adjuvant setting. The ultimate goal for multimodal therapy is achieving complete (margin-negative) tumor resection while maximally preserving function. At our institutions, we prefer using neoadjuvant radiation therapy whenever possible. Preoperative radiation allows for smaller radiation dose and radiation field with improved tumor pseudocapsule formation that can aid in a close-margin resection. While there are lower local recurrence rates and better long-term functional outcomes, there is an approximately 30% increase in postoperative wound complications. With this incidence, the surgeon must take into consideration the need for utilizing secondary closure techniques versus planned flap coverage at the time of the operation [10]. Preoperative radiation can potentially aid in limb-salvage surgery by shrinking the size of the tumor and creating a pseudocapsule to help dissection around critical structures. In contrast, postoperative radiation has been shown to lead to increased edema, postradiation fibrosis, risk of pathologic fracture, and joint stiffness, with overall lower functional outcome. Postoperative radiation generally treats a larger field and requires higher total radiation dose. If a large dose of radiation is required around a long bone that will also need extensive periosteal resection for negative margins, frequently surgeons will consider prophylactic stabilization [11, 12]. The most common scenario to consider prophylactic stabilization would be femur intramedullary rod placement approximately 6–12 weeks after massive sarcoma resection about the femur involving the vastus intermedius and requiring bone resection or >15 cm of periosteal stripping and neoadjuvant radiation over 5000 cGy [11, 12].

Before the implementation of multimodal treatment regimens, amputation was the standard of care when surgically treating sarcomas of the extremities. With the addition of combined treatment regimens with radiation therapy and/or chemotherapy, there has been a shift toward limb-salvage procedures to preserve function without loss of survival [13, 14]. Amputation is now used in only approximately 5% of patients, as limb-sparing surgery is generally associated with less functional compromise. Amputation may be considered when it is impossible to achieve adequate tumor-free margins (due to involvement of major neurovascular structures or multiple compartments), if prosthesis is anticipated to provide better functional than a preserved limb (e.g., below-knee amputation and prosthetic leg) or if the patient has major complications from radiation as anticipated from dose and volume considerations [10, 13, 14].

Surgical treatment without the use of adjuvant treatment is typically reserved for stage I disease. This is less common as most extremity soft tissue sarcomas are typically found in later stages. Surgery alone is typically reserved for low-grade tumors or T1/T2 disease where resection with negative margins (R0) can be obtained. Studies have shown that local recurrence of low-grade, large lesions can be treated with re-resection without increasing overall mortality and producing a disease-free

patient survival [7, 13]. It must be reinforced that surgery alone must only be considered after a complete and thorough workup has been done showing no distant spread that would preclude a cure.

Limb-sparing multimodal treatment for soft tissue sarcomas is defined as surgical excision of the gross tumor with negative margins and adjuvant radiotherapy. Initially, limb-salvage was considered if the operation could achieve complete removal of the tumor with several centimeters of the peripheral tissue allowing for negative margins of 1–2 cm. Amputation was frequently recommended due to the inability to achieve the proposed "wide" margins. Since sarcomas are typically painless in nature, these tumors frequently go unrecognized until they grow large enough to create a mass effect on adjacent critical structures such as vessels, nerves, or bones. With the advent of the multimodal combined treatment regimens, limb-salvage procedures have become the more common treatment choice because acceptable negative margin size is now generally accepted to be as small as 2 mm [10, 13, 14].

As limb-salvage surgery prevalence continues to increase, the discussion of what constitutes adequate margins has become a topic of debate. The general consensus for a surgeon to determine adequate margins in the setting of planned surgery often correlates with the aggressiveness of the tumor determined on histologic grading. The original description of *wide resection* was described as resection of the tumor pseudocapsule with a normal cuff of the tissue surrounding tumor capsule but did not give any proposed measurements. Studies have proven that a margin of 2 mm is acceptable, as there was no difference in local recurrence found between 2 mm and greater than 2 cm margins [14]. Adding to the discussion of adequate margins, there is also the topic of planned positive margins. When carefully planning for resection, it was found that, with the use of multimodality treatment, planned positive margins of R1 (microscopic tumor cells) or a surgical margin of <1 mm of residual tumor cells had similar local recurrence rates to R0 margins. This allows for limb-salvage surgery even when critical structures are adjacent to the tumor bed. The local recurrence rates were found to be similar when compared to comparative resections that sacrificed those critical structures as part of the wide excision. To clarify, planned positive margins are not to be confused with inadvertent positive margins (defined as unexpected positive margins in the setting of trying to achieve R0) which carried a worse prognosis due to the decreased rate of local control [14, 15].

1.4.4 Integration of Primary Surgery with Multimodality Treatment

The rationale for combining RT and surgery is to optimize likelihood of local control while limiting the functional and cosmetic deficits of radical resection and the late consequences of high doses of radiation alone to large volumes of normal tissues. For stage II or III soft tissue sarcomas in particular, complete resection with limb-preserving surgery combined with RT (+/− chemotherapy) can replace limb amputation [16, 17] and is the current standard of care. The role of chemotherapy is

controversial; it is generally reserved for large and/or unresectable tumors and may be used for high-grade lesions due to the increased risk of distant metastases.

For a combined modality approach, surgical considerations include that surgical scars are at risk for subclinical disease. Therefore, scars should be oriented longitudinally in the extremity, as circumferential irradiation of scars oriented other than in a longitudinal fashion will have much greater impact on lymphatics draining the extremity, leading to lymphedema. Surgical clips should be used to mark the tumor bed and the tumor volume to aid in patient positioning for treatment planning. If there is concern for residual disease, a second excision should be considered, as positive margins greatly increase the risk of local recurrence, even when postoperative irradiation is given.

For stage IV disease, chemotherapy is the mainstay of therapy. If the patient has overall controlled disease on systemic therapy, surgical resection of the primary disease and metastatic sites (metastatectomy) should be attempted in selected patients with limited metastases to improve survival. SBRT (stereotactic body radiation therapy) can be used to effectively treat oligometastatic disease in the lungs or spine. Metastasectomy (in medically fit patients) or interventional radiology procedures such as percutaneous thermal ablation and arterial embolization are additional options in the oligometastatic setting.

If the patient is not a surgical candidate due to comorbidities or due to disease presentation, definitive radiation to doses greater than 70 Gy is needed for local control. Carbon ion radiotherapy for nonsurgical extremity STS yielded a five-year local control and overall survival of 76% and 56%, respectively [18].

1.4.5 Areas of Controversy

While it is clear that there is a benefit to multimodality treatment of extremity sarcomas with courses including radiation, there are some areas of controversy, particularly in the management of small, low-grade tumors and treatment sites in the hands and feet.

In terms of treatment of low-grade disease, Yang et al. randomized patients with eSTS to limb-sparing surgery and radiation therapy, with the addition of chemotherapy if high grade; the addition of radiation therapy did significantly improve local control for both high- and low-grade tumors [17]. Pisters et al. prospectively examined patients with T1 disease, carefully selected to have conservative limb-sparing salvage options in the setting of recurrence. Margin-negative patients did not receive radiation therapy, and observed patients had low rates of a ten-year local recurrence, 10.6% percent overall [19]. As such, patients with small low-grade tumors may be able to defer radiation treatment following a margin-negative resection, provided that conservative salvage options exist in the case of recurrence.

Many surgeons are reluctant to treat tumors of the hands and feet with radiation therapy due to concern for poor long-term function. This area of concern has been investigated by Bishop et al., who reviewed long-term outcomes and morbidity in patients treated with radiation therapy and surgery in the hands and feet. They found minimal impact on limb function, even though the majority of patients received

relatively high doses of radiation therapy in the postoperative setting (median dose of 6000 cGy); 2% of patients had a limb functional limitation and 4% experienced severe limitations requiring surgical procedures. Local control outcomes were very good, 86% at 5 years [20].

1.5 Radiation Therapy Techniques

Preoperative radiation therapy should be completed 4–6 weeks before surgery. Alternatively, postoperative radiation therapy may start as early as 2–3 weeks after surgery and should start no later than 8 weeks after surgery. External beam radiation therapy (conventional three-dimensional conformal radiation therapy (3D CRT) or intensity-modulated radiation therapy (IMRT)) and brachytherapy [16, 21] have both demonstrated improvement in locoregional control in patients with high-grade tumors and positive surgical margins [22].

Radiation therapy in moderate doses (6000–6500 cGy in 6–7 weeks, generally at 180 cGy per fraction delivered daily) is effective in eradicating microscopic extension of the excised gross lesion [23]. IMRT has been shown to have improved local control over brachytherapy [24] and over conventional 3D CRT [25]. Meanwhile, emerging research is exploring the role of hypofractionated radiation/SBRT.

1.5.1 Technical Considerations

1.5.1.1 CT Simulation

Because soft tissue sarcomas initially remain confined to the muscle compartment of origin, knowledge of the anatomic location of these muscle groups is important to the radiation oncologist to permit appropriate positioning of the limb. This in turn ensures that the compartment at risk is encompassed, that the tumor receives adequate coverage during radiation therapy (RT), and that compartments that are not involved are avoided. For instance, the frog-legged position may be beneficial when using two-dimensional or three-dimensional techniques for treatment of an inner thigh sarcoma, whereas when using IMRT, the affected limb should be straight if possible. Moving the contralateral limb further from the affected limb may offer increased flexibility in beam angles. Occasionally, treatment of posterior lesions in the prone position may be beneficial, but comfort should be assessed as it may affect reproducibility.

Immobilization of the proximal and distal joints to the lesion and comfortable, reproducible positioning are critical. Proximal joints can be immobilized with a Vac-Lok bag. Distal joints can be molded into an AccuForm/Moldcare cushion and then further immobilized with an Aquaplast mask over the top; this is particularly crucial when the sarcoma is located in the hand or foot (Fig. 1.1 with hand sarcoma setup). When using IMRT techniques, it is important to include the entire length of any irradiated weight-bearing bone in the scanned volume, as several dosimetric constraints require the total bone volume for accurate calculations (Fig. 1.2 with extremity setup for the lower limb).

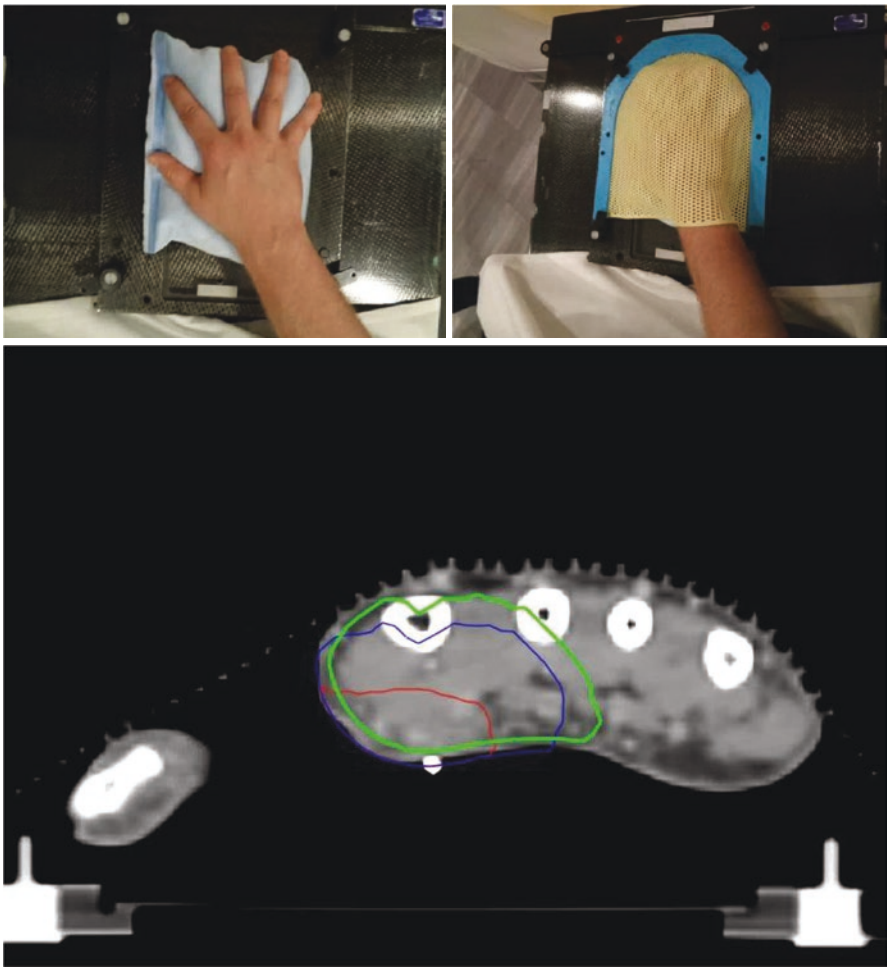

Fig. 1.1 Simulation for preoperative radiation therapy for sarcoma of the right hand (second metacarpal ray). Patient places his/her hand into a Moldcare cushion and is secured with Aquaplast mask; prone setup with remainder of the right upper limb immobilized with Vac-Lok bag

1.5.1.2 Target Definitions

MRI-based imaging should be used to define preoperative extent of tumor. The gross tumor volume (GTV) is defined using T1 contrast-enhanced MRI images and suspicious edema seen on MRI T2 images (Fig. 1.3). Classically, the clinical target volume (CTV) was created from a 5 cm longitudinal and 2 cm radial expansion (along muscle planes) from the GTV, and the planning target volume (PTV) is generated by an additional 0.7–1.0 cm isotropic expansion off of the CTV. Of note, early studies did not benefit from modern MRI imaging and image guidance.

In contemporary studies, MRI has become standard, and CTV margins have been reduced, generally 3–4 cm in the longitudinal direction (along muscle planes)

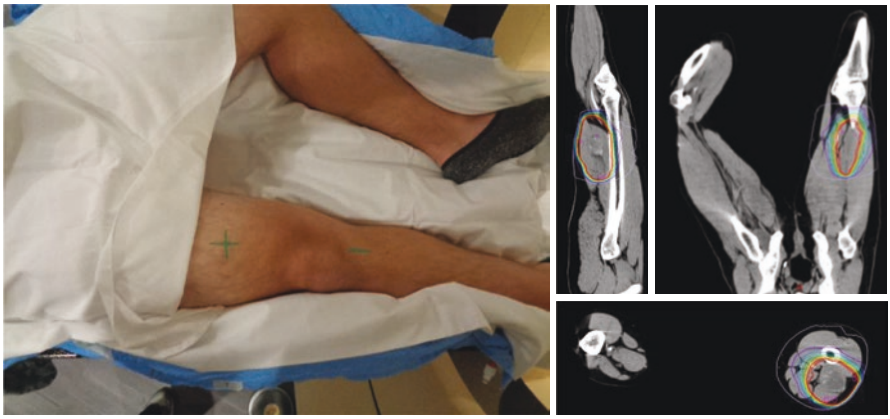

Fig. 1.2 Simulation for preoperative radiation therapy for sarcoma of the right posterior thigh (posterior compartment). Patient is scanned reversed (feet first) on the table with long Vac-Lok bag immobilization at the hip, knee, and ankle; treated leg straight and the contralateral limb frog-legged out of the way

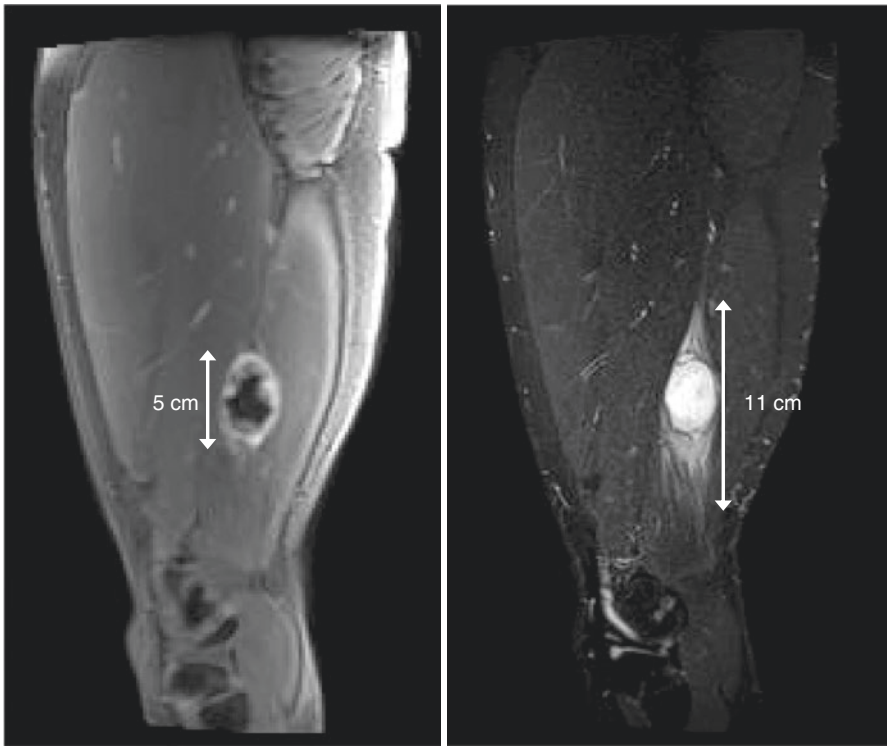

Fig. 1.3 Preoperative treatment planning imaging for high-grade extremity sarcoma. Note that tumor mass itself is approximately 5 cm (sagittal T1 post), but suspicious peritumoral edema extends >10 cm (sagittal T2 STIR)

and 1–1.5 cm radially [25, 26]. It may be possible to reduce these margins further with image guidance; in RTOG 0630, preoperative treatment with reduced target volumes (both CTV and PTV) with image-guided radiation therapy (IGRT) was explored. In this single-arm phase II study, patients were treated to a longitudinal CTV expansion of 3 cm and radial margin of 1.5 cm for high-grade tumors or GTV ≥8 cm or to a longitudinal CTV expansion of 2 cm and radial margin of 1 cm for low-grade tumors or GTV <8 cm, with PTV expansions of 0.5 cm. In their initial report, this resulted in reduced late toxicities (10.5% grade ≥2 vs 37% grade ≥2 in historic control without IGRT) without compromising early local control [27]. This remains to be validated with long-term follow-up but has been implemented at many institutions.

At our institution where all patients undergo MR staging unless otherwise indicated and are treated with IGRT, we generally expand the CTV by 3–4 cm longitudinally and 1–1.5 cm radially for high-grade tumors and by 2–3 cm longitudinally and 1 cm radially for low-grade tumors. Final GTV to CTV margin expansion is influenced by radiographic appearance of the tumor; liposarcomas tend to be more encapsulated and have a more regular margin, so we favor the smaller expansion, while undifferentiated pleomorphic sarcomas are more locally invasive with irregular margins, and we favor the larger expansion. Elective nodal coverage is not generally recommended. Finally, a 0.5 cm CTV to PTV expansion is felt to be sufficient when using image-guided radiotherapy (IGRT); otherwise, a margin of 0.7–1 cm is recommended. Guidelines for preoperative and postoperative external beam radiotherapies for extremity STS are summarized in Table 1.2.

Table 1.2 Dose and volume definitions for extremity soft tissue sarcoma

	Preoperative	Postoperative
Dose	5000–5040 cGy, 180–200 cGy fractions to PTV (consider boost for close/positive margin postoperatively)	4500–5040 cGy, 180–200 cGy fractions to PTV1, followed by a boost of 1000–1600 cGy to high-risk tumor bed (PTV2)
Volume	CTV—GTV plus 3–4 cm in the longitudinal direction (along muscle planes) and 1–1.5 cm radially, including peritumoral edema but not expanded beyond the bone surface, joints, or fasciae. PTV—CTV plus 0.5–1 cm depending on setup reproducibility and image guidance. *(PTVeval structure can be used by pulling in PTV 0.3 cm from the skin surface)*	CTV1—Tumor bed plus 3–4 cm in the longitudinal direction (along muscle planes) and 1.5 cm radially, including peritumoral edema, surgical clips, scar, and drain site but not expanded beyond the bone surface, joints, or fasciae. PTV1—CTV1 plus 0.5–1 cm depending on setup reproducibility and image guidance. CTV2—Tumor bed plus 1–2 cm in the longitudinal direction and 1–1.5 cm radially, including peritumoral edema but not expanded beyond the bone surface, joints, or fasciae. PTV2—CTV2 plus 0.5–1 cm depending on setup reproducibility and image guidance (PTVeval structure can be used by pulling in PTV 0.3 cm from the skin surface)

1.5.1.3 Radiation Planning

Three-dimensional treatment planning is important to ensure coverage of the target area while sparing normal tissues. A combination of photons and electrons may enhance optimization of the dose in the treated volume, although electrons are rarely needed if IMRT techniques are used. Beam energies of 4–6-MV photons (or higher) are necessary to ensure homogeneity of radiation dose delivery.

In the preoperative setting, bolus is rarely used as the high-risk skin is planned to be surgically excised. PTV expansions may often extend out of the skin; for planning purposes, a "PTVeval" structure can be generated that excludes the outer 0.3 cm of the skin. In the postoperative setting, bolus may be used when there is concern for microscopic residual skin or superficial subcutaneous tissue involvement by tumor; in this setting, one should bolus scar or drain sites to 5000 cGy unless adequate coverage can be obtained using tangential beams. Gonadal shielding is used for fertility preservation in men undergoing irradiation for lower-extremity sarcomas. To reduce risk of lymphedema, it is important that at least a 1 cm strip of the skin is spared. In RTOG 0630, the goal was that no more than 50% of this strip of the skin would receive 2000 cGy; out of our institution, we avoid hot spots in a delineated lymphatic basin and keep the mean dose less than 3000 cGy. Additionally, radiation dose to joint spaces should be limited wherever possible; for example, when treating a posterior compartment sarcoma, we delineate the popliteal joint space (including posterior and anterior cruciate ligaments) and avoid hot spots in that area as well as limiting the mean dose to <4000 cGy. The use of IMRT-based approaches has been shown to reduce risk of grade ≥2 radiation dermatitis and edema [25].

One of the most important considerations in the use of intensity-modulated radiation therapy (IMRT)-based planning for extremity soft tissue sarcomas is to reduce and modulate dose to weight-bearing bones. The overall rate of radiation-associated fracture in eSTS is about 4–6%, mostly in the thigh [11, 28–30]. Studies have shown that the maximum dose to the femur is associated with increased risk of fracture [11] and circumferential doses to the weight-bearing bone exceeding 5000 cGy can also increase risk for fracture [31]. Other dose-volume constraints have been suggested based on dosimetric studies [32–35], including the following (Table 1.3):

Investigators from the Princess Margaret Hospital (PMH) incorporated dosimetric and clinical factors (such as age, gender, tumor size, location/compartment, and periosteal stripping) into a predictive model or nomogram [33]. While not prospectively validated, in studies that have studied fracture risk after IMRT, there does appear to be a benefit to modulating dose to the weight-bearing bone; for example,

Table 1.3 Suggested dosimetric constraints for weight-bearing bones using IMRT

Total dose or volume ≤ limit	To:
64% total bone volume	$V_{4000\ cGy}$
3700 cGy	Mean dose
6600 cGy	Max point dose
Full circumference of the bone	5000 cGy

a study by Folkert et al. demonstrated a cumulative risk of fracture at 5 years of 6.7% versus an expected risk of 25.6% based on the PMH nomogram [36].

1.5.2 Preoperative External Beam Radiation Therapy

Preoperatively, a dose of 5000 cGy in 25 fractions is generally given (5000–5040 cGy in 25–28 fractions of 180–200 cGy). Preoperative radiation therapy has the potential advantages of rendering an unresectable tumor resectable, allowing limb-salvage surgery, and reducing the risk of seeding at the time of surgery. Due to smaller treatment volumes, preoperative radiation therapy has fewer late treatment side effects, such as fibrosis, edema, and joint stiffness, compared to postoperative treatment [37]. In 110 patients with locally advanced disease treated with preoperative radiation therapy, the local failure rate was 10%, and the local control rate was 83% at 5 years [38]. Suit et al. [39] reported a local failure rate of 10% with 181 patients treated in a similar fashion.

In the event that the patient who has received preoperative radiation and then undergone surgery is found to have positive margins, observation or additional postoperative boost radiation therapy can be considered. Generally, treatment is 1600–1800 cGy in 180–200 cGy fractions for microscopic residual disease and 2000–2600 cGy in 180–200 cGy fractions for gross residual disease. Whenever possible, repeat resection should be considered for microscopic or gross residual disease.

1.5.2.1 Hypofractionation

While conventional fractionation (180–200 cGy/fraction) is felt to be the standard treatment for patients with eSTS, investigators have explored the use of hypofractionated courses of therapy with fraction sizes ≥300 cGy. There may be some radiobiological benefit to this as the α/β for sarcomas is felt to be in the range of 4–5; thus, the biological equivalent dose, or BED for a 5000 cGy course in 25 fractions would be approximately 72, roughly equivalent to the BED for a 3000 cGy course in 5 fractions of approximately 70. In a large prospective trial by Kosela-Paterczyk et al., of which 86.4% had eSTS, patients received 2500 cGy in 5 fractions prior to wide local excision (with a boost of 3000 cGy in 15 fractions for R1 resection). Local control was approximately 80% at 3 years with this regimen, with acceptable toxicity [40]. For patients with myxoid liposarcomas, local control with this regimen was 90% at 5 years [41]. In the adjuvant setting, for elderly patients, a course of 3900–4800 cGy in 300 cGy fractions has been implemented and was well tolerated, with local control of approximately 85% at 3 years [42].

Dose-escalated hypofractionation has been further explored to higher doses per fraction. While only in abstract form, Kalbasi et al. reported on their preoperative regimen of 3000 cGy in 5 fractions in 16 patients. Pathologic necrosis at resection was 57%, and 19% of patients had wound complications [43]. Kubicek et al. reported on a small series of patients (n = 13 patients, 14 tumors) with sarcomas of the leg, arm, or groin and delivered 3500–4000 cGy in five fractions preoperatively.

Median tumor necrosis at resection was 60%, and only one local recurrence has been observed at a median follow-up of 1 year. Limited acute skin toxicity was noted and all wound complications resolved [44].

Hypofractionation has also been explored extensively with concurrent chemotherapy and will be discussed further below.

1.5.3 Postoperative External Beam Radiation Therapy

When radiation is planned postoperatively, a total dose of 5940–6600 cGy in 180–200 cGy fractions is given. Even with this dose, which is higher than preoperative dose, local failure rates range from 10% to 22% for postoperative irradiation [17, 39, 45, 46]. This is perhaps because this timing of radiation and surgery does not have the advantage of sterilization of clonogens, potentially allowing more seeding at the time of surgery. A randomized trial of preoperative versus postoperative radiotherapy in soft tissue sarcomas of the limb [10] revealed no differences in local recurrence rate, regional or distant failure rate, or progression-free survival between the two arms, though overall survival was slightly better in those who received preoperative radiation therapy. While preoperative RT was associated with a significantly increased rate of wound complications compared to postoperative RT (35 vs 17%), postoperative RT was associated with worse long-term functional impact due to fibrosis, edema, or joint stiffness [37].

1.5.4 Brachytherapy

While brachytherapy has been used less frequently with increasing use of external beam approaches, indications exist for treatment of extremity sarcomas, such as pediatric and reirradiation cases. Consensus recommendations for therapy have been published by the American Brachytherapy Society (ABS) [47, 48]. Brachytherapy offers the advantage of an abbreviated course of therapy and more targeted distribution of dose relative to external beam approaches. Adjuvant brachytherapy improves local control after complete limb-sparing resection of soft tissue sarcomas; an early study by Pisters et al. demonstrated that limb-sparing surgery with adjuvant brachytherapy did not compromise survival relative to amputation [21]. This improvement in local control was later observed to be limited to patients with high-grade histopathology. Brachytherapy alone may therefore be recommended in the setting of high-grade lesions less than 10 cm in size with negative margins on resection. In these cases, the lesion will be treated to 3000–5000 cGy in 200–400 cGy fractions delivered twice daily. For larger lesions or lesions with close/positive margins, external beam radiation therapy is generally added [49].

Brachytherapy treatment is delivered following placement of multiple catheters into the operative bed at the time of the surgery, placed 1–1.5 cm apart, generally with a single-plan implant. The treatment region should extend at least 2 cm longitudinally past the extent of the tumor bed and at least 1 cm laterally. Treatment

delivery is performed >5 days postoperatively to reduce the risk of complications but can be done earlier with staged reconstruction. Treatment depth is 0.5–1 cm from the applicators.

1.5.5 Intraoperative Radiation Therapy (IORT)

Intraoperative radiation therapy with electron beam radiation therapy or high-dose-rate brachytherapy may be given at the time of surgery, either to supplement preoperative therapy or as an initial dose of radiation to be followed by postoperative radiation therapy. About 1000–1500 cGy is generally given as a single fraction for microscopic residual disease, and 1500 cGy or higher can be given for gross residual disease with the benefit of increased infield control [48, 50, 51].

1.6 Chemotherapy

1.6.1 Overview

Numerous clinical trials have investigated the value of chemotherapy for patients with soft tissue sarcomas, but the data are difficult to interpret because of the heterogeneity of the tumors studied, the relatively small number of patients in each trial, and the variety of drugs and dosage schedules investigated [52]. In an early study by Rosenberg et al. who considered the question of limb-sparing surgery versus amputation, they also investigated the role of adjuvant chemotherapy (doxorubicin, cyclophosphamide, and methotrexate); they found that the addition of chemotherapy improved both disease-free survival (92% vs 60%, $P = 0.0008$) and overall survival (95% vs 74%, $P = 0.04$) [16].

Contemporary data clearly indicate that multidrug chemotherapy regimens, combined with radiation therapy, may have a significant impact on improving local control and ultimate outcome. A meta-analysis by Pervaiz et al. showed that adjuvant chemotherapy improves local control and reduces risk of distant metastases [53]. The most common regimens include combinations of methotrexate, ifosfamide, cyclophosphamide, vincristine, doxorubicin (Adriamycin), actinomycin D, gemcitabine, docetaxel, and dacarbazine. Methotrexate, doxorubicin, and ifosfamide all have published response rates >20%, with doxorubicin felt to be the most active single agent [54]. Combinations of these drugs, particularly doxorubicin and ifosfamide, have been shown to have increased response rates, at the cost of greater toxicity [55, 56]. The addition of ifosfamide to doxorubicin improved overall survival as well [53]. In leiomyosarcoma, gemcitabine and docetaxel combinations have shown activity [57].

In general, certain sarcomas such as synovial sarcoma, leiomyosarcoma, myxoid liposarcomas, pleomorphic sarcoma, and angiosarcoma are considered sensitive to single-agent or combination regimens [58]. Resistant sarcomas include alveolar soft part sarcoma, clear cell sarcoma, well-differentiated liposarcoma, and malignant

solitary fibrous tumor [59]. In the United States, patients with stage II and III (high-grade) tumors currently are generally offered multi-agent chemotherapy. Utilization of immunotherapy, biologic agents, and novel combinations of radiation and systemic treatment are areas of active investigation.

An appropriate washout period for full-dose systemic therapy should be observed before radiation therapy is begun. For instance, 2 or 3 days should elapse before and after administration of doxorubicin (Adriamycin) before starting radiation therapy.

1.6.2 Combinations of Radiation Therapy and Chemotherapy

Integration of systemic therapy directly into neoadjuvant therapy for high-risk eSTS has been explored using an interdigitated or "sandwich" regimen. In the prospective study published by Delaney et al., they treated patients with high-grade tumors ≥8 cm with alternating courses of chemotherapy and radiation therapy; patients received 1 cycle of mesna, adriamycin, ifosfamide, and dacarbazine (MAID), followed by 2200 cGy in 11 fractions, a second cycle of MAID and additional 2200 cGy in 11 fractions, and finally another cycle of MAID before resection. For patients with positive margins, another 1600 cGy in eight fractions was given postoperatively, and three additional cycles of MAID were planned in the adjuvant setting. Oncologic outcomes in this high-risk disease setting were quite good with local control rates at 5 years of 92%; distant metastases were also favorable compared to historical controls, with a five-year freedom from distant metastases of 86% [60].

Investigators have also examined the role of concurrent chemotherapy with radiation therapy. A range of combinations have been explored, including combining radiation therapy with doxorubicin, ifosfamide, taxanes, and trabectedin (a synthetic chemical based on a marine toxin that has a range of anticancer activities, including affecting DNA binding and repair, transcriptional inhibition, and modifying the tumor microenvironment) [61, 62]. Combinations with ifosfamide have been used extensively and have oncologic outcomes available; Stubbe et al. published their work on neoadjuvant radiation therapy for soft tissue sarcoma (60% in the extremities) with a course consisting of ifosfamide (1.5 g/m(2)/day, d1–d5, q28) and doxorubicin (50 mg/m(2)/day, d3, q28) plus concurrent radiotherapy with a target dose of 5000–6400 cGy (median 6000 cGy). Local control at 5 years was 90%, and distant metastasis-free survival at 5 years was 67% [63].

In some cases, these regimens have also been combined with hypofractionated regimens. MacDermed et al. published on the results of their institutional experience using the Eilber regimen developed at the University of Chicago, consisting of ifosfamide (2.5 g/m^2 per day for 5 days) with concurrent radiation therapy (2800 cGy in 350 cGy daily fractions) for locally advanced (stage III and IV) soft tissue sarcomas of an extremity. For patients undergoing resection, local control at 5 years was 89%, with distant metastasis-free survival rates of 53.4% in stage III patients [64]. Pennington et al. published on their long-term results with concurrent ifosfamide and hypofractionated radiation therapy. In 116 patients receiving 2800 cGy in eight fractions with concurrent ifosfamide followed by limb-sparing surgery, they saw an

actuarial local recurrence rate of 17% at 6 years and distant failure rate of 35% at 6 years [65]. Lu et al. published on their results from their phase II study in which they treated high-risk eSTS with dose-intense chemotherapy with preoperative hypofractionated radiation; patients received epirubicin and ifosfamide pre- and postoperatively and ifosfamide concurrently with 2800 cGy in eight fractions. Local control at 5 years was 87%, and distant metastasis-free survival was 56% [66].

1.6.3 Role of Biologic Therapy in Combination with Radiation Therapy

A particularly exciting area of interest is the combination of radiation therapy and biologic therapy. After single-agent pazopanib (a multikinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-KIT, and FGFR) was shown to have a progression-free survival benefit compared to placebo in metastatic non-adipocytic soft tissue sarcoma [67], it has been explored in combination with radiation therapy [68]. In the PAZNTIS trial (ARST1321/ ClinicalTrials.gov Identifier: NCT02180867), while only presented in abstract form so far, in children and adults with intermediate–/high-risk non-rhabdomyosarcoma and soft tissue sarcoma treated in patients with the addition of pazopanib to preoperative chemoradiation, the rate of ≥90% pathologic necrosis (near-complete pathologic response) was 58.3% with pazopanib versus 22.2% without [69]. This is being investigated further with dose-reduced preoperative radiation therapy (3600 cGy in 18 fractions) in the PASART-2 trial (ClinicalTrials.gov Identifier: NCT02575066).

1.7 Sequelae of Treatment and Dose Constraints

Short-term sequelae of radiation therapy usually are limited to moist desquamation in the high-dose volume, particularly if the beams are tangential to the skin. The risk is increased in patients with more than 50% of the diameter of the extremity included in the field, as well as in those receiving concurrent doxorubicin [52]. Notably, radiation recall reactions are described with doxorubicin. Major wound complications (requiring a subsequent invasive procedure) occur in approximately 10% of patients after surgical resection, with or without postoperative irradiation. This rate may be somewhat higher in patients treated with preoperative irradiation or brachytherapy within 5 days after surgical resection [52, 70]. On the other hand, high-dose radiation does not appear to compromise the viability of skin grafts used to repair defects after sarcoma surgery, assuming adequate time is allotted for healing (at least 3 weeks).

Long-term sequelae after conservative surgery and irradiation for extremity lesions may significantly limit the function of the preserved limb. These sequelae include decreased range of motion and muscle strength, contracture of the joint, edema, pain, and bone fracture. Complications can be reduced by sparing a strip of

the normal tissue and uninvolved muscle to allow lymphatic drainage from the extremity and prompt referral to physical therapy. Mobility of the extremity should be stressed, and patients should be placed on an exercise and range-of-motion program early in the course of therapy. Finally, secondary malignancy risk is a major consideration especially in the pediatric or adolescent population.

Multiple dose constraints are used to reduce the risk of bone fracture, V40Gy <64% and maximum point dose <59 Gy [32], or avoid circumferential bone coverage with the 50 Gy isodose line [31]. Other factors which increase the risk of fracture include periosteal stripping during surgery and perioperative chemotherapy [30, 31, 33]. A nomogram has been created to predict the risk of femoral fracture after combined modality treatment of STS of the thigh [33], although with the use of IMRT, this fracture rate appears to be significantly lower [36]. Additionally, one should strive to achieve mean dose <30 Gy to vessels and <40 Gy to joint spaces. IMRT can permit enhanced target volume coverage in soft tissue sarcomas while maximally sparing normal tissues with the goal of decreased morbidity as well as potentially improved local control [25].

1.7.1 Follow-Up/Surveillance

Indefinite (lifelong) follow-up is recommended due to the risk of late recurrence and potential late effects from surgery, radiation therapy, and chemotherapy. Physical examination, functional assessments, and primary/local site and chest imaging should be performed every 3 months for the first two posttreatment years, every 4 months for posttreatment year three, every 6 months for posttreatment years four and five, and then annually thereafter. If it is needed, refer the patient to physical therapy as soon as possible.

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Retroperitoneal Sarcoma

2

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2.1 Introduction to Retroperitoneal Sarcoma

Retroperitoneal sarcomas (RPS) are relatively rare tumors, with an average incidence of 2.7 cases per million population [1]. Approximately 10–15% of adult soft tissue sarcomas (STS) arise in the retroperitoneum, the anatomic space in the abdominal cavity posterior to the peritoneal cavity and anterior to the paraspinous musculature. The majority of RPS present with large masses (median size of 15 cm) as they typically produce few symptoms until they are large enough to compress or invade surrounding structures [2]. The most common histologies of RPS in adults include well-differentiated and dedifferentiated liposarcoma and leiomyosarcoma, followed by undifferentiated/unclassified STS [3, 4]. The most common histologies of RPS in children are extraskeletal Ewing sarcoma/primitive neuroendocrine tumor, alveolar rhabdomyosarcoma, and fibrosarcoma [5]. Oncologic outcomes including patterns of spread differ based on the histologic subtype and grade of the tumor. In the future, these differences may impact treatment strategies including the role of neoadjuvant/adjuvant therapy and follow-up surveillance after definitive treatment.

2.2 Historical Outcomes

Studies have demonstrated that aggressive surgical management including a complete surgical resection is one of the most important prognostic factors in localized disease for RPS [6, 7]. In contrast to extremity sarcomas, even with a complete resection, locoregional recurrence is the majority of first recurrences in RPS with approximately 5% per year from time of initial operation [8]. Moreover, local recurrence is the site of first failure in 90% of cases even after complete resection. Distant

metastases develop in 20–30% of patients, with an increased risk for those patients with high-grade tumors. Overall five-year survival rates for this disease range from 50 to 70% [6, 9–11]. Given these suboptimal outcomes, the role of neoadjuvant/adjuvant treatment including radiotherapy and chemotherapy is a current area of study.

2.3 Management Principles

A thorough workup with multidisciplinary review is necessary to guide treatment decisions (see Table 2.1). A key component to the evaluation of a patient with a retroperitoneal mass includes a complete radiographic evaluation. Preferred diagnostic studies include contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis. A chest CT is included as the lung is the most common site of metastasis, and a CT of the abdomen and pelvis helps determine the anatomic relationship of the mass relative to other structures. Magnetic resonance imaging (MRI) of the abdomen and pelvis is helpful for assessing disease in the pelvis and to better assess involvement of the bone or muscle. MRI is better at defining the extent of the local tumor involvement and can be helpful in planning for radiation therapy. Other advanced images such as PET (positron emission tomography) can also be utilized to enhance detection of metastatic disease. Criteria for unresectability include radiographic evidence of peritoneal implants, distant metastases (not potentially resectable for cure), spinal cord involvement, and extensive vascular involvement that cannot be reconstructed. Kidney function workup is necessary in any patient who may receive ipsilateral nephrectomy as part of a surgical resection. Careful evaluation of liver function may also be necessary in selected cases where partial liver resection is recommended.

Table 2.1 Workup

- H&P
- CBC/CMP
- CT chest/abdomen/pelvis with IV contrast (consider abdominal/pelvic MRI with and without IV contrast)
- Advanced imaging such as PET to enhance detection of metastasis as needed
- Image-guided core needle biopsy
- Confirm function of contralateral kidney:
  - Radionuclide functional renal scan (Tc-99mMAG3) versus CT with IV contrast + GFR.
  - If renal function is borderline, consult nephrology and discuss risks of dialysis with patient.
- Consider genetic testing for personal/family history suggestive of genetic syndromes, including li-Fraumeni syndrome, FAP (familial adenomatous polyposis), Gardner syndrome, retinoblastoma, and neurofibromatosis
- Multidisciplinary tumor board discussion

Tissue diagnosis recommendations with image-guided percutaneous core needle biopsy are recommended unless imaging is diagnostic and surgical resection planned first step in treatment. Risk of needle track seeding is minimal and therefore not a reason to avoid a core needle biopsy. If a retroperitoneal mass is found incidentally during surgical exploration for another procedure or it is thought to be an adnexal mass, biopsies should not be done at the time of surgery to avoid contamination of the peritoneal cavity. The patient should have appropriate imaging and then proceed with image-guided core biopsies [12]. Frozen biopsies for diagnostic purposes are not performed as management should be determined after final pathology and discussion at a multidisciplinary tumor board.

Defining the optimal treatment paradigm is difficult given the rarity of RPS and the complexity of treatment. A number of consensus groups comprised of sarcoma experts have recommended that RPS cases should be referred to high-volume centers with multidisciplinary expertise in order to optimize outcomes. However, even among clinical sarcoma experts, there remains equipoise as to the best treatment strategy (see Table 2.2, [12–15]). Thus, enrollment on clinical trials (to be discussed later) or prospective data registries is advised.

Table 2.2 Brief overview of consensus-based guidelines for initial treatment of resectable RPS

Expert groups	Consensus statement
National Comprehensive Cancer Network (NCCN, United States, 12)	• For potentially resectable tumors, surgical resection with negative margins (R0) is emphasized. • Intraoperative radiotherapy (IORT), preoperative external beam radiation therapy (EBRT), and preoperative chemotherapy are options. • EBRT with simultaneous integrated boost to high-risk margin in experienced centers only. • Routine administration of postoperative EBRT is not recommended except in highly selected cases in which local recurrence would result in undue morbidity.
European Society for Medical Oncology (ESMO, 13)	• For potentially resectable tumors, wide resection with negative margins (R0) is recommended. • Preoperative treatments (EBRT, chemotherapy, regional hyperthermia, and combinations) are not established but can be considered in technically unresectable/borderline cases that could be converted to resectable cases. • Postoperative EBRT may be an option in well-defined areas at high risk for local recurrence though otherwise is of limited value with significant toxicity. • Brachytherapy is of unproven value and is associated with significant short- and long-term complications. • IORT is of unproven value. • Role of adjuvant chemotherapy is not established but principles may be extrapolated from extremity STS.

(continued)

Expert groups	Consensus statement
Trans-Atlantic retroperitoneal sarcoma working group (TARPSWG, 14)	• For potentially resectable tumors, resecting the tumor en bloc including adherent structures even if not overtly infiltrated to achieve macroscopically negative margins and minimize microscopic positive margins is recommended. • Neoadjuvant therapy (chemotherapy, chemotherapy + regional deep wave hyperthermia, EBRT, or chemoRT) is safe for well-selected patients and may be considered after careful review by a multidisciplinary sarcoma tumor board. It is appropriate to consider for borderline/unresectable cases. • IORT is of no study-proven value. Although it may be considered for margins considered at risk, the field often is too large for its practical application. • Brachytherapy and postoperative EBRT after complete resection are of no study-proven value and may be associated with significant toxicity.
International expert panel (15 academic radiation oncologists specialized in sarcoma treatment, 15)	• For potentially resectable tumors, macroscopic surgical resection (R0/R1) is emphasized. • Role of preoperative RT for RPS has not been proven. Intensity-modulated RT is preferred unless three-dimensional conformal RT can meet dosimetric parameters. • Preoperative boost dose with dose painting is not recommended as standard practice and is best used only as part of a protocol or at experienced centers. • There is no comment on chemotherapy. • IORT benefit has not been demonstrated in controlled studies and is best delivered at experienced centers and/or on protocol.

2.4 Surgery

Surgical resection traditionally has been the mainstay curative treatment for localized RPS. The primary treatment for RPS is gross en bloc resection with the goal for a R0 (microscopically negative margins) surgery. Multiple studies have demonstrated that other than histology, the most important prognostic factor for local control and overall survival (OS) is the ability for a complete surgical resection R0 to be performed [3, 4]. While R0 resection may be the primary surgical goal, this is often difficult to achieve due to tumor size and anatomic constraints, and approximately 30–40% of RPS resections are R1 (microscopically positive margins). En bloc resection should include adherent organs to best achieve a negative microscopic resection with a goal of a negative rim of the tissue. This may not always be able to be achieved with critical neurovascular structures. The surgeon must determine the risk versus the benefit of the resection based on the individual patient and tumor characteristics, for instance, if the tumor abuts the liver and pancreas. A multidisciplinary team of surgeons may need to be assembled for their expertise including tumors involving major vascular resection and reconstruction, bone resection, and other visceral organs that may be involved. Once the specimen has been resected, the pathologist must be thoughtful to carefully select the samples of the

tissue for pathologic evaluation given that it is generally not feasible to evaluate the entire specimen. Thus, determining true margin status can be challenging and prone to error.

Surgical specimens will often include en bloc removal of nearby organs suspected to be involved by tumor which commonly include the kidney, colon, small bowel, psoas muscle, and in selected cases spleen, pancreas, partial liver, gallbladder, adrenal gland, peritoneum, diaphragm, adnexae, bladder, and other structures. A 2009 retrospective analysis of 382 patients by Bovalot et al. suggested a potential benefit of more aggressive resection described as a systematic resection of noninvolved contiguous organs to ensure wide margins. They reported improved five-year OS rates of 86% versus 66% and 3.29-fold lower rate of abdominal recurrence compared to simple resection of tumor and a correlating three-year abdominal recurrence of ~10% versus 50%. R1 resections resulted in worse locoregional control (49% vs 79% at 3 years) and an OS detriment (54% vs 67% at 5 years) [3]. While other studies have concluded that local control is improved with an R0 resection, whether this translates into a survival benefit is less certain with survival being most strongly associated with grade and histology [16, 17]. Gronchi suggested a similar retrospective pattern of benefits in 288 patients after a shift in institutional surgical approach to systematically remove organs and tissues not clinically involved but located within 1–2 cm of tumor, resulting in an improved five-year local recurrence rate of 48% versus 28% and a statistically nonsignificant improvement of a five-year OS rate 51% versus 61% [18].

Despite the aforementioned results, the extent of surgery remains controversial given the retrospective nature of the above data and potential for patient selection and confounding bias, as well as neglecting rates of reoperation and postoperative complications. In addition, some retrospective data involving less aggressive approaches has demonstrated similar outcomes. In one large series of 675 patients with primary RPS treated at the Memorial Sloan Kettering, 73% of patients had 0–1 organs removed with an R0 rate of 50% and R1 rate of 35%. This translated to a five- and ten-year disease-specific survival of 69% and 55% and a five- and ten-year local recurrence rate of 39% and 45% which was similar to the above series [19]. Bremjit reported comparable outcomes in 132 patients, 30.3% of whom received preoperative RT, whose surgical approach involved only removing contiguous organs when they were grossly involved; 60.5% of patients had 0–1 organs removed. This resulted in 45.5% R0 and 44.7% R1 resections with two-year and five-year OS of 85% and 71% [20].

Appropriate recommendations for surgical extent may partly depend on tumor histology and grade. For example, well-differentiated liposarcoma (WD-LPS) has a high risk of local recurrence but rarely invades other organs and is widely thought to have virtually no capacity for metastasis [21]. Therefore, deferring an aggressive approach in this case may be prudent. MD Anderson retrospectively assessed 83 patients with retroperitoneal WD-LPS, 46% of whom received concomitant organ resections and 54% had no organs removed, collectively achieving a 92% R0/R1 resection rate. Fifteen percent of patients with organs removed showed organ invasion. However, in multivariate analysis, concomitant organ resection was not

associated with improved OS or DFS (disease-free survival), and concomitant organ resection was associated with higher complication rates and longer hospital stays [22]. Thus, some experts emphasize the need for histology-guided approach to RPS surgical management [14, 15, 23]. Lastly, the role of debulking surgery (R2 resection) is typically reserved for palliation of large unresectable WD-LPS as gross residual disease and tumor rupture have been suggested as the worst indicators for OS [24].

2.5 Radiotherapy

Radiotherapy in the context of extremity STS is well established and based on multiple prospective randomized trials in the preoperative, intraoperative, and postoperative settings with significant improvement in local control allowing for limb-salvage therapy [25–27]. SEER (Epidemiology and End Results) and NCDB (National Cancer Database) analyses have suggested OS benefits in patients with high-grade extremity STS who received radiation therapy [28, 29]. Specifically in RPS, the primary treatment failure after resection is local, highlighting the potential importance of radiotherapy. However, due to lack of prospective randomized data to drive treatment decisions, the role of radiotherapy for RPS remains an area of debate. Currently, in most institutions, multidisciplinary teams with expertise in RPS recommend RT on a case-by-case basis.

There are a number of studies that have performed analyses of cancer registries to determine both practice trends in delivering adjunct radiotherapy and whether radiotherapy is a predictor for improved oncologic outcomes. Recently, Nussbaum and colleagues published the largest NCDB analysis of RPS sarcoma in which they performed a case control, propensity score-matched analysis of patients receiving preoperative or postoperative radiotherapy (PORT) versus surgery alone. Of 9068 patients, 563 patients received preoperative radiotherapy, 2215 received PORT, and 6290 received surgical resection alone. The authors demonstrated that both preoperative radiation therapy and PORT were significantly independent predictors for improved OS (preoperative radiotherapy vs no radiotherapy, 110 vs 66 months, $p < 0{\cdot}0001$; and PORT vs no radiotherapy, 89 versus 64 months, $p < 0{\cdot}0001$) [30]. Several limitations of the paper included the potential selection bias regarding those who received radiotherapy, lack of data for type of resection, and ability to analyze histologic subtypes separately. In a recent National Cancer Database (NCDB) analysis of a total 2264 patients, 727 (32.1%) of patients had perioperative radiotherapy. Of those who underwent radiotherapy, 27.9% received radiotherapy in the neoadjuvant context. Perioperative radiotherapy was independently associated with decreased mortality (HR 0.72). When stratified, radiotherapy was associated with an OS benefit for high-grade RPS, tumor less than 15 cm, and leiomyosarcoma histology [31]. An analysis of the Multi-Institutional Collaborative Retroperitoneal Sarcoma Working group demonstrated that radiotherapy was a significant independent predictor for local control but did not demonstrate an association with OS [21]. These analyses suggest that while radiotherapy confers a local control benefit, the effect of radiation on OS however is less certain.

Historically, radiotherapy in the postoperative setting has been employed in the setting of positive margin and/or high-risk histologies. The main advantages of this approach include proceeding immediately to surgical resection and the ability to better select patients who require adjuvant treatment due to having the full specimen available for pathologic review. Although many patients undergoing complete surgical resection have microscopically positive margins, there is no high-level evidence that postoperative radiation improves outcomes and retrospective data regarding the benefit of PORT is mixed [2, 32]. Most consensus groups do not favor postoperative RT for RPS for a number of reasons (Table 2.2). Most notably, once the tumor is removed, the bowel can "fall into" the previously occupied space, and postoperative adhesions are formed. This may result in significantly higher volume of *fixed bowel* (small and large bowel that do not move in and out of the radiation field) being irradiated. Additionally, the appropriate dose in postoperative setting (60–66 Gy) is not tolerable to large volumes in the abdomen and pelvis, and the postoperative target volume may be very difficult to delineate. Thus, risks for treatment-related toxicities are increased with postoperative treatment [33].

While the improved toxicity profile of preoperative radiotherapy in extremity STS has been confirmed in prospective and randomized controlled trial settings [34, 35], this question has not been explored prospectively in the setting of RPS. In contrast to postoperative radiotherapy, there are a number of practical and theoretical advantages in favor of neoadjuvant radiotherapy (see next section for further discussion). We await the final manuscript of STRASS EORTC 62092–22,092 trial to better define the role of preoperative radiotherapy in RPS (see Sect. 2.15 for further discussion).

2.5.1 Intraoperative Radiotherapy and Postoperative Brachytherapy

The delivery of intraoperative radiotherapy (IORT) allows for targeted delivery of radiotherapy boost to high-risk area of positive margins, most commonly delivered with MeV electrons (IOERT (intraoperative electron radiotherapy)). In 1993, the National Cancer Institute published their prospective study demonstrating higher locoregional control 60% versus 20% in patients who underwent a gross total resection for RPS followed by IOERT 20 Gy using 2–6 fields and EBRT (35–40 Gy) compared to postoperative RT (PORT) alone [36]. However, there was no benefit in OS, and 44% of patients who received IOERT developed radiation-related moderate-to-severe peripheral neuropathy compared to 0% in the arm that received PORT alone. More recent retrospective and prospective studies continue to suggest the potential improvement of local control with IOERT using median doses of 12–15 Gy (range 8.75–30), fewer treatment fields, and less field overlap with reduced grade 3–4 toxicities attributed to IOERT alone (see table below) [36–40]. Recently, a newly innovative unidirectional IORT technology (CivaSheet) is used to treat RPS [41]. A multicenter trial is currently planned to treat RPS using this IORT technology in combination with perioperative radiotherapy. Table 2.3 includes published experiences in utilization of IORT in

Table 2.3 IORT/IOERT boost experiences in RPS

	National Cancer Institute [36]	Mass General Hospital [37]	Mayo Clinic [38]	MD Anderson [39]	German Cancer Research Center [40]
Study	Prospective RCT	Retrospective	Retrospective	Phase I	Phase I/ phase II interim analysis
Number of points (1° and recurrent disease in each trial)	35 42% received IOERT, No prior chemo or RT	37 55% received IOERT	87 100% received IOERT	35 76% received IOERT	27 85% received IOERT, No prior RT
Margin	Not stated, all cases thought to be resectable, R0/R1 attempt	R0/R1 78% R2 10%, rest not applicable	R0/R1 83% R2 17%	R0/R1 only	R0 22% R1 74% R2 4%
EBRT	IOERT + PORT 35–40 Gy vs postoperative 50–55 Gy alone adjuvant doxorubicin, cyclophosphamide/ MTX in six patients	Preoperative 45 Gy	Median preoperative dose 47.6 Gy (10–65 Gy), received by 77%	Preoperative dose escalation up to 50.4 Gy with concurrent doxorubicin	Preoperative 45–50 Gy to PTV and 50–56 Gy to GTV
IOERT	20 Gy; 11–15 MeV; 90% isodose line all received misonidazole	10–20 Gy R0 10 Gy, R1 12.5–15 Gy, R2 20 Gy; 9–15 MEV	Median 15 Gy, range 8.75–30 Gy; 90% isodose line	15 Gy; 90% isodose line; 9 MEV	Median 12 Gy Range 10–20 Gy; 6–12 Mev
Number of fields	2–6 fields	1, rarely 2+	1 field in 76% 2–4 fields in 24%	1	Multiple fields allowed only if no overlap
Local control (LC)	Improved LC IOERT 60% vs PORT 20%, median follow-up, 8 years	Improved five-year LC with IOERT 83% vs 61%	23% local failure at median follow-up 3.5 years. Estimated LC five years 41% for R2, 60% R1, and 100% R0	–	Median follow-up 33 months, 26% local failure (two points outside EBRT field, two points after 5 years) Estimated three- and five-year LC 72%

(continued)

Table 2.3 (continued)

	National Cancer Institute [36]	Mass General Hospital [37]	Mayo Clinic [38]	MD Anderson [39]	German Cancer Research Center [40]
OS	Median OS IOERT 3.7 years vs PORT 4.3 years (NS)	Improved five-year OS with IOERT, 74% vs 31%	53% at median follow-up 3.5 years, estimated 5 years 37% R2 vs 52% R1/R0	–	Median follow-up 33 months 78% OS Estimated three- and five-year OS 74%
AE	Moderate-to-severe neuropathy 44% IOERT vs 0% PORT, enteritis 13% IOERT vs PORT 50%	IOERT group: Three points with neuropathy, three with hydropathy, one With SBO (small bowel obstruction), and two with fistula	G3–G4 GI toxicity in two points and G3 neuropathy secondary to IOERT	No IOERT complications in 21/22 pts. one point with bilateral urethral stricture	No late GI/ GI/ neurological G3+ toxicity

RPS. However, technical challenges and limited availability have prevented the widespread use of IORT or postoperative brachytherapy. Thus, the consensus guidelines recommend IORT to be delivered only at experienced centers and/or on protocol.

Other centers have attempted delivery of additional dose to the high-risk margin with low-dose-rate or high-dose-rate brachytherapy. However, postoperative brachytherapy has been associated with more severe acute and late toxicities in the upper abdomen. In 2002, the Princess Margaret Hospital performed a prospective nonrandomized trial that studied the outcomes of patients treated with preoperative EBRT followed by surgery ± postoperative Ir-192 (iridium-192) brachytherapy. Forty-one patients with localized RPS were treated to a median preoperative dose that was 45 Gy (range 42–50 Gy). No patients required hospitalization and none terminated radiotherapy because of acute toxicity. Twenty-three patients then received postoperative brachytherapy (median dose 25 Gy, range 7.3–30 Gy). Of these, one patient was admitted for duodenitis/gastric outlet obstruction, another patient developed life-threatening small bowel obstruction, and two patients died during treatment due to perforation following NJ (nasojejunal) tube insertions for duodenal stricture, each following brachytherapy in the upper abdomen. The rate of fatal toxicity (2/41, 5%) prompted investigators to limit subsequent use of brachytherapy to the lower abdomen [42].

2.6 Systemic Therapy

To date, the role of systemic therapy in the treatment of localized RPS is very limited and largely extrapolated from retrospective and phase II extremity STS data in which neoadjuvant, adjuvant, or interdigitated chemotherapy with or without concurrent chemoradiotherapy has been utilized in patients with large, high-grade, or locally recurrent disease [43–48]. Due to conflicting results of these studies, the use of chemotherapy in localized sarcoma remains controversial and warrants further investigation. When delivered, chemotherapy is generally doxorubicin based with the most widely studied regimes including neoadjuvant mesna, adriamycin (doxorubicin), and ifosfamide (collectively known as MAI) or the above with added dacarbazine (MAID), neoadjuvant and concurrent with radiotherapy (RT) followed by surgery and additional adjuvant cycles.

In RPS, there have been small phase I and II studies assessing similar approaches in patients with histologies at high risk for distant progression such as leiomyosarcomas and undifferentiated pleomorphic sarcomas. Gronchi reported the results of a phase I/phase II trial of 83 patients with localized RPS demonstrating the feasibility of neoadjuvant concomitant chemoradiation with three cycles of high-dose long-infusion ifosfamide and 50.4 Gy RT with 72% of patients completing the protocol and no patients failing to obtain surgery due to toxicity [49]. As noted above, MD Anderson's phase I trial demonstrated the feasibility of neoadjuvant EBRT up to 50.4 Gy with concurrent doxorubicin followed by definitive surgery and IOERT 12 Gy with high-grade III–IV acute GI toxicity (18%) and hematological toxicity (27%) [39].

A prospective phase II RTOG (Radiation Therapy Oncology Group) trial studying the role of sequential neoadjuvant MAI followed by radiation for intermediate- or high-grade primary or recurrent RPS commenced in 2003, however, was closed early due to lack of accrual (RTOG 0124). NRG-DT001 is an open phase IB trial of neoadjuvant AMG 232 concurrent with preoperative radiotherapy in wild-type p53 STS, discussed below [50]. Without more robust prospective data, routine systemic therapy has not been adopted and should only be performed in the context of a clinical trial or at experienced centers.

2.7 Radiotherapy Techniques and Planning

The large tumor size and complex anatomy of retroperitoneum create a therapeutic challenge in the management of RPS. Delivery of conventional radiotherapy is difficult as the dose required to effectively treat the tumor can exceed the tolerance of the adjacent organs at risk, both in the preoperative and postoperative settings. However, in contrast to postoperative radiotherapy, there are a number of practical and theoretical advantages in favor of preoperative radiotherapy. These include the following:

(a) The gross tumor can be precisely identified and targeted.
(b) The tumor displaces the adjacent abdominopelvic viscera from the high-dose treatment field improving plan dosimetry.

(c) Potential to allow the delivery of higher RT doses.
(d) The clinical target volume (CTG) may be smaller and typically will contain the less normal tissue in the treatment field.
(e) Potential reduction of intraperitoneal tumor dissemination at time of operation.
(f) Increased biological effectiveness in the preoperative setting secondary to better oxygenation with an intact vasculature.
(g) Improved resectability secondary to a "rind" formation of the acellular tissue following radiotherapy.
(h) Potential to convert an initially unresectable tumor to resectable.

Smaller treatment volumes associated with preoperative treatment are thought to correlate with improved toxicity profiles compared to postoperative RT. This is well documented in extremity STS which resulted significantly lower rates of late fibrosis, edema, and joint stiffness resulting in improved long-term functioning though with higher wound complication rates [34, 35]. Multiple prospective and retrospective studies have demonstrated that preoperative radiotherapy in RPS is well tolerated and feasible [31, 39, 49, 51–53].

Without prospective data available, the decision to treat should be made on a case-by-case basis by a multidisciplinary team experienced in the treatment of RPS.

Preoperative EBRT is our recommended treatment strategy for patients in whom radiotherapy is recommended. Other techniques including intraoperative radiotherapy (often delivered with MeV electrons), postoperative brachytherapy, postoperative radiotherapy, and proton therapy may have selected roles within experienced institutions and in the context of clinical trials. These treatment options are less available, and their role established through multiple international consensus groups continues to evolve (see Table 2.2).

2.8 CT Simulation

Appropriate CT simulation in RPS (see Table 2.4) enables treatment planning that will maximize target coverage and minimize treatment of critical OARs (organs at risk) such as small bowel, spinal cord, cauda equina, and the contralateral kidney. Motion management with 4DCT (four-dimensional computed tomography) can be

Table 2.4 CT simulation

Supine position
Immobilization: Vac-Lok bag, lower leg immobilizers. Per institutional standards.
IV and PO contrast preferred
Consider simulation and daily bowel preparation based on tumor proximity to the rectum
Four-dimensional motion CT strongly recommended for tumors above the iliac crest
If >1 cm motion, respiratory control recommended: Gating, abdominal compressions, and breath holds
Field: Tracheal bifurcation to lesser trochanter of the femur
3 mm slices

Table 2.5 Fusions (co-registered images)

Diagnostic contrast-enhanced CT AP
MRI T1—Post-contrast highly recommended
MRI T2

considered in any case but is highly recommended for any tumor arising above the pelvic brim. In the rare circumstance of >1 cm motion, respiratory control techniques are recommended as above. IV (intravenous) and PO contrasts at time of simulation are not critical but may facilitate tumor and bowel delineation, respectively. All available diagnostic images should be utilized for target delineation (Table 2.5). Gross tumor is most easily identified on MRI T1 post-contrast sequences. T2 sequences may be useful for identifying suspicious edema that may warrant inclusion in the CTV.

2.9 Target Volumes

There are no universally accepted guidelines to delineating target volumes in preoperative radiotherapy for RPS. Here, we have listed several reasonable approaches created by expert group consensus or defined by ongoing major prospective clinical trial protocols (Tables 2.6, 2.7, and 2.8).

Table 2.6 *Red Journal Expert Consensus Guidelines* for target volumes [15]

Above the pelvic brim, four-dimensional imaging present	Below the pelvic brim, no four-dimensional imaging	Above the pelvic brim, no four-dimensional imaging present
iGTV[a]	GTV[a]	GTV[a]
ITV[b] = iGTV + 1.5 cm (CTV expansion)	CTV[b] = GTV + 1.5 cm	CTV[b] = GTV + 2–2.5 cm superiorly/inferiorly, 1.5–2.0 cm radial
PTV = ITV + 5 mm if IGRT. 9–12 mm if no IGRT	PTV = ITV + 5 mm if IGRT. 9–12 mm if no IGRT	PTV = ITV + 5 mm if IGRT. 9–12 mm if no IGRT

[a]As defined by CT, MRI, and 4DCT if available
[b]Edit CTV/ITV as follows: (1) Uninvolved retroperitoneal compartment, bone, kidney (unless planned resection), and liver: 0 mm at interface. (2) Bowel/air cavity: 5 mm at interface. (3) Under the skin surface: 3–5 mm according to institutional preference. (4) If tumor extends to the inguinal canal, expand iGTV/GTV by 3 cm inferiorly. (5) Do not need to cover biopsy tract

Table 2.7 NRG DT001 protocol for target volumes [50]

GTV or iGTV[a]
CTV[b] = GTV or iGTV + 1.0 cm
PTV[c] = CTV + internal margin (if no 4DCT, size unspecified) + setup margin (5 mm). Daily IGRT mandatory

[a]As defined by CT, MRI, and 4DCT if available
[b]Edit CTV as follows: (1) CTV should not be extended beyond the other organs, compartment, intact fascia, or bone. (2) If tumor extends to the inguinal canal, expand iGTV by 3 cm inferiorly and radial margin in the thigh 1.5 cm but not beyond the compartment/intact fascia/uninvolved bone
[c]Allows for reduction of PTV margin by 5 mm in direction of the skin and spinal canal

Table 2.8 STRASS (EORTC 69092-22,092) protocol for target volumes (55)

GTV or iGTV[a]
CTV[b] = GTV or iGTV + 5 mm (if CT slice 5 mm) vs 6 mm (if CT slice 3 mm)
PTV[c] = CTV + 9 mm (anteriorly/medially) + 12 mm (superiorly, inferiorly, posteriorly, laterally)

[a]As defined by CT, MRI, and 4DCT if available
[b]Edit CTV as follows: (1) Remove the fascia, bone, skin, and air gaps not at risk for microscopic disease. (2) May include suspicious edema (T2-weighted images) in CTV. (3) Exclude the vertebral body and biopsy tract from CTV.
[c]PTV internal for dosimetric evaluation removes 5 mm off body/external contours (Fig. 2.1)

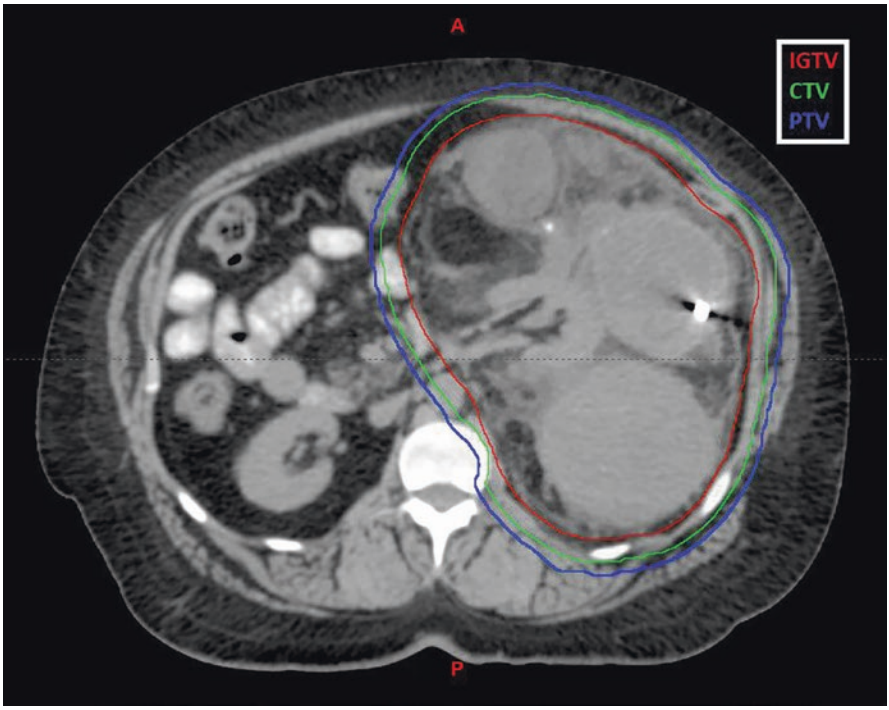

Fig. 2.1 Example of target volumes for a 58-year-old woman with left retroperitoneal well-differentiated liposarcoma involving the left kidney, adrenal gland, ovary, and mesentery of the duodenum. iGTV in red using 4DCT imaging. CTV in green with a 1.0 cm expansion of iGTV. PTV in red with a 0.5 cm expansion of CTV. These volumes most closely resemble the NRG DT001 protocol

They are all similar in defining GTV (gross target volume) (or iGTV (internal gross target volume)) by CT, MRI, and 4DCT if available. CTV expansion for microscopic disease ranges from 0.5 to 1.5 cm or more if four-dimensional imaging is not available. Two protocols recommend expanding GTV versus iGTV by 3 cm inferiorly when creating the CTV if the inguinal canal is involved. Careful CTV editing is required in each protocol to remove natural anatomic boundaries such as

the uninvolved bone, organs, muscle compartments, and intact fascia not at risk for microscopic disease. With daily image-guided radiation therapy (IGRT), two protocols recommend adding 0.5 cm for PTV.

2.10 Prescription Dose

In the absence of strong, prospective, randomized data, appropriate prescription dose is adapted from expert consensus statements and ongoing treatment protocols as above.

Acceptable options include the following:

- 50 Gy/25 fractions to PTV [15]
- 50.4 Gy/28 fractions to PTV [15, 54]
- 45 Gy/25 fractions to PTV with 5.4 Gy SIB (simultaneous integrated boost) to GTV [50]

2.11 Boosts to High-Risk Margin and GTV

EBRT boost to the high-risk margin is under investigation in an attempt to improve local control (see Sect. 2.15). With limited prospective data, we do not recommend routine boosts to either GTV or high-risk margin off clinical protocol.

2.12 Target Coverage

- At least 95% PTV receives over 95% dose.
- At least 99–100% CTV receives over 95%.
- No more than 10% of the PTV receives more than 107% of prescription dose.

2.13 Radiation Technique

Given the close proximity of radiosensitive organs including the small bowel, spinal cord, and cauda equina and the importance of sparing postoperative contralateral kidney function and/or compromised liver function, complex treatment planning is often needed to meet normal tissue constraints. IMRT (intensity-modulated radiation therapy) allows the planner to define the orientation and energies of all beams as in three-dimensional planning. Additionally, specific dose constraints for both normal structures and the target volume are achieved through a technique referred to as inverse planning, which uses specialized optimization algorithms that determine.

nonuniform intensities to tiny beamlets, or subdivisions of beams, resulting in increased control over radiation dose. This allows for the delivery of highly conformal dose to the grouse disease and high-risk subclinical disease regions while minimizing dose to the surrounding critical structures.

In 2003, Koshy and colleagues demonstrated that IMRT in the preoperative setting can be utilized in RPS and enhanced tumor coverage and better sparing of dose to *critical normal structures* such as the small bowel, liver, and kidney [55]. In RPS, Swanson and colleagues published their dosimetric analysis showing that IMRT (and three-dimensional conformal proton therapy) were more conformal and homogeneous than 3DCRT (three-dimensional conformal radiation therapy). Moreover, this resulted in improved dosimetric benefits [56]. Bossi published results of 16 3DCRT versus IMRT plans that showed superior sparing of high dose to small bowel and the contralateral kidney while maintaining target coverage and other critical constraints [57].

Not only is IMRT superior to 3DCRT in terms of normal structure sparing and improved conformality, but IMRT also can be utilized for dose escalation (or dose painting) to the region at high risk for a positive margin. In 2006, Tzeng and colleagues published their experience treating with preoperative radiation to a dose of 45 Gy in 25 fractions with a simultaneous integrated boost to 57.5 Gy to the margin at risk contoured in conjunction with the operating surgeon. This study demonstrated acceptable acute side effect profile and no severe postoperative morbidity or mortality. A two-year local control in the cohort of 16 patients was high at 80% [58]. In 2017, Washington University reviewed their institutional experience treating RPS with IMRT in perioperative setting. In their cohort of 30 patients, median RT dose to the high-risk area was 55 Gy and 60.4 Gy in the pre- and postoperative setting, respectively. Preoperative RT (compared to postoperative RT) was associated with improved LC. Despite the majority of patients treated in the postoperative setting (19/30) to high doses, there were low incidences of grade 3 toxicity and no grade 4 or 5 toxicity underlying the importance of IMRT treatment technique [59].

Often, delivery of IMRT plans for large RPS can take 20–30 min which can reduce the target uncertainty and OAR dose calculations secondary to intra-fraction motion. Volumetric-modulated arc therapy (VMAT) can overcome this secondary to fast delivery of the treatment. In a dosimetric analysis comparing VMAT to IMRT, Taggar and colleagues demonstrated that VMAT planning for large RPS demonstrated improved conformality index, reducing delivery time with comparable critical structure sparing [60].

Compared to photon radiotherapy, several theoretical advantages of proton beam radiotherapy (PBRT) exist secondary to the physical properties of the proton beam compared to photons. Protons' energy loss per unit path length is relatively small and constant as it traverses the tissue until near the end of the proton range where the residual energy is lost over a short distance and the proton comes to rest, resulting in a distinctive sharp rise in the tissue absorbed dose known as the Bragg peak. Thus, PBRT offers additional advantages over IMRT and 3DCRT most notably almost no exit dose. Thus, PBRT reduces the radiation of adjacent normal organs and tissues by approximately 60% and allows delivery of the prescription dose to the tumor with greater sparing of adjacent organs and structures. Whether PBRT offers a clinical advantage for any given patient depends on the location of the tumor and the adjacent normal tissues. More recently, the advent of intensity-modulated proton therapy, a highly precise type of radiation therapy allowing intricate treatment planning and precise proton beam delivery, results in modulating the intensity of the beam in order to shape and match the contours of the tumor and minimizing exit dose. Dose

Table 2.9 IGRT protocol

Daily imaging recommended
CBCT (cone-beam computed tomography) or MVCT (megavoltage computed tomography) or MRI at least weekly or more
kV imaging on days volumetric imaging not performed

escalation utilizing intensity-modulated proton radiotherapy (IMPT) or IMRT is currently the focus of phase I/phase II study (see Sect. 2.15).

2.13.1 Image-Guided Radiation Therapy (IGRT)

Image-guided radiation therapy (IGRT) is a broad term which involves the use of imaging modalities to augment target and normal tissue localization for radiotherapy planning and delivery, by providing opportunities for reviewing and adjusting the treatment delivery taken at the treatment console immediately prior to treatment. As a result of this improved certainty, planning treatment volume (PTV) margins can be reduced. An additional benefit is that the radiation treatment plan can be adapted to reflect anatomical/tumor changes during treatment. RTOG 0630 demonstrated significant reduction of late toxicities with extremity sarcoma with the use of IGRT (both 3DCRT and IMRT allowed) compared to historical cohorts without any marginal-field recurrences at a median follow-up of 3.6 years [35]. Image guidance is especially relevant for RPS as there can be significant setup area in irradiating the retroperitoneum as the immobilization device is not as rigid compared to other sites. Moreover, given the typical close proximity of retroperitoneal tumors to organs at risk for significant acute and long-term toxicity, daily image guidance can ensure that these organs are not falling into the treatment volume on a day-to-day basis. As such, most protocols now recommend daily image-guided radiation therapy for treatment of RPS (see Table 2.9).

2.14 Organs at Risk and Radiation Tolerance Doses

Radiotherapy for patients with RPS is complex secondary to the large treatment fields and proximity to critical anatomic structures. In addition to the potential toxicity to the bowel and liver, other structures at risk for late radiation-related injury include the ureters, kidneys, and spinal cord. Strict adherence to normal structure constraints is essential to reduce acute toxicity to an acceptable level and avoid long-term adverse radiotherapy effects.

2.14.1 DVH (Dose Volume Histogram) Considerations

Dose volume constraints in the setting of RPS have been mainly extrapolated from the gynecology and gastrointestinal (GI) literature. In a recent study quantifying GI toxicity during preoperative radiotherapy for RPS, Mak and colleagues reviewed 56 patient cases with RPS who underwent preoperative RT and found that acute

gastrointestinal (GI) toxicity was very low (5% grade ≥ grade 3 toxicity) despite the bowel bag dose exceeding a number of established constraints taken from GI and gynecologic cancers. Tumor size and V25 ≥ 650 mL of bowel bag was significantly associated with grade ≥2 toxicity using RTOG criteria [51]. Further assessment of dose volume constraints specific for treatment of RPS is needed. In Table 2.10, a list of normal structure constraints is listed for treatment of RPS.

Table 2.10 Normal structure constraints (adapted primarily from DT-001, Ref. [50])

Structure	DVH metric	Dose	Variation acceptable	Toxicity endpoint
Spinal cord	D0.03 cc [Gy]	≤45 Gy	≤48 Gy	Myelopathy
Ipsilateral kidney[a]	Not applicable			
Contralateral kidney	V18 Gy [%]	<15%		Renal dysfunction
Bilateral kidneys[a]	Mean [Gy] V20 Gy [%]	<14.4 Gy <30%	≤16 Gy <33%	Renal dysfunction
Peritoneal cavity (bowel bag including large/small bowel)[b]	V15 Gy [cm^3] (Ref. [61]) V45 Gy [%]	<830 cm^3 <20%	≤30%	G3+ toxicity
Liver	Mean [Gy]	<30 Gy <26[b]	≤33 Gy	RILD (radiation-induced liver disease) in the normal function liver
Stomach	D0.03 cc [Gy] D2% [Gy] D25%[Gy]	<52 Gy ≤50 Gy ≤45 Gy	≤54 Gy ≤54 Gy ≤54 Gy	Ulceration
Rectum	V50 Gy [%] V70 Gy [%]	<50% <20%	≤60% ≤25%	G3+ toxicity
Anus	V30 Gy [%] V50 Gy [%]	<50% <20%	≤60% ≤25%	G3+ toxicity
Bladder	V50 Gy [%] V70 Gy [%]	<50% <20%	≤60% ≤25%	G3+ toxicity
Vulva	V30 Gy [%]	<50%	≤60%	Moist desquamation
Femoral heads (Ref. [15])	D0.03 cc [Gy] V40 Gy [%] Mean [Gy]	<50 Gy <64% <37 Gy		Necrosis
Testis[c]	V1 Gy [%] D0.03 cc [Gy]	<50% <18 Gy	≤60%	Infertility
Ovaries[c]	V5 Gy [%] D0.03 cc [Gy]	<50% <3 Gy	≤60%	Infertility

[a]If the ipsilateral kidney is to be resected, no dosimetric parameter is applicable. Refer to contralateral kidney constraints, as low as reasonably achievable

[b]Shown to offer roughly equivalent V45 compared to contouring individual bowel segments expanded by 1 cm to account for motion. Advantage in being much easier to contour [62]

[c]Required only if fertility preservation desired. Consider cryopreservation

2.15 Current Trials

Given the lack of prospective data in RPS sarcoma, we recommend enrollment on clinical trials and/or cancer registries and referral to high-volume center. In this section, we identify three pivotal trials that will help to define the role of neoadjuvant radiotherapy in the treatment of RPS and when employed whether we can improve outcomes with dose escalation or concurrent systemic treatment.

2.15.1 STRASS EORTC 62092-22092 (ClinicalTrials.gov NCT01344018), Ref [54]

This EORTC trial is a multicenter and international phase III trial that enrolled patients with RPS and randomized them to preoperative RT followed by surgery or surgery alone. The studies' primary endpoint is abdominal recurrence-free survival (ARFS), and secondary endpoints were recurrence-free survival, OS, acute toxicity of RT, perioperative and late complications, and quality of life. The abstract form was presented at ASCO (American Society of Clinical Oncology) in 2019 and were published in Lancet Oncology in 2020. The results failed to demonstrate a benefit in ARFS of preoperative RT for RPS for the entire cohort. However, there were twice as many local recurrences observed in the surgery group than in the radiotherapy plus surgery group. In the liposarcoma subgroup, an exploratory analysis demonstrated an improvement in a three-year ARFS 75.7% versus 65.2% in favor of preoperative radiotherapy [63].

2.15.2 Phase I/Phase II Trial of Preoperative IG-IMPT or IMRT with Simultaneous Integrated Boost (SIB) for Retroperitoneal Sarcomas (ClinicalTrials.gov NCT01659203), Ref [64]

Given the dosimetric benefits of IG-IMPT and IMRT, Delaney and colleagues have sought to determine the role of SIB to high-risk margin determined by the radiation oncologist and operating surgeon. In 2017, Delaney and colleagues published the phase I results of the IG-IMPT cohort in which they utilized preoperative dose of 50.4 Gy in 28 fractions to the CTV1 (gross tumor and adjacent tissues at risk for subclinical risk) with selective escalated radiation dose to tumor volume considered at high risk for positive margins with the aim to reduce local recurrence [65]. See Fig. 2.2 for an example treatment plan of a patient on protocol. Eleven patients showed increased IMPT dose levels from 60.2 to 63.0 GyRBE in 28 fractions utilizing SIB technique. The acute toxicity was mild with no radiation interruptions. There was one patient who developed hydroureter from treatment. At median 18-month follow-up, there were no local recurrences in this cohort, and the phase II study of IMPT is currently accruing patients to that dose. We await this data as well as the results from the phase I IMRT cohort.

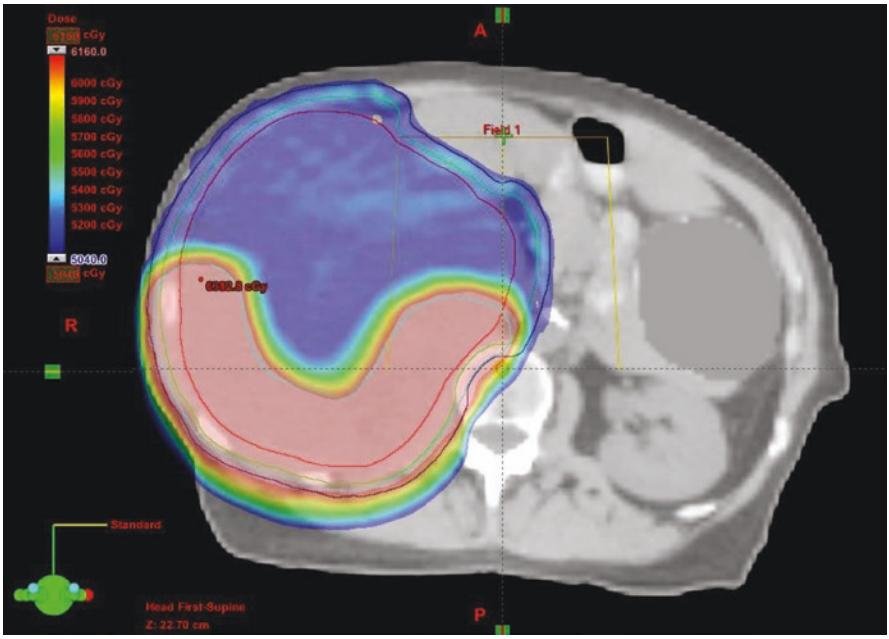

Fig. 2.2 Treatment plan of a 75-year-old woman with right retroperitoneal dedifferentiated liposarcoma (15.5 × 14.7 × 18.3 cm) displacing the natural right kidney anteriorly/medially. Patient treated on ongoing Delaney phase I/phase II protocol with preoperative photon IMRT 50.4 Gy/28 fractions with SIB to 61.6 Gy. Treatment delivered with helical tomotherapy system. Following radiation, patient underwent resection of primary tumor as well as the uninvolved right kidney, right adrenal gland, right hemicolon, and diaphragm showing ~50% necrosis and negative surgical margins. No adjuvant treatments. Patient remains disease free 2 years following treatment
Red = GTV
Green = CTV [GTV + 1.5 cm with editing]
Dark blue = PTV 50.4 Gy [includes ITV if available +5–10 mm]
Cyan = PTV SIB 61.6 Gy (area of high risk for + margins)

2.15.3 NRG-DT001 (ClinicalTrials.gov NCT03217266), Ref [50]

NRG-DT001 is a phase IB trial of neoadjuvant AMG 232 concurrent with preoperative radiotherapy in wild-type p53 STS. MDM2 is a selective small molecule inhibitor of MDM2 that blocks the protein-protein interaction between MDM2 and p53. This study was based on strong preclinical evidence suggesting that an MDM2 inhibitor and radiotherapy may have additive or synergistic antitumor activity in p53 WT STS. While this study's primary objectives are to evaluate the safety and tolerability of this novel agent and to determine the maximum tolerated dose, its secondary objective is to observe and record antitumor activity as well as to determine percentage necrosis and pathologic complete response rate. Other exploratory objectives include determining tumor volume changes via advanced imaging such as MRI and characterize clinical outcomes by genomic biomarkers. This study highlights the potential for novel targeted agents that can improve the therapeutic ratio as well as the utilization of genomics to help prognosticate and eventually to better tailor treatment algorithms.

2.16 Future Directions

We await results from the currently ongoing trials to better help determine the best treatment paradigm for RPS and further improve the therapeutic ratio through novel systemic agents and technological advancements. We understand that retroperitoneal sarcoma represents a rare entity with diverse histologies. The need for histology-driven databases to be utilized to better determine the optimal treatment paradigms for each subtype of retroperitoneal sarcomas is needed. Moreover, the use of molecular profiling via next-generation sequencing may be useful in guiding treatment choices for patients with unresectable or recurrent/metastatic disease. The integration of genomics and radiomics (the process of extracting imaging biomarkers) may allow for outcome modeling and decision support for personalized treatment of RPS. Other EBRT techniques on the horizon including MRI-guided Linac may assist to continue to improve the precision of EBRT treatment delivery and reduce treatment planning target volume margins with the hope to improve outcomes in this difficult disease.

2.17 Treatment Algorithm

A brief treatment algorithm for the treatment of retroperitoneal sarcoma is shown in Fig. 2.3. As described above, enrollment in clinical trials is highly recommended.

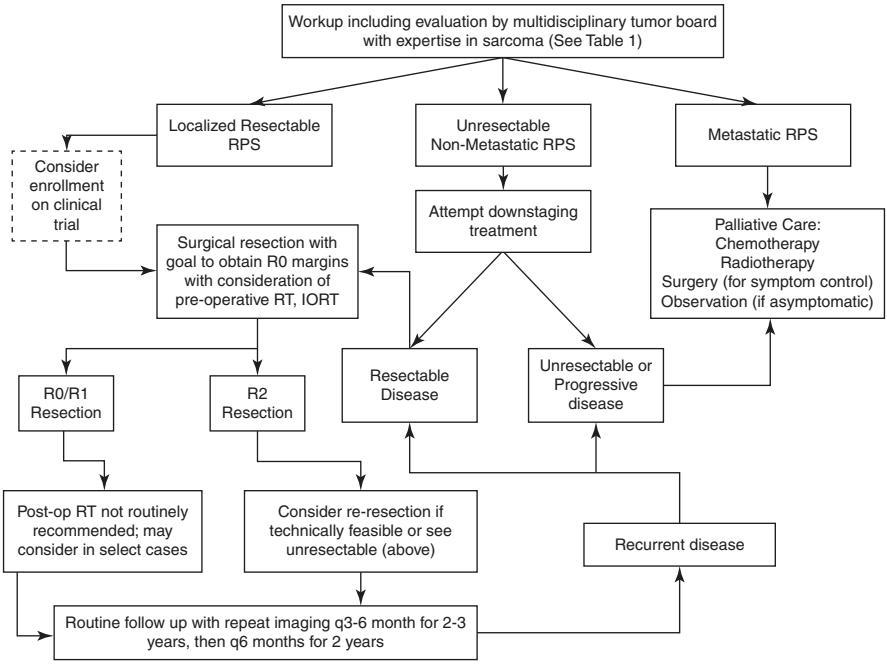

Fig. 2.3 Suggested treatment algorithm for the management of RPS

2.18 Summary

- The treatment of RPS is complex, and all patients should be treated in centers with multidisciplinary tumor boards and expertise in the treatment of sarcomas.
- Surgical resection is the mainstay treatment for localized RPS. However, local recurrence remains the most common site of first failure even after complete resection.
- The role of radiotherapy is unclear and is currently being investigated.
- When recommended, radiotherapy is optimally delivered in preoperative setting using image-guided IMRT.
- Dose escalation with dose painting to the region at high risk for margin positivity is not recommended as standard practice and is best used only as part of a protocol or at experienced centers.
- IORT/IOERT is best delivered at experienced centers and/or on protocol.
- The use of systemic therapy in localized setting should only be performed in the context of a clinical trial or at experienced centers.
- Enrollment on clinical trials or prospective data registries is advised.

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Gynecologic Sarcomas

3

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3.1 Introduction

3.1.1 Epidemiology and Risk Factors

Female genital tract sarcomas are a rare disease with an incidence estimated to be between 8 and 9.6 cases per million people and increase with age [1–3]. The most common site of disease is the uterus and accounts for 83% of all cases of gynecologic sarcoma but still only accounts for less than 4% of uterine cancer. Other sites are listed in Table 3.1.

Epidemiologic risk factors for gynecologic sarcomas have not been well established with the exception of prior radiotherapy and possibly tamoxifen use which have been associated with uterine sarcomas [5–7]. The majority of these have been associated with aggressive histology.

3.1.2 Histopathology of Gynecologic Sarcomas

Although the histopathological subtypes of gynecologic sarcomas are variable, there is consistent data on morphologic data for uterine sarcomas. Practically,

Table 3.1 Most commonly encountered sites of gynecologic sarcomas (adapted from Francis et al. and Pietzner et al.) [1, 4]

Anatomical site	Percentage of cases (%)
Uterus	83–88%
Ovary	5–8%
Cervix	3%
Vagina	2%
Vulva	2%
Broad ligament	1%
Overlapping lesion of genital organs	1%
Parametrium	<0.1%
Fallopian tube	<0.1%
Round ligament	<0.1%
Others	<0.1%

Table 3.2 Histopathological subtypes of intrauterine sarcomas (derived from Francis et al. and Major et al.) [1, 2]

Histological variant	Percentage of cases (%)
Adenosarcoma	4–5%
Endometrial stromal tumor	15–20%
Leiomyosarcoma	13–50%
Malignant mixed Mullerian tumor	20–60%
Others	1%

stratification of uterine sarcomas follows that proposed by Kempson et al. and is usually stratified according to those originating within the endometrium and those originating from within the myometrium of the uterus [8, 9]. Endometrial stromal tumors are derived from the endometrium solely, leiomyosarcomas arise solely from the myometrium, and malignant mixed Mullerian tumors arise from both compartments. There is disagreement between two large studies regarding the relative rates of each histopathological subtype (Table 3.2). This is possibly related to differences in histologic interpretation between pathologists.

3.1.3 General Management Strategy

The general treatment paradigm for gynecologic sarcomas has involved surgical resection for all grossly resectable lesions. This is often followed by systemic therapy and/or radiotherapy for high-grade histology or advanced disease. Observation has often been employed for lower-grade early-stage disease [10]. Studies regarding adjuvant radiotherapy management for uterine sarcomas have shown inconsistent results but suggest that there may be a reduction in disease recurrence overall [11].

3.1.4 Current Staging for Gynecologic Sarcomas

An internationally endorsed and most commonly used staging system for all gynecologic malignancies is the International Federation of Gynecology and Obstetrics (FIGO) staging system [12]. For uterine sarcomas, tumors are practically divided as leiomyosarcoma and endometrial stromal sarcomas versus adenosarcomas. The former two are staged by tumor size and locoregional and distal extent while adenosarcomas are staged according to depth of myometrial invasion and locoregional and distal extent (Table 3.3) [13]. For other sites, generally prognosis is dictated by tumor size and invasion into local structures.

3.1.5 Prognosis by Tumor Stage

In general, the prognosis for gynecologic sarcomas is poor. Overall, five-year survival rates are approximately 50% after definitive treatment [1]. For uterine

Table 3.3 FIGO staging of gynecologic sarcomas for uterine and cervical sites of disease [13]

Stage group	Uterine leiomyosarcoma/ endometrial stromal sarcoma	Uterine adenosarcoma	Cervical sarcoma
IA	Tumor ≤5 cm	Tumor limited to endometrium/ endocervix	IA1—Microscopic disease with <3 mm of stromal invasion IA2—Microscopic disease with 3–<5 mm of stromal invasion
IB	Tumor >5 cm	Tumor invades ≤ one-half of myometrium	IB1—Lesion with 5–<20 mm of stromal invasion IB2—Lesion 2–<4 cm in greatest dimension IB3—Lesion ≥4 cm in greatest dimension
IC	--	Tumor invades >1/2 of myometrium	–
IIA	Tumor involves adnexa	Tumor involves adnexa	IIA1—Lesion <4 cm in greatest dimension involving upper two-thirds of the vagina IIA2—Lesion ≥4 cm in greatest dimension and involving the upper two-thirds of the vagina
IIB	Tumor involves other pelvic tissues	Tumor involves other pelvic tissues	Tumor involves parametria but not out to sidewall
IIC	--	--	–
IIIA	Tumor involves one abdominal site	Tumor involves one abdominal site	Tumor involves lower one-third of the vagina
IIIB	Tumor involves >1 abdominal site	Tumor involves >1 abdominal site	Tumor extends to the pelvic wall and/or hydronephrosis of the kidney is present
IIIC	Regional lymph node metastases	Regional lymph node metastases	IIIC1—Pelvic lymph node metastasis(es) are present IIIC2—Para-aortic lymph node metastasis present
IVA	Tumor invades the bladder or rectum	Tumor invades the bladder or rectum	Tumor invades mucosa of the bladder or rectum
IVB	Distant metastasis	Distant metastasis	Distant metastasis

sarcomas, the overall recurrence rate for early-stage disease is approximately 50% with the first site of recurrence being within the pelvis in up to 20% of patients [2]. In a cohort of 1066 German patients, Pietzner et al. observed five-year relative survivals of 53% for uterine sarcomas and 46% for ovarian sarcomas [4]. When stratified by disease extent, survival was 60% in patients with uterine sarcoma confined to the pelvis and 14% in those with abdominal spread of disease. For ovarian sarcomas, survival was 50% in patients with pelvic-confined disease.

3.2 Management Principles

3.2.1 Presentation, Diagnosis, and Staging Workup

Most commonly, patients with uterine sarcoma present with abnormal vaginal bleeding. Uncommonly, uterine sarcomas are diagnosed at time of hysterectomy for presumed uterine fibroids [14]. Other uncommon presentations of uterine sarcomas include pelvic pain, urinary frequency, or palpable masses. Cervical sarcomas present in a similar fashion or may be detected on speculum examination during routine cervical cancer screening. In contrast, ovarian sarcomas typically present with either pelvic pain or as an incidental finding. Patients with vulvar or vaginal sarcomas often present with pruritic or tender, often easily palpated masses.

Initial workup for patients presenting with vaginal bleeding should include a complete history and physical examination including abdominal examination, bimanual examination, pelvirectal examination, and thorough speculum examination of the vagina and cervix. A papanicolaou test should also be performed. In cases where obvious cervical, vulvar, or vaginal masses are seen, the authors recommend an in-clinic biopsy to expedite diagnosis. For patients where no obvious lesions are seen, transvaginal ultrasound and endometrial biopsy aid with the diagnosis.

In cases where the endometrium is thickened on ultrasound but endometrial biopsy is negative or indeterminate, a hysteroscopy with dilatation and curettage of the endometrium is recommended to establish a diagnosis [15, 16]. For cases where a malignant mesenchymal sarcoma is a suspected finding on imaging, morcellation should be avoided.

In the case of adnexal masses, transabdominal ultrasound is recommended as a first diagnostic test [17]. This can often be followed by diagnostic MR. For suspected malignant etiology, direct referral to gynecologic oncology for surgical consideration is recommended.

The recommended staging evaluations by tumor site are given below.

3.2.2 Uterine Sarcoma

For uterine sarcomas, completion workup should include preoperative computed tomography (CT) imaging of the chest, abdomen, and pelvis. MRI pelvis should be used to quantify extent of intrauterine disease and to assess surgical resectability [18]. In cases who underwent hysterectomy with an incidental finding of uterine sarcoma or having an incompletely resected uterus, possible tumor morcellation CT chest and pelvic/abdominal MRI imaging is recommended. In addition, positron emission tomography (PET/CT) imaging can be considered to clarify ambiguous findings from CT or MRI.

3.2.3 Cervical Sarcoma

For cervical sarcomas, completion workup can include direct evaluation of tumor extent through examination under anesthetic (EUA). At the time of EUA, recommended evaluations include speculum examination, pelvirectal examination, and bimanual examination performed by two independent practitioners (either radiation oncologist or gynecologic oncologist). Further evaluation with cystoscopy and flexible sigmoidoscopy should be performed at the time of EUA to assess for bladder or rectal involvement. After diagnosis is established, the authors recommend imaging workup including MRI of the pelvis and CT imaging of the chest, abdomen, and pelvis. For cases with ambiguous findings, PET/CT imaging can be considered to aid with staging.

3.2.4 Vaginal/Vulvar Sarcoma

All cases of vaginal and vulvar sarcoma should be first evaluated in clinic. In patients intolerant of pelvic examination due to pain, EUA should be considered to better visualize extent of disease. Otherwise, staging evaluations should include CT chest, abdomen, and pelvis with consideration of MRI for lesions invading into the vagina and/or perirectal, periurethral lesions. For superficial lesions limited to the vulva, MRI is often unnecessary. PET/CT imaging may be considered to clarify any ambiguous findings.

3.2.5 Ovarian Sarcoma

Staging evaluations for ovarian sarcoma should include CT imaging of the chest and abdomen/pelvis and MRI imaging of the pelvis. In cases of ovarian sarcoma diagnosed incidentally on oophorectomy specimens, staging evaluations should include CT imaging of the chest and pelvic/abdominal MRI to evaluate extent of disease and identify any potential residual disease. PET/CT imaging may be considered to clarify any ambiguous findings.

3.2.6 Management of Gynecologic Sarcomas

In general, wherever possible, initial management of nonmetastatic gynecologic sarcomas should be surgical excision with no fragmentation of the tumor and negative margins or inclusion on a clinical trial protocol. For uterine sarcomas, this has been shown to improve survival [19–21].

3.2.7 Uterine Sarcoma

In cases of uterine sarcomas, primary surgical excision often provides definitive diagnosis and is therapeutic. Total abdominal hysterectomy with resection of all

tumors, performed by an experienced gynecologic oncologist, is a recommended standard of care [10, 22]. The extent of surgical excision remains controversial. In particular, bilateral salpingo-oophorectomy is often performed at the time of surgery despite conflicting evidence for its utility [23–25]. In particular, *Nasioudis* et al. demonstrated no difference in overall survival when ovarian preservation was employed for stage I uterine sarcomas ($p = 0.22$; Fig. 3.1) [25]. In stage II or higher disease, oophorectomy is still recommended. In appropriately staged uterine sarcomas, there is low diagnostic value to inclusion of lymph node resection at the time of surgery.

In cases of recurrent or isolated metastatic disease, repeat cytoreductive surgery improves survival and is recommended [26–28]. Often in cases of recurrent disease, surgery involves pelvic exenteration. Furthermore, the efficacy of resection for isolated lung metastases has been established [29].

For uterine sarcomas, radiotherapy treatment is typically considered as an adjuvant treatment modality for advanced disease (stages II–IVA) or for palliation. The rationale for including adjuvant radiotherapy in uterine sarcomas has been established by Sampath et al. who showed improvement in local-regional failure-free survival in a large cohort of patients (Fig. 3.2) [11]. A randomized controlled trial by the EORTC (European Organisation for Research and Treatment of Cancer) included 224 patients with stage I and II (FIGO 1998) uterine leiomyosarcomas (46%), carcinosarcomas (41%), and endometrial stromal sarcomas (13%) [30]. Patients were either treated with pelvic radiation or observed. There was an improvement in local control, but radiotherapy had no effect on survival. On subset analyses, the local control effect was only seen in carcinosarcoma; there was no improvement seen with the addition of radiotherapy in leiomyosarcoma, and there were too few endometrial stromal sarcomas to see an effect. Of note, patients with leiomyosarcoma included in this study would now be considered as exclusively having FIGO stage I disease. Retrospective studies have evaluated leiomyosarcoma

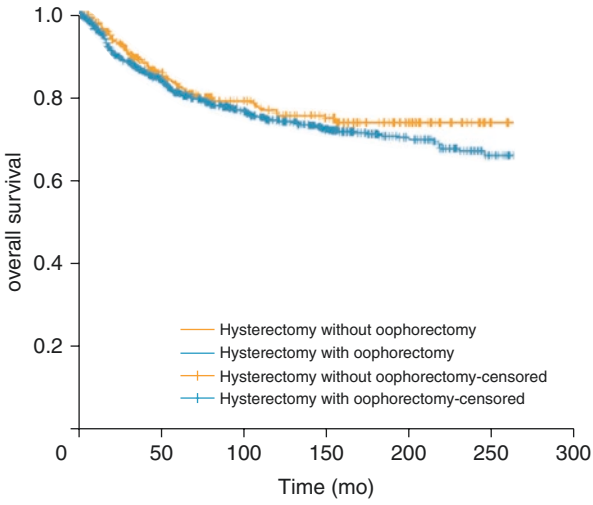


Fig. 3.1 OS of women diagnosed with FIGO stage I uterine sarcoma stratified by performance of oophorectomy at the time of hysterectomy [25]

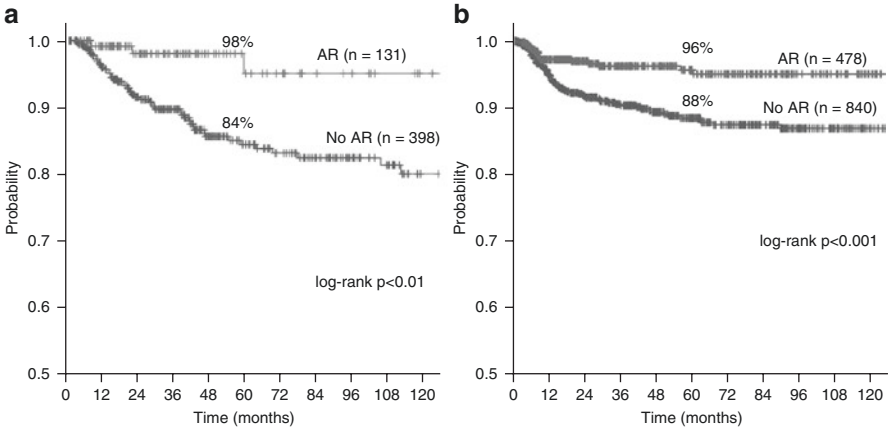


Fig. 3.2 Kaplan-Meier estimated local-regional failure-free survival in patients with (**a**) leiomyosarcoma and (**b**) any sarcoma with negative nodal sampling [11]. (Reproduced with permissions)

patients with more advanced disease, and there is suggestion that radiation improves local control, specifically for patients with morcellation in the OR, positive margins, and large tumor size [31].

In select inoperable cases, definitive treatment with combined modality external beam radiotherapy and brachytherapy can be considered.

The radiotherapy approach for palliation, adjuvant, and definitive management is discussed in detail in the "Radiation Therapy Techniques and Planning" section. In brief, palliative radiotherapy should encompass gross tumor with a margin to planning target volume that accounts for bladder filling/emptying as applicable. Adjuvant radiotherapy plans should aim to treat the upper vaginal vault while accounting for bladder filling. Additionally, the parametrial space and regional lymphatics are included in the clinical target volume with a planning target volume margin. For definitive radiotherapy, the uterus, cervix, parametrial tissues, and regional lymphatics are included in a clinical target volume. This is expanded to planning target volume. When followed by brachytherapy, the entire uterus receives a brachytherapy boost.

The use of adjuvant systemic therapy is established in endometrial stromal sarcomas [21, 32, 33]. Approximately, 80% of endometrial stromal sarcomas express estrogen and progesterone receptors. This has led to a variety of hormonal regimens which have been trialed for typically advanced (stage III or IV) disease [34]. As there is limited prospective data for this practice, the drug of choice and duration of therapy have not been well established. Common regimens include aromatase inhibitors, GnRH analogs, and medroxyprogesterone 250 mg or megestrol 160 mg daily for 2 years [35, 36].

In recurrent and metastatic endometrial stromal sarcomas, a variety of agents have been trialed with varying efficacies in small cohort studies. In addition to hormonal therapies, doxorubicin and docetaxel/gemcitabine are commonly used.

Table 3.4 Systemic treatment regimens for metastatic unresectable ovarian or uterine leiomyosarcoma [37]

Agent(s)	Dose	Cycle length
Doxorubicin	60 mg/m^2	Every 3 weeks
Gemcitabine	1000 mg/m^2	3 weeks on, 1 week off
Ifosfamide	1.5 g/m^2 × 5 days	3 weeks
Pazopanib	800 mg oral daily	N/A
Trabectedin	1.5 mg/m^2 over 24 h	3 weeks
Combination regimens		
Dacarbazine + temozolomide	–	–
Doxorubicin + ifosfamide	–	–
Fixed dose-rate gemcitabine + docetaxel	–	–

Ifosfamide has also been shown efficacious [34]. Additionally, several clinical trials are evaluating the role of targeted treatments such as sunitinib, pazopanib, and deforolimus but have yet to be published. In the specific case of leiomyosarcoma, consensus guidelines for management of metastatic disease have been made (Table 3.4) [37].

With regard to uterine adenosarcomas, systemic treatment options and indications are similar to endometrial stromal sarcomas with one study showing 90% expression of estrogen or progesterone receptors [38]. When considering leiomyosarcoma, treatment is often reserved for recurrent disease. For recurrences within 6 months of surgery, doxorubicin has been shown to have good efficacy with an acceptable toxicity profile [34]. Other regimens including docetaxel with gemcitabine have been used. For recurrences occurring after 6 months from surgery, there is a higher probability of expressing hormone positivity, and targeted treatment with or without resection of oligometastases may be preferred [23, 39].

3.2.8 Cervical Sarcoma

Sarcoma of the cervix is a rare disease accounting for <1% of cervical neoplasms. The optimal treatment regimen for these tumors has not yet been established [40]. With a five-year overall survival ranging from 90% (stage IA) to 11% (stage IVB) after radical hysterectomy, given the lack of evidence, this may be a reasonable approach as opposed to radical chemoradiotherapy with brachytherapy [40]. In the case of leiomyosarcoma, evidence does not support the use of elective pelvic lymph node dissection.

A role for adjuvant radiotherapy or chemotherapy has not been definitively established in cervical sarcomas. However, either of these or both in combination can be considered for patients with positive margins or locally advanced disease (stages III–IV) [41]. One exception to this is embryonal rhabdomyosarcoma which typically occurs in the pediatric population. Here, typical treatment includes surgical excision followed by adjuvant chemotherapy. Various agents have been trialed

with success noted in vincristine, actinomycin D, and cyclophosphamide (VAC) combination therapy [42].

3.2.9 Vaginal/Vulvar Sarcoma

Wherever possible, vulvovaginal sarcoma should be surgically excised, and for leiomyosarcomas, adjuvant radiotherapy should be considered [43–45]. In most cases, benefit can be inferred for resection of the primary mass and selective metastases [46]. Here, surgery consists of a radical vulvectomy. Adjuvant radiotherapy and chemotherapy can be considered for locally advanced (node positive or gross invasion into the bladder/rectum) disease. In rare cases where the lesion may become surgically excisable with neoadjuvant therapy, neoadjuvant radiotherapy to the tumor can be considered.

In the case of vaginal sarcoma, surgery typically either consists of a radical hysterectomy with upper vaginectomy or pelvic exenteration. For small volume localized disease, wide local excision can be considered. For more advanced disease, pelvic exenteration or radical hysterectomy with vulvovaginectomy can be considered. In selected patients who are not surgical candidates and with reasonable performance status, combined treatment with external beam radiotherapy and interstitial brachytherapy can be considered for the treatment of vaginal disease.

In the case of limited metastatic disease, surgical resection followed by chemotherapy should be considered. Otherwise, palliative radiotherapy may be used for symptom relief.

3.2.10 Ovarian Sarcoma

Ovarian sarcomas are rare and aggressive entities. Typical primary management is bilateral oophorectomy and/or cytoreductive surgery [47]. Total abdominal hysterectomy is typically performed at the time of oophorectomy. When compared to their epithelial cell counterparts, prognosis is generally poor [48, 49]. In a recent literature review, *Shylasree* et al. found no randomized evidence addressing the use of adjuvant chemotherapy or radiotherapy for ovarian sarcomas [50]. Given the lack of evidence, chemotherapy is commonly reserved for treatment of metastatic disease.

In the case of unresectable metastatic disease, various chemotherapy regimens have been trialed. Recent GCIG (Gynecologic Cancer InterGroup) guidelines suggest a series of agents for leiomyosarcoma of the ovary or uterus (Table 3.4) [37].

3.2.11 Recurrent Disease/Palliation

In pelvic recurrent disease, stereotactic body radiotherapy or interstitial brachytherapy can be considered for salvage as a means to avoid pelvic exenteration in highly motivated patients. However, this practice should be restricted to centers with specialized

expertise and ideally within the context of a prospective study. Otherwise, pelvic exenteration should be considered as standard of care whenever disease is resectable. In patients with unresectable and/or disseminated disease, palliative systemic therapy and radiotherapy for symptomatic relief should be considered as standard of care.

3.3 Radiation Therapy Techniques and Planning

3.3.1 Uterine and Cervical Sarcoma

3.3.1.1 Adjuvant Radiotherapy

In the majority of cases, radiotherapy for uterine or cervical sarcomas is given adjuvantly after definitive surgery. In these cases, the uterus and a large portion of the parametrial tissue have been removed. Elective radiotherapy volumes are intended to cover the residual vagina, parametrial, and select nodal volume(s).

3.3.1.2 Simulation

Patients should undergo CT simulation imaging from the T12 to mid femur with bladder full and empty scans. In facilities where it is available, MR simulation is preferred for better vaginal vault delineation. Patients should be simulated supine with arms across their chest and legs supported with an ankle rest. Localizer tattoos marked with bb's are utilized for setup guidance. With regard to internal volumes, the primary organs for consideration are the rectum and the bladder. Patients should be instructed to assume a regular bowel routine, and therapists should not accept any scan where the rectal anterior-posterior dimensions measure greater than 4 cm. Patients should maintain this regimen and a comfortably full bladder throughout the course of treatment. In addition, daily cone beam CT imaging is considered the current standard for daily treatment positional confirmation.

3.3.1.3 Volume Delineation

All organ at risk volumes should be contoured on the bladder full CT simulation scan. Suggested volumes for contouring include the bladder, bilateral femoral heads, peritoneal space, rectum, and sigmoid (Fig. 3.3). A description of each contour is discussed below:

1. Bladder—the entire bladder should be contoured including all urine. Contour should be extended superiorly and the coronal imageset used to differentiate superior edge of the bladder from potential loops of the bowel.
2. Femoral heads—the left and right femoral heads should be contoured separately and extend from the top of the femoral acetabulum superiorly to the bottom of the ischial tuberosities inferiorly.
3. Rectum—the inferior margin of the rectal contour should be at the level of the ischial tuberosities. Superiorly, the rectal contour ends at the rectosigmoid junction which is delineated as the region where the large bowel both flexes anteriorly and narrows.

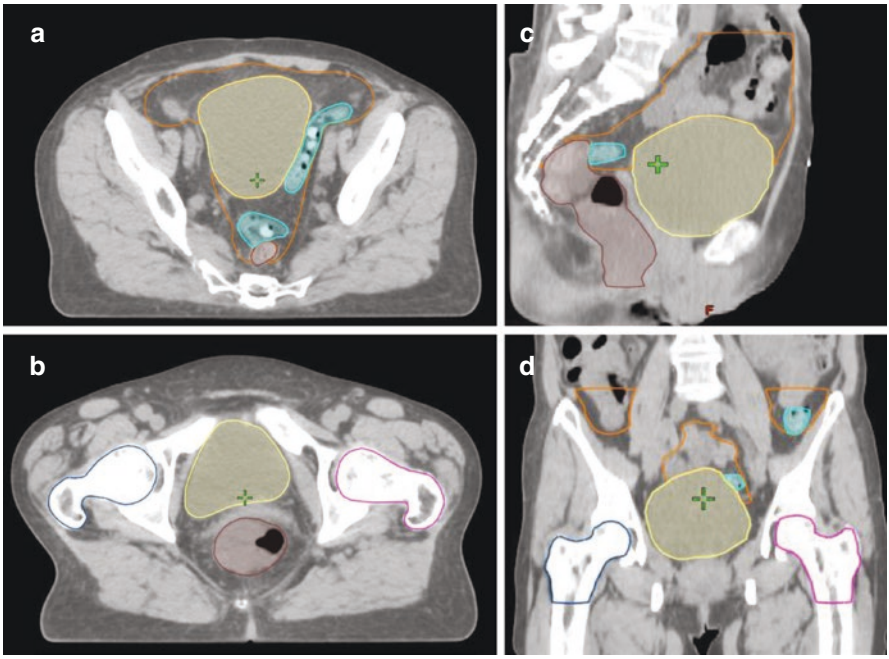


Fig. 3.3 Examples of contours of the (1) bladder, yellow; (2) rectum, brown; (3) femoral heads, left magenta, right blue; (4) sigmoid, cyan; and (5) peritoneal space, orange. Images are (**a**) axial superior pelvis, (**b**) axial pelvic brim, (**c**) midsagittal, and (**d**) coronal

4. Sigmoid—the sigmoid contour starts at the rectosigmoid junction (the region of large bowel that shifts anteriorly and briefly narrows). The sigmoid should be followed superiorly to the L4/L5 vertebral body level.
5. Peritoneal space—the peritoneal space contour begins at the lowest level where a non-rectal loop of the bowel is delineated. The rectum and bladder should be removed from this contour. An alternative to contouring peritoneal space can include contouring individual bowel loops.

In most adjuvant cases of cervical or uterine sarcoma, all diseases have been resected, and no gross residual disease is present. Hence, there is generally no gross tumor volume. In cases where gross residual disease is present on pre-simulation magnetic resonance imaging (MRI), the MRI should be registered to the simulation CT or MR imagesets. GTV should be contoured as all T2-weighted abnormalities visualized on the MRI. If gross tumor is visualized on the CT imageset, then it should be contoured on both the bladder full and empty imagesets. If MR simulation has been used, the GTV should be contoured on both bladder full and empty scans.

In the absence of gross residual disease, the clinical target volume (CTV) should be contoured as separate volumes and booleaned into a final CTV. The first portion of CTV that is contoured is the vaginal vault and parametrial tissues (CTVvp_full

and CTVvp_empty). This is contoured on both bladder full and empty images and combined into a single ITV (internal target volume) (Fig. 3.4). CTVn can be considered in most cases of uterine or cervical sarcoma; however, given the rarity of nodal metastases for gynecologic sarcomas, the benefit of this can be debated. The authors typically select to include elective nodal coverage given the limited added toxicity. The ITV and CTVn are then combined into a final CTV margin and expanded to planning target volume (PTV):

1. CTVvp_full/empty—CTV volume that encompasses the at-risk vaginal tissue (typically the upper one-third or 3 cm of vaginal vault). The inferior border of this volume is often estimated at the mid obturator foramina on topographical image views or the center of the pubis bone. Laterally, this volume is confined by the levator ani and obturator internus muscles. Additionally, the contour can be abbreviated at the medial edge of the internal and external iliac vessels. Anteriorly, CTVvp_empty/full is confined by the posterior bladder wall, and posteriorly the contour remains anterior to the rectum and mesorectal fascia (unless originally disrupted by tumor—then the mesorectal fascia should be encompassed in the CTV volume).
2. ITV—the combination of CTV full and empty. Special consideration to this volume can be made to ensure the entire anterior/posterior range of motion of the vaginal vault is incorporated in the volume.
3. CTVn—elective nodal volumes should include the external iliac, internal iliac, presacral, and distal common iliac chains. A standard 7 mm symmetric expansion about the iliac vessels is trimmed to the bone, muscle, and bowel. The external iliac contours end inferiorly at the level of the femoral acetabulum. For presacral volumes, 1 cm anterior to the bone is contoured from L5/S1 to the S3/S4 interspace. Additionally, a 1 cm strip medial to the levator muscle is used to delineate the obturator portion of the internal iliac chain. The internal iliac/obturator contour ends at the pubic symphysis. For grossly involved nodal disease, inclusion of the proximal common iliac can be considered. For tumors extending to the distal third of the vagina or anal canal, elective coverage of the inguinal nodal regions can be considered but is typically not recommended.
4. CTV—the final combined volume of CTVn and ITV volumes.
5. PTV—the planning target volume is defined as a symmetric margin. For consideration of PTV, both the ITV and elective nodal volumes should be considered separately and should be institution specific. Suggested margins may range from 0.5–0.7 cm (nodal portion of CTV) to 0.7–1.0 cm (ITV portion of CTV).

3.3.1.4 Treatment Planning Considerations

The preferred dose and fractionation for gynecologic sarcomas have not been established in the adjuvant setting. In the absence of gross residual disease, common dose and fractionation schedules include 4500 cGy in 25 fractions delivered daily over 5 weeks, 5000 cGy in 25 fractions delivered daily over 5 weeks, and 5040 cGy in 28 fractions delivered daily over 6.5 weeks. To maintain consistency with other

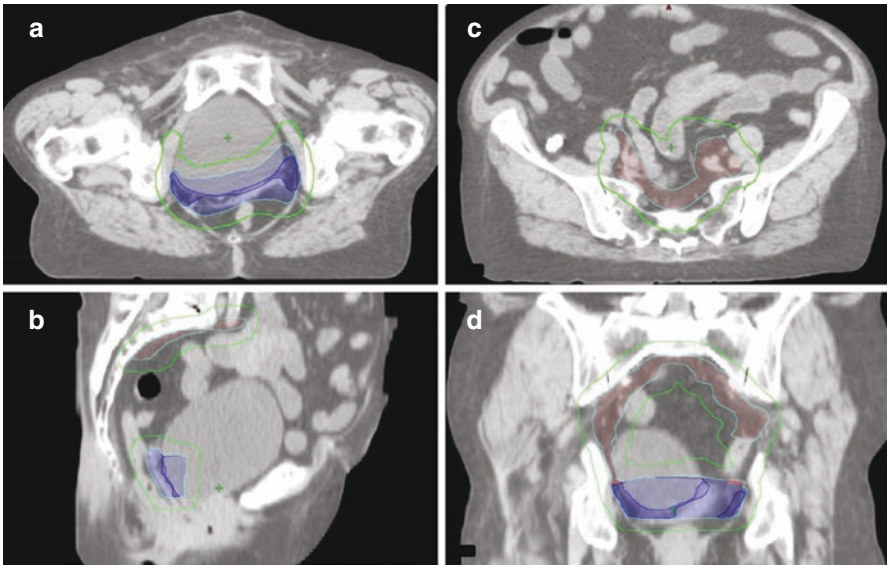


Fig. 3.4 Example of contours for (1) CTVvp_full, blue segment; (2) CTVvp_empty, translucent blue; (3) ITV, translucent red; (4) CTVn, pink segment; (5) CTV, cyan; and (6) PTV, green. *Note: The ITV is often modified to ensure it will account for all positions of the vagina with all levels of bladder filling. Images are in the following planes: (**a**) axial at level of pubic symphysis, (**b**) mid-sagittal, (**c**) axial at the level of S1, and (**d**) coronal

sarcoma treatment sites of the authors, prefer 5000 cGy in 25 fractions delivered daily over 5 weeks.

In the cases where gross residual disease is present, the GTV subvolume with an appropriate PTV margin should undergo either simultaneous integrated or sequential boost to an equivalent dose of 66Gy in 33 fractions delivered daily over 6.5 weeks. In well-selected cases and at centers with considerable expertise, an interstitial brachytherapy boost can be considered.

Treatment planning should take into account the resources available in the treating center. There is some evidence for reduced toxicity when intensity-modulated radiotherapy is used in treating non-sarcomatous cervical cancer; therefore, arguments can be made for using advanced radiotherapy planning [51]. However, four-field box technique is well studied and considered safe at least in the setting of adjuvant radiotherapy without a planned boost. In cases where radiotherapy doses above 5000 cGy are anticipated, IMRT (intensity-modulated radiotherapy) should be considered either via step and shoot, sliding window, or full volumetric-modulated arc therapy (VMAT) technique. Other techniques that may be explored include tomotherapy or proton therapy treatments ideally under an investigational protocol.

When planning with four-field box technique, typically the entire volume is encompassed by the anterior/posterior and lateral pairs. A margin of 5–7 mm beyond the PTV should be used to field edge to allow for appropriate scatter

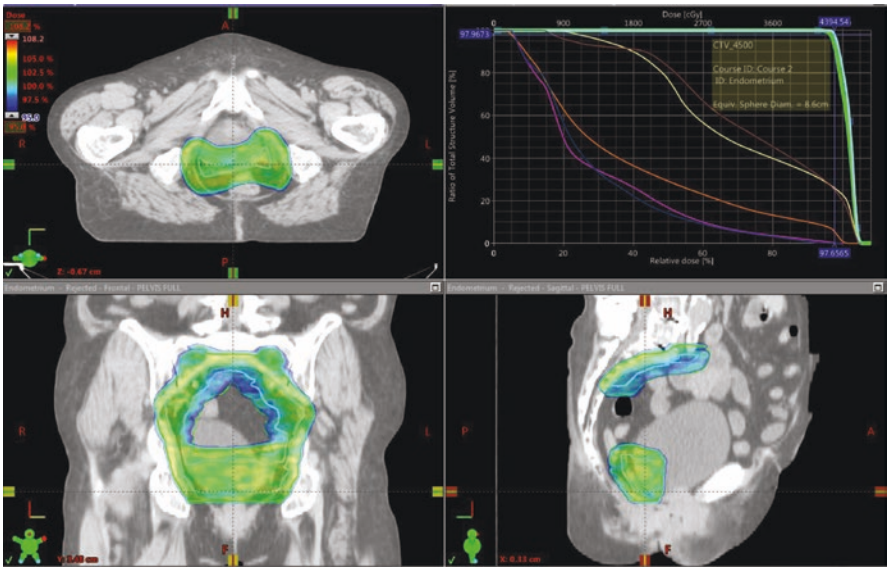


Fig. 3.5 Example of VMAT plan for adjuvant treatment of a gynecologic sarcoma. The dose color wash shows the 95% isodose level, and green line indicates PTV volume. Top left—accompanying DVH

equilibrium. Classically, the field edges will extend into the mid sacrum, 1 cm into the pelvis laterally. The superior border is typically at the level of mid L5/S1 joint space, and the inferior border is at the bottom of the obturator foramina. For VMAT or other IMRT techniques, optimization objectives should prioritize target coverage and homogeneity (Fig. 3.5). In considering the PTV volume coverage, planning objectives should aim for at least 97% of the PTV volume receiving 95% of the prescribed dose (although minor deviations allowing for 95% of the PTV volume receiving 95% of the prescribed dose are acceptable). Hot spots should be limited to be inside the PTV and <106% of the prescribed dose (up to 108% may be acceptable in certain circumstances). Otherwise, objectives for reduced dose to the peritoneal space should be prioritized over the rectum, femoral heads, and bladder (dose constraints described below) and are usually met without issue. In static field IMRT techniques, a minimum of five fields is recommended, and 7–9 fields are preferred. These should include a direct anterior and additional equi-spaced fields avoiding direct entry through the rectum posteriorly and hips laterally if possible. For VMAT plans, two 359-degree arcs with a collimator rotation of 90 degrees between them are recommended. Avoidance zones can be added for cases of artificial hip(s).

3.3.1.5 Definitive Radiotherapy/Chemoradiotherapy

In motivated patients not eligible for surgical treatment, primary radiotherapy and/or chemotherapy can be considered. In these cases, the intact uterus provides a

unique challenge to modern planning and must be considered during simulation and treatment. The primary volume should receive dose escalation, and elective regions consisting of the parametrial tissue bilaterally, uterus, cervix, and upper vagina should be included. Elective nodal radiation is also considered.

3.3.1.6 Simulation

CT or MR simulation imaging is similar to that required for adjuvant radiotherapy treatment for cervical or uterine sarcomas. Furthermore, as all patients will have gross disease, registration of pretreatment diagnostic MR imaging onto the simulation datasets should be considered. One additional consideration is that patients who have ureteric obstruction from the primary mass should have nephrostomy tubes and/or ureteric stents placed prior to CT simulation imaging. Otherwise, daily cone beam CT imaging is recommended for daily setup guidance.

3.3.1.7 Volume Delineation

All organ at risk volumes should be contoured as per adjuvant radiotherapy for uterine or cervical sarcomas (Fig. 3.3). Often the peritoneal space contour should be extended given uterine positions above L5/S1 interspace. Target delineations should proceed as follows:

1. GTV—the GTV should be delineated on all available imagesets where it is well visualized. In cases where MR simulation imaging is available, the GTV should be contoured on both bladder full and empty imaging (GTV_full, GTV_empty).
2. ITV_HR—the GTV_full and GTV empty should be booleaned into a primary ITV volume. This volume should be adjusted such that the entire range of motion of the GTV with varying bladder filling would be encompassed.
3. CTV_HR—a 1.5 cm symmetric expansion about the ITV_HR should be employed to generate the CTV_HR. This volume is then trimmed to the bowel, bone, and muscle. In cases where the bowel is sitting directly on top of GTV, then the volume may be extended 0.5 cm into the bowel. Where the bowel is grossly invaded, it may be encompassed in the CTV_HR volume.
4. PTV_HR—a 0.5–1.0 cm symmetric expansion about the CTV_HR is used to generate the PTV_HR.
5. CTV_vpu_full/empty/MR—the parametria, entire uterus, and upper vagina should be contoured as an elective CTV volume (CTV_vpu). For this contour, the parametrial borders are defined inferiorly as the levator ani muscle and laterally as the medial edge of the iliac vessels or the obturator internus muscle. Anteriorly, the parametrial border is the bladder wall inferiorly and the broad ligament cranially. The superior parametrial contour is stopped at the level of the broad ligament of the uterus.
6. ITV_LR—this should encompass the CTV_vpu for each of the three scans above (empty/full/MR).
7. CTVn—elective nodal coverage can be considered as for the case of adjuvant radiotherapy above.

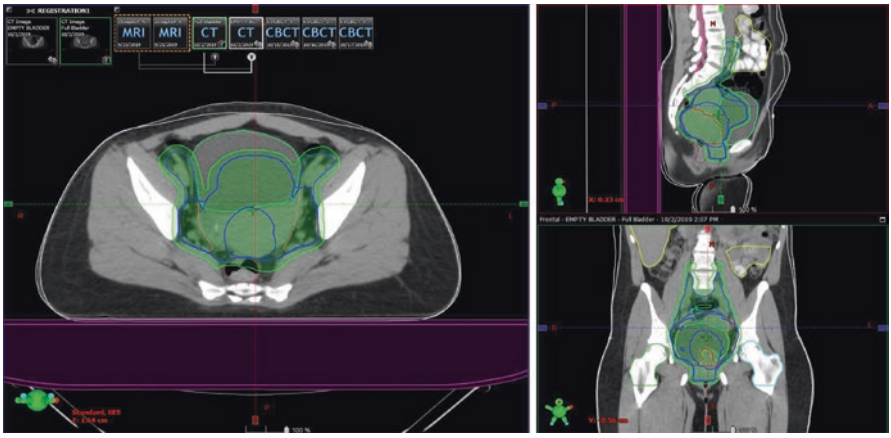


Fig. 3.6 Examples of contours for a cervical sarcoma: (1) GTV, red; (2) ITV_HR, inner blue contour; (3) CTVvpu_full/empty/MR, translucent blue contours; (4) ITV, dark blue; (5) CTVn, salmon; (6) CTV_total, light blue; and (7) PTV, green segment. *Note: The ITV is often modified to ensure it will account for all positions of the uterus with all levels of bladder filling. Images are in the following planes: left, axial at the mid bladder; right upper, midsagittal; and right lower, coronal

8. CTV_total—this should encompass CTVn, ITV_LR, and CTV_HR.
9. PTV_total—a 0.5–1 cm symmetric expansion around CTV_total is employed to generate the final PTV.

Examples of contours for a cervical sarcoma are given in Fig. 3.6.

3.3.1.8 Treatment Planning Considerations

The preferred dose and fractionation for gynecologic sarcomas have not been established in the definitive setting. For coverage of elective volumes (such as PTV_total above), dose and fractionation schedules could include 4500 cGy in 25 fractions delivered daily over 5 weeks, 5000 cGy in 25 fractions delivered daily over 5 weeks, and 5040 cGy in 28 fractions delivered daily over 6.5 weeks. To maintain consistency with other sarcoma treatment sites of the authors, prefer 5000 cGy in 25 fractions delivered daily over 5 weeks. When considering dose to the gross tumor, equivalent doses of at least 66Gy in 2Gy fractions (60Gy EQD2) should be considered as a boost to the PTV_HR when using external beam radiotherapy alone.

The principles of planning are similar to those of external beam radiotherapy in the adjuvant setting. In all cases, intensity-modulated radiotherapy via inverse optimization planning is recommended. However, the volume irradiated with an intact uterus is larger, and special attention to motion of the primary uterine mass with bladder filling should be made. The proximity of bowel loops to the uterus may limit the portion of the PTV_HR that can effectively receive the full prescribed boost irradiation dose (66Gy EQD2). In considering bladder irradiation, the authors

do not recommend compromising coverage but do recommend that no areas of normal bladder mucosa receive >100% of the prescribed boost irradiation dose.

In centers with considerable expertise, well-selected patients with good performance status may undergo intercavitary or interstitial brachytherapy as a means for boost irradiation to the gross tumor. This approach is well adapted in non-sarcomatous cervical and uterine/endometrial cancers and may reduce overall toxicity when considering uterine or cervical sarcoma treatment. In such cases, boost irradiation doses should be carefully selected to ensure the gross residual tumor at the time of brachytherapy receives at least a total dose of 66Gy EQD2 from all irradiation sources and preferably doses >80Gy EQD2. Given the known microscopically infiltrative nature of sarcomas, consideration of CTV margin at the time of brachytherapy can be made, but there is no recommended standard practice.

3.3.2 Vulvar/Vaginal Sarcoma

3.3.2.1 Adjuvant Radiotherapy

The role of radiotherapy in vulvar and vaginal sarcomas is primarily limited to the adjuvant setting. In these cases, considerations for simulation and radiotherapy planning are largely similar to those of cervical and uterine sarcomas. However, several distinct differences exist.

3.3.2.2 Simulation

Patients with upper vaginal tumors should undergo CT simulation imaging from T12 to the mid femur with bladder full and empty scans. In patients with only distal one-third vaginal or vulvar involvement of disease, CT imaging with bladder full is suffice. In facilities where it is available, MR simulation is preferred for better surgical site and vaginal and urethral delineation. Patients should be simulated supine with arms across their chest and legs supported with an ankle rest. Localizer tattoos marked with bb's are utilized for setup guidance. Furthermore, all surgical scars should be wired, and a 0.5–1.0 cm bolus over the vulva and inguinal folds should be considered and can be placed at the time of simulation or virtually created in the treatment planning system and then placed during each treatment. With regard to internal volumes, the primary organs for consideration are the rectum and the bladder. Patients should be instructed to assume a regular bowel routine, and therapists should not accept any scan where the rectal anterior-posterior dimensions measure greater than 4 cm. Patients should maintain this regimen and a comfortably full bladder throughout the course of treatment. In addition, daily cone beam CT or X-ray imaging can be used for daily treatment positional confirmation.

3.3.2.3 Volume Delineation

All organ at risk volumes should be contoured as per adjuvant radiotherapy for uterine or cervical sarcomas (Fig. 3.3). Pre- and postsurgical MR imaging (both T2 and T1) should be registered to the simulation images. Target delineations should proceed as follows:

1. GTVres—all gross residual disease post-surgeries as delineated on postsurgical MRI or clinically demarcated at the time of CT simulation (wired) should be contoured as residual GTV volume. In the case of upper vaginal disease, this GTV volume should be demarcated on both bladder full and empty simulation CT scans and booleaned together and modified to form an ITV_HR volume that encompasses the entire range of motion of the tumor with bladder filling.
2. CTV_HR—a 1.5 cm symmetric expansion about the GTVres or ITV_HR volume should be employed to generate the CTV_HR. This volume is then trimmed to the mesorectal fascia, bone, and muscle. In cases where GTVres volumes extend to the rectum, the volume may be extended 0.5 cm into the rectum. Where the bladder or anal canal/rectum is grossly invaded, the gross disease and at least 2 cm of the anorectum or bladder should be encompassed in the CTV_HR volume. In cases where the urethra is/was grossly involved by tumor, CTV_HR should extend at minimum 2 cm along the urethra. In cases where the vagina is/was grossly invaded by tumor, the entire vagina should be included in CTV_HR. In all cases, CTV_HR should be trimmed to the skin surface.
3. PTV_HR—a 0.5–1.0 cm symmetric expansion about the CTV_HR is used to generate the PTV_HR.
4. CTV_LR—elective vulvovaginal coverage should include the entire vulva and vagina. In cases where the anorectum is involved with disease, elective coverage of the mesorectal fascia can be considered. Additionally, CTV_LR should include the entire surgical bed and all areas where GTV was delineated on the presurgical MRI imageset with an additional 1.5 cm margin and trimmed to anatomical boundaries.
5. CTVn—elective nodal coverage can be considered for vulvovaginal sarcomas. In all cases except tumors limited to the upper two-thirds of the vagina, if elective nodal irradiation is considered, volumes should include the inguinal nodal regions. The anatomical boundaries for inguinal nodal contours are as follows: (1) inferior, the lesser trochanter of the femur or the level at which the deep femoral artery separates off from the common femoral artery; (2) superior, the superior most slice where the femoral acetabulum is visualized, (3) lateral, the lateral edge of the femoral artery/vein, (4) medial, the medial contour which is bounded by the muscle or inguinal fold, (5) anterior, 0–0.3 cm from the skin surface; and (6) posterior, the posterior edge of the femoral vessels or muscle as appropriate. In cases of lower vaginal or vulvar disease and without node positivity, elective coverage of the distal common iliac lymphatics can be omitted from the volume. Otherwise, elective nodal coverage is similar to the uterine/cervical sarcoma cases.
6. CTV_total—this should encompass CTVn, CTV_LR, and CTV_HR.
7. PTV_total—a 0.5–1 cm symmetric expansion around CTV_total is employed to generate the final PTV.

Examples of contours for a vulvar sarcoma are given in Fig. 3.7.

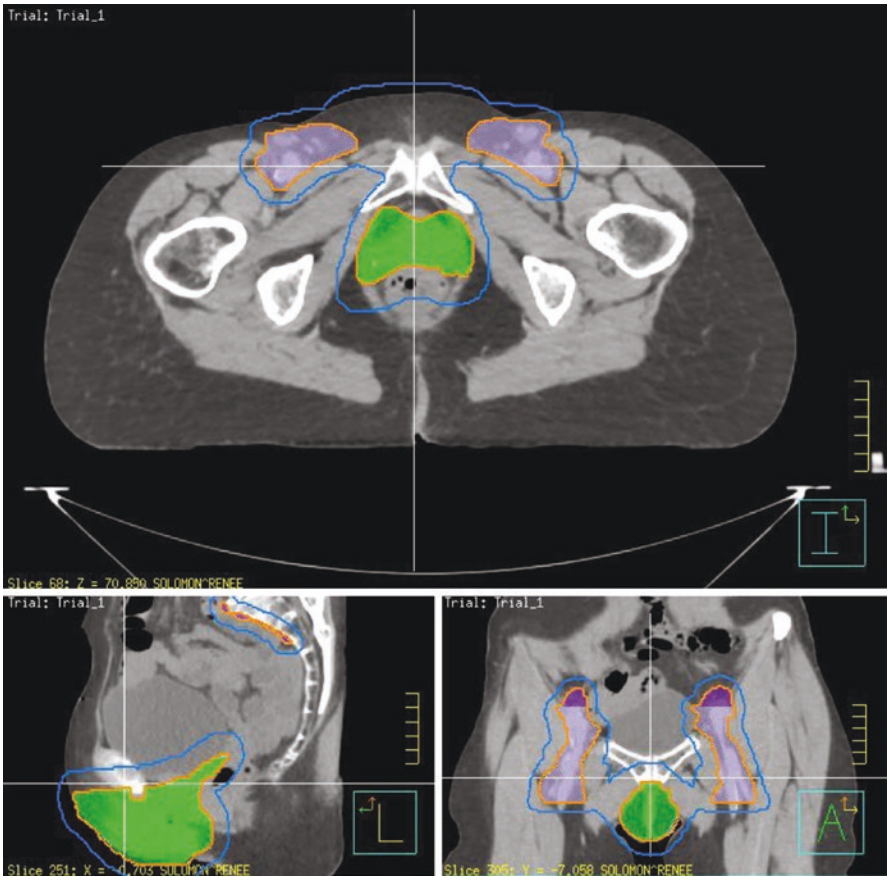


Fig. 3.7 Examples of contours for vulvar sarcoma. Contours are as follows: (1) CTV_LR, green segment; (2) CTVn, purple segment; (3) CTV_total, orange segment; and (4) PTV, blue. Images are top, axial at level of pubic symphysis; bottom left, midsagittal; and bottom right, coronal

3.3.2.4 Treatment Planning Considerations

Treatment planning and dose and fractionation schedules used should reflect those used in the adjuvant setting for cervical or uterine sarcomas. In brief, doses between 4500 cGy in 25 fractions and 5040 cGy in 28 fractions should be considered. For cases where residual disease is present, the PTV_HR volume should receive boost irradiation to an equivalent dose of 6600 cGy in 33 fractions (EQD2).

Treatment planning should utilize intensity-modulated radiotherapy techniques except in cases where organ at risk tolerances are better met with three-dimensional conformal techniques. Additionally, modalities other than linear accelerator-based megavoltage photon treatment may be considered including proton therapy or tomotherapy in centers with considerable expertise.

3.3.2.5 Definitive Radiotherapy/Chemoradiotherapy

In the definitive setting simulation imaging, volume delineation and planning considerations are similar to those described for adjuvant radiotherapy for vulvovaginal sarcomas. In these cases, the single exception to volume delineation is one that does not need to consider coverage of the postoperative bed in the CTV_LR. Furthermore, in some scenarios, surgical excision may be planned after neoadjuvant radiotherapy. If this is a consideration, doses should be limited to 5000 cGy in 25 fractions preoperatively, and boost doses of 1000 cGy in 5 fractions or 1600 cGy in 8 fractions can be considered for any microscopically or grossly positive margin postoperatively. CTV boost volumes in these cases should include the surgical bed and a minimum 1 cm symmetric margin around the site of positive margins.

3.3.3 Ovarian Sarcoma

At present, the role of radiotherapy in ovarian sarcoma is limited to palliation of advanced disease. In cases of limited disease, stereotactic body radiotherapy may be used in lieu of cytoreductive surgery (see stereotactic body radiotherapy and palliative radiotherapy treatments below).

3.3.3.1 Radiation-Related Toxicities and Radiotherapy Dose Constraints for Organ at Risk Volumes

In general, radiotherapy dose constraints for organs at risk follow those outlined by QUANTEC (Quantitative Analysis of Normal Tissue Effect in the Clinic) [52]. Often toxicities encountered acutely include skin erythema, moist/dry desquamation, pelvic hair loss, nausea, urinary urgency/frequency/dysuria, fecal urgency/frequency/diarrhea, and an increase in pelvic pain. Longer-term toxicities include chronic skin dryness or color changes, vaginal dryness/dyspareunia, potential vaginal adhesions/stenosis, urethral narrowing/structuring, difficulties with urinary urgency, induction of early menopause, and increased cramping and gassiness. Uncommon long-term risks include risks of femoral neck fracture, radiation cystitis, proctitis, chronic diarrhea, bowel obstruction, and fistula formation. The organ at risk dose constraints and accompanying rate(s) of anticipated toxicities are described in Table 3.5.

3.3.4 Recurrent and Metastatic Disease

3.3.4.1 Interstitial Brachytherapy

In cases of locally recurrent disease to the vagina, interstitial brachytherapy can be used for both local palliation and attempt at salvage treatment with intent to avoid pelvic exenterative surgery. This procedure involves insertion of interstitial catheters through the perineum and directly into the tumor using one of many

Table 3.5 Organ at risk dose constraints and accompanying toxicity rates

Contour	Toxicity outcome	Dose constraint
Small bowel loops	<10% G3+ acute toxicity	V15 < 120 cc
Peritoneal space	<10% G3+ acute toxicity	V45 < 195 cc
Rectum	<10% G3+ late toxicity	V50 < 50%
Rectum	<10% G3+ late toxicity	V60 < 35%
Rectum	<10% G3+ late toxicity	V70 < 20%
Bladder	<10% G3+ late toxicity	V65 < 50%
Bladder	<10% G3+ late toxicity	V70 < 35%
Femoral head	<5% G3+ late toxicity	V50 < 50%
Sigmoid	<10% G3+ late toxicity	D2cc < 75Gy (BT)
Rectum	<10% G3+ late toxicity	D2cc < 75Gy (BT)

BT Brachytherapy dose constraint from standard cervical cancer treatment

available templates. Spacing between catheters is usually maintained at less than 1 cm. Usually, this is performed under spinal or general anesthetic, and transrectal ultrasound guidance is used to ensure catheter placement. Once inserted, all catheters are advanced to at least 1 cm beyond the tumor (intrusions into the bladder, bowel, and rectum are common but unlikely cause complication) [53]. Once placed, the patient undergoes CT- or MR-based simulation imaging, and dedicated brachytherapy planning software is used to optimize catheter dwell positions to deliver doses between 2100 cGy in three fractions and 4000 cGy in six fractions to the recurrent vaginal mass, depending on the clinical scenario and previous radiation. The most common brachytherapy source used to deliver these treatments is iridium-192. These treatments should be performed in specialized treatment centers with considerable expertise in interstitial brachytherapy for gynecologic tumors.

3.3.4.2 Stereotactic Body Radiotherapy

The use of stereotactic body radiotherapy (SBRT) for metastatic disease is expanding worldwide. In cases of limited metastatic disease that is not amenable to surgical excision, there may be a role for using SBRT as an alternative to surgical resection. In the special case of limited metastatic disease to the brain or spinal cord, single fraction stereotactic radiosurgery may be performed. In cases of SBRT, MR imagesets may be fused to CT simulation images with patients immobilized on a spine board or in a vacuum immobilization bag. In the upper abdomen and lungs, 4DCT (four-dimensional computed tomography) simulation is used. The GTV is contoured and a direct expansion to PTV of 0.3–0.5 mm is used. Often nearby vessel calcifications or clips are used to aid with daily treatment image matching. All treatments are carried out using cone beam CT image matching based on both boney structures and if visible the tumor itself (the preferred matching structure). Dose and fractionation regimens for SBRT are dependent on the anatomical site of metastatic disease and typically range from

2000–2400 cGy in 1–2 fractions to 5000 cGy in 5 fractions. For isolated metastatic disease to the abdomen or pelvis, the authors routinely utilize doses of 3500 cGy in five fractions. In these specific cases often, small bowel presents as a dose-limiting organ at risk, and compromise to a portion of the PTV volume is made to accommodate this. Another consideration when planning SBRT is there is often no specific constraint applied to the maximum dose to target. Often isodose levels of 125–130% are found within the PTV, or the prescribed dose is to a lower isodose level than the 100% (commonly the 70–80% isodose levels). SBRT treatments should only be administered in centers with expertise and by experienced personnel.

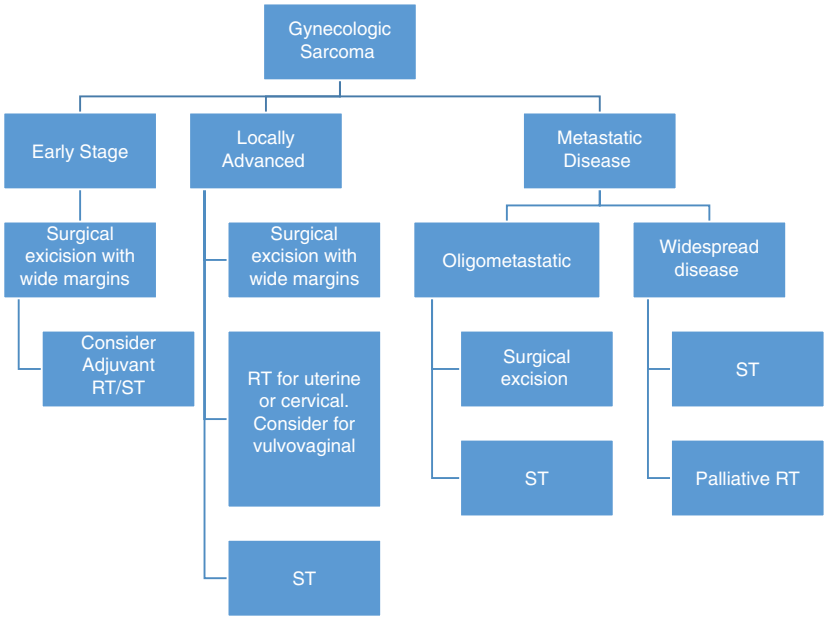
3.3.4.3 Palliative Radiotherapy Treatments

A variety of radiotherapy doses and planning techniques are acceptable when delivering palliative radiotherapy treatments for gynecologic sarcomas. Given their simplicity and widespread availability, the most common palliative radiotherapy treatments to the pelvis include 2000–3000 cGy in 5–10 fractions delivered via three-dimensional conformal radiotherapy. In patients with limited life expectancy or who wish to avoid multiple daily treatments, a single fraction of 600–1000 cGy is often safe. Palliative radiotherapy is often useful in reducing pelvic bleeding, pain, nausea from tumor compression of the bowel, skin ulceration, abnormal vaginal discharge, and other symptoms of disease.

3.3.4.4 Physics and Quality Assurance Considerations

Quality assurance considerations should follow institutional best practice for three-dimensional conformal and intensity-modulated radiotherapy planning, respectively. In brief, all treatment units should undergo extensive acceptance testing and commissioning. Positional accuracy at the time of treatment delivery should be within 5–10 mm, and radiotherapy dose delivery accuracy should be within 5% from all sources of error. Monthly quality assurance checks should be performed on all machines delivering IMRT treatment, and during this gantry angle and collimator angle, collimator walkout checks should be completed. Beam profiles should be measured; couch positional accuracy, laser alignment, jaw positioning, and MLC checks are completed. On daily treatment, cone beam imaging or kV (where appropriate) should be used to confirm positioning. For each plan, phantom dose distribution measurements of a single fraction are recommended prior to treating the patient. Additional physics checks for IMRT planning should include consideration of minimizing monitor units used based on plan complexity, ensuring CTV and PTV contours are contained and appropriate (e.g., GTV does not extend beyond CTV boundary and CTV contained within PTV). Finally, routine radiation oncology peer review of contoured volumes and treatment plans for these rare malignancies is recommended.

3.3.4.5 Treatment Algorithm



*RT–radiotherapy; ST-systemic therapy

Summary

- Gynecologic sarcomas are rare diseases
- The preferred management of gynecologic sarcomas consists surgical excision whenever possible
- In advanced uterine sarcomas there is an established role for adjuvant radiotherapy and chemotherapy
- In vulvovaginal sarcomas neoadjuvant and adjuvant radiotherapy can be considered
- Definitive radiotherapy can be considered in select non-operative cases
- Palliative radiotherapy and chemotherapy should be considered for non-resectable metastatic disease

**RT* Radiotherapy, *ST* Systemic therapy

3.4 Summary

- Gynecologic sarcomas are rare diseases.
- The preferred management of gynecologic sarcomas consists surgical excision whenever possible.
- In advanced uterine sarcomas, there is an established role for adjuvant radiotherapy and chemotherapy.

- In vulvovaginal sarcomas, neoadjuvant and adjuvant radiotherapy can be considered.
- Definitive radiotherapy can be considered in select nonoperative cases.
- Palliative radiotherapy and chemotherapy should be considered for non-resectable metastatic disease.

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Radiation Therapy for Oligometastatic Sarcomas

4

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Contents

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4.1 Systemic Therapy for Oligometastatic Sarcoma

Most sarcomas metastasize hematogenously, and the lungs are a common site of metastatic spread for extremity bone and soft tissue sarcomas (STS). Exceptions include myxoid-round cell liposarcoma, which has a tendency to metastasize to the spine and paraspinous tissues and other non-pulmonary locations, and several sarcomas that are known to spread to regional lymph nodes and are associated with the acronym SCARE—synovial sarcoma, clear cell sarcoma, angiosarcoma, rhabdomyosarcoma, and epithelioid sarcoma.

The use of adjuvant or neoadjuvant chemotherapy in the treatment of soft tissue sarcoma has been debated. There have been clinical trials and meta-analyses suggesting that treatment with a combination of anthracycline and ifosfamide chemotherapy, particularly in patients with high-risk (large, high-grade) tumors, may increase odds of disease-free or overall survival [2–4], but there have been several negative trials as well [5, 6]. Recent retrospective analysis of one of the largest negative trials, EORTC 62931, using an app-based nomogram called Sarculator, demonstrated that among the highest-risk patients, adjuvant chemotherapy did result in survival benefit [7]. Overall, available data suggests that for selected patients, those with high-risk extremity sarcoma of a histologic type that is potentially chemosensitive, perioperative combination anthracycline-ifosfamide chemotherapy may be warranted.

Systemic therapy may have a role in the treatment of selected patients with metastatic sarcoma, depending on the clinical situation, the histologic type of sarcoma, and the patient's desire and fitness to undergo treatment. Metastatic sarcoma is generally not considered curable, and so treatment is given with the goal of prolonging survival and/or palliating symptoms. Median overall survival (OS) for patients with advanced STS has improved in recent decades, from 12–15 months in the 1980s and 1990s [1, 8] to 18–26 months in the past decade [9–11]. There are multiple reasons for this improvement in outcomes overall, but it is likely due in part to the increasing number of effective systemic therapy options for sarcomas during this time period. Chemotherapy clearly has a role in the treatment of patients who present with metastatic Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma, since these sarcomas are likely to be chemosensitive, and aggressive multidisciplinary management may be associated with long-term remissions in a subset of patients [12–15].

In patients with oligometastatic STS who are undergoing treatment with other modalities, such as surgical metastasectomy or radiation therapy, the decision to use systemic therapy would depend on the clinical situation and histologic subtype. For example, a patient with a solitary lung metastasis noted 3 years after primary treatment for extremity myxofibrosarcoma may be less likely to undergo chemotherapy in addition to metastasectomy, whereas a patient with myxoid-round cell liposarcoma who develops two lung metastases and a paraspinal metastasis 6 months after completing primary treatment would more likely consider chemotherapy. There is limited data to guide this decision-making, and the available data is mixed [16, 17]. If used, administration of systemic therapy prior to metastasectomy will provide information about the efficacy of the treatment.

4.1.1 Standard Chemotherapy

Anthracycline chemotherapy agents, including doxorubicin, epirubicin, and liposomal doxorubicin, are considered standard first-line therapy for STS, and doxorubicin is a component of first-line regimens for Ewing's sarcoma and osteosarcoma [18]. Objective response rates for single-agent doxorubicin range from 12 to 23% [9, 19–21] (Table 4.1). Common side effects include nausea, alopecia, fatigue, mucositis, and neutropenia. At equimolar doses, epirubicin has similar efficacy and less toxicity compared to doxorubicin [22]; high-dose epirubicin is more toxic, but without increase in efficacy over doxorubicin [23]. Pegylated liposomal doxorubicin (PLD) and doxorubicin produce similar response and stable disease rates, with PLD associated with significantly less myelosuppression and alopecia [24]. Aldoxorubicin was associated with a higher six-month progression-free survival than doxorubicin in a randomized phase II study of patients with advanced STS [25]. Data from a randomized, phase III study comparing aldoxorubicin to the investigator's choice of several standard chemotherapy agents was presented in 2017; there was no progression-free survival (PFS) benefit with aldoxorubicin. This agent has not gained FDA (Food and Drug Administration) approval [26]. Doxorubicin was compared to gemcitabine and docetaxel combination as first-line therapy in patients with advanced STS, and the treatments produced equal 24-week PFS, and median PFS of 23.3 and 23.7 weeks, respectively [20].

Treatment of metastatic STS with the combination of doxorubicin and other cytotoxic chemotherapy agents, such as ifosfamide or dacarbazine, may produce higher response rates than would be expected with single-agent doxorubicin [19, 21, 27, 28], but it has not been shown to significantly improve survival [21]. For this reason, single-agent doxorubicin and PLD are reasonable first-line therapies. Combination therapy with doxorubicin and ifosfamide, or doxorubicin and

Table 4.1 Standard systemic therapies for advanced soft tissue sarcoma

Agent	Indication	Outcomes	Citation(s)
Doxorubicin	Advanced STS	ORR 19–23%, PFS weeks	[9, 19–21]
Liposomal doxorubicin	Advanced STS, off-label	ORR similar to doxorubicin	[24]
Ifosfamide	Advanced STS, off-label, especially synovial sarcoma	ORR 10–25%	[31, 32]
Dacarbazine	Advanced STS	ORR 7.5–18%	[37, 38]
Gemcitabine	Advanced STS, off-label	ORR 4–6%	[41, 42]
Gemcitabine/ docetaxel	Advanced STS, off-label	ORR 16–18%; 53% uterine LMS	[48, 50, 51]
Pazopanib	Advanced non-liposarcoma STS	PFS 4.6 months	[68]
Trabectedin	Advanced liposarcoma and leiomyosarcoma	PFS 4.2 months; ORR 51% myxoid-round cell LPS	[55, 56]
Eribulin	Advanced liposarcoma	OS 15.6-month liposarcoma	[59, 60]

dacarbazine especially for leiomyosarcoma [28], may be considered when the benefit of significant response (e.g., for symptom relief) is expected to outweigh the increased toxicity associated with combination chemotherapy.

In recent years, several new agents have been studied in combination with doxorubicin, in hopes of improving on existing treatment options for metastatic STS. Unfortunately, addition of palifosfamide (active metabolite of ifosfamide), evofosfamide (hypoxia-activated prodrug of bromo-isophosphamide mustard), and olaratumab (anti-PDGFRα monoclonal antibody) to doxorubicin was not found to provide significant survival benefit over single-agent doxorubicin in randomized, phase III studies [9, 10, 29].

Ifosfamide has single-agent activity against STS, and synovial sarcoma has a higher likelihood of response than other histologies [30]. A strong dose-response relationship has been demonstrated [31, 32]. For example, a total dose of 9 g/m^2 over 3 days is significantly more likely to achieve objective response (25%) than a dose of 5 g/m^2 given on day 1 of each chemotherapy cycle (10%) [31]. Bolus dosing has been associated with higher response rates than continuous infusion [33]. High-dose ifosfamide in the range of 12–14 g/m^2 given over 3–6 days has activity in advanced soft tissue and bone sarcoma but has been associated with significant toxicity [34–36].

Dacarbazine has antitumor activity and is reasonably well tolerated, in patients with previously treated, advanced STS [37, 38]. It is a component of the MAID regimen, along with adriamycin (doxorubicin), ifosfamide, and the uroprotectant mesna, which was developed when the newer drug ifosfamide was added and augmented the activity of the combination of doxorubicin and dacarbazine [39]. More recently, anthracyclines (doxorubicin, epirubicin) and ifosfamide, without dacarbazine, have been studied in the neoadjuvant and adjuvant settings. Temozolomide, an oral alkylating agent similar to dacarbazine, achieved an overall response rate of 15.5% among pretreated, advanced STS patients in one small study, including 5 of 11 patients with gynecologic leiomyosarcoma [40].

Gemcitabine, used as a single agent, produces a low objective response rate in treatment of patients with advanced bone sarcoma and STS in general, but responses have been noted in patients with leiomyosarcoma and angiosarcoma [41–44]. Prolonged or fixed-dose rate infusion of gemcitabine has been associated with longer survival in pancreatic cancer, compared to 30-min infusions [45]. While there are no comparative studies in sarcoma, there is preclinical evidence that suggests potentially increased activity with the prolonged infusion [46]. A number of the gemcitabine combination regimens have been studied using prolonged infusion of gemcitabine [47–49]. Gemcitabine combined with docetaxel is shown to have activity in bone sarcoma and STS, with higher response rate and survival noted in treatment of leiomyosarcoma [50, 51]. In a randomized study, gemcitabine-docetaxel combination was associated with better response rate, PFS, and OS, than single-agent gemcitabine, but significantly more patients in the gemcitabine-docetaxel arm stopped due to toxicity [48]. In first-line treatment of metastatic STS, doxorubicin and gemcitabine-docetaxel were associated with similar PFS and OS, with no statistically significant difference even among leiomyosarcoma patients [20]. Another

study supports the combination of dacarbazine with gemcitabine [52], with 49% of patients with advanced STS attaining response or stable disease. Clinical benefit was noted in 25% of advanced STS patients treated with gemcitabine-vinorelbine combination, with acceptable toxicity [49].

Trabectedin, a DNA minor groove binding agent, has activity in pretreated, progressing, advanced STS, with 24–29% of patients remaining progression-free at 6 months [53, 54]. Neutropenia and transaminase elevations are among the more common adverse effects. Trabectedin was approved in the United States in 2015 for treatment of advanced leiomyosarcoma and liposarcoma previously treated with anthracycline-based chemotherapy, based on significant improvement in PFS compared to dacarbazine [55]. Myxoid-round cell liposarcoma, characterized by balanced chromosomal translocations t(12;16) and t(12;22), is particularly responsive to trabectedin, with a 51% response rate and 14-month median PFS, as noted in one analysis [56]. Trabectedin has been shown to improve PFS in translocation-related sarcomas, compared to best supportive care [57]. Doxorubicin-trabectedin combination in first-line treatment of advanced leiomyosarcoma produced response rates of 59.6% in uterine leiomyosarcoma and 39.4% in soft tissue leiomyosarcoma. Toxicity was considerable, including 24% febrile neutropenia and 39% grade 3–4 ALT (alanine transaminase) elevations [58].

Eribulin was compared to dacarbazine as treatment for patients with pretreated liposarcoma and leiomyosarcoma, in a randomized, phase III study. Eribulin was associated with better, longer OS, 13.5 months versus 11.5 months [59]. On subgroup analysis, the significant benefit was seen in the liposarcoma subgroup; OS was significantly improved in the eribulin arm of the study, 15.6 months, compared to 8.4 months in the dacarbazine arm [60]. On this basis, eribulin was FDA approved for advanced liposarcoma, previously treated with anthracycline-based chemotherapy, in 2016.

Taxane chemotherapy agents, paclitaxel and docetaxel, have not been shown to have significant single-agent utility in the treatment of sarcoma, except for angiosarcoma. Paclitaxel has single-agent activity [61–63]. Addition of bevacizumab to paclitaxel did not improve efficacy compared to single-agent paclitaxel but did increase toxicity [64]. Docetaxel has been less studied, but it also has activity against cutaneous angiosarcoma, in particular [65]. Gemcitabine, docetaxel, and bevacizumab demonstrated activity against angiosarcoma in a single-arm phase II study [66].

4.1.2 Targeted Therapies and Emerging Systemic Treatments

Pazopanib is an oral, tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR), which had encouraging 12-week progression-free rates in several strata of advanced STS subtypes, excluding liposarcomas, which did not meet the study's endpoint [67]. This was the basis for the phase III PALETTE study, which compared pazopanib to placebo in patients with advanced, non-adipocytic STS [68].

Median PFS was 4.6 months for pazopanib-treated patients, compared to 1.6 months with placebo; this led to FDA approval for non-adipocytic advanced STS in 2012. Pazopanib also has activity against alveolar soft part sarcoma [69].

Sunitinib is a multi-kinase inhibitor against VEGF receptors, PDGFR, KIT, FLT3, RET, and CSF-1. It has limited activity when tested against sarcoma in general [70, 71]. Antitumor activity has been demonstrated in several subtypes of sarcoma, including difficult-to-treat histologies such as solitary fibrous tumors [72], alveolar soft part sarcoma [73], and extraskeletal myxoid chondrosarcoma [74]. Sunitinib is commercially available in the United States and is FDA approved for gastrointestinal stromal tumors (GIST) but not approved for other sarcoma treatments.

Regorafenib is another multi-kinase inhibitor of VEGFR and other receptor tyrosine kinases, approved for treatment of GIST, but not other types of STS. Like pazopanib, it has demonstrated activity against non-liposarcoma STS. Regorafenib improved PFS in leiomyosarcoma, synovial sarcoma, and other sarcomas versus placebo [75]. It also improved PFS in patients with pretreated, progressing advanced osteosarcoma [76, 77].

NTRK inhibitor larotrectinib was approved by the FDA in 2018 for patients with TRK fusion-positive advanced cancer, regardless of tumor type, based on a series of trials with 55 patients who showed an overall response rate of 75%, and good tolerability. Additionally, 86% of patients continued on treatment or underwent curative intent resection at median follow-up of 9.4 months [78]. This analysis included 7 patients with infantile fibrosarcoma, 3 patients with GIST, and 11 patients with other STS.

Amplification of the CDK4 gene is seen in over 90% of well-differentiated/dedifferentiated liposarcoma (WD/DDLPS). Inhibitors of CDK4/CDK6 have been studied as targeted therapeutic options. Palbociclib treatment resulted in a 12-week PFS rate of 57%, meeting the primary endpoint. Median PFS was approximately 18 weeks [79]. Abemaciclib was studied in 30 patients with progressing DDLPS, resulting in 12-week PFS in 76% of subjects and a median PFS of 30.4 weeks. One patient had a partial response and three others had a greater than 10% decrease in tumor size [80].

Loss of INI1 expression is a characteristic of epithelioid sarcoma and is found in several other tumor types, including malignant peripheral nerve sheath tumors, malignant rhabdoid tumors, and others. Loss of INI1 epigenetic regulation allows EZH2 to drive oncogenesis. Tazemetostat, an inhibitor of EZH2, has been studied in INI1-negative tumors. In patients with advanced, INI1-negative epithelioid sarcoma, treatment with tazemetostat resulted in an objective response in 15% of patients and a disease control rate, defined as response or stable disease lasting at least 32 weeks, of 26% [81].

Immune therapy approaches, led by immune checkpoint inhibitors, have had a significant impact on cancer treatment in general, and there is evidence that some sarcoma patients may also benefit from these approaches. At this point, inhibitors of PD1 have been most successful. Pembrolizumab single-agent treatment of patients with advanced STS resulted in an 18% objective response rate, including four of ten

patients with undifferentiated pleomorphic sarcoma and two of ten patients with dedifferentiated liposarcoma [82]. In another study of patients with advanced STS, single-agent nivolumab produced a disappointing response rate of 5%, while the combination of nivolumab and ipilimumab had a response rate of 16% [83]. Checkpoint inhibitor therapy has not been highly successful in all types of sarcoma. Undifferentiated pleomorphic sarcoma, which is characterized by a relatively high mutational burden, generates more immune response than synovial sarcoma, which is driven by a translocation, or liposarcoma [84]. Reliable biomarkers have not been established for prediction of response. Combination therapy studies have been initiated, with chemotherapy agents, novel agents, and other modalities, aiming to broaden the applicability of checkpoint inhibitor therapy. Pembrolizumab was studied with axitinib, a VEGF receptor tyrosine kinase inhibitor, in a phase II study. The response rate among evaluable patients was 25%, with a six-month PFS of 46.9%. Eleven of the patients evaluated had alveolar soft part sarcoma (ASPS), and six of these patients achieved partial response (ORR 54.5%) [85]. Early results from trials combining doxorubicin with pembrolizumab [86], and trabectedin with nivolumab and ipilimumab [87], suggest antitumor activity without significant additive toxicity. This is a rapidly evolving field, and new information about efficacy and predictive biomarkers is anticipated.

Cellular immune therapy is being evaluated in sarcoma. NY-ESO is a cancer testis antigen expressed on 70–80% of synovial sarcomas and 80–90% of myxoid-round cell liposarcomas. Several studies have been undertaken to assess the activity of autologous T cells, transduced with retrovirus to express T cell receptors with affinity for NY-ESO, in patients with advanced NY-ESO-positive synovial sarcoma. Objective responses were documented in 50% [88] and 61% [89] of these patients.

Other immune therapy approaches, such as vaccines and intra-tumor immune agonists, are under study as well.

4.2 Metastasectomy of Sarcoma Oligometastases

Long-term results of lung metastasectomy from the International Registry of Lung Metastases on 5206 cases treated with surgery alone have demonstrated that complete resection of pulmonary oligometastasis is a safe and potentially curable procedure with very low morbidity and mortality (Table 4.2). The procedure of removing all detectable cancer metastases may provide a long-term survival in selected cases including sarcoma [90]. The overall operative mortality rate was 1.0% and ranged from 2.4% after incomplete resections to 0.8% after complete metastasectomy. In this select group of patients, mortality increased with the resection volume: 0.6% for sublobar resections, 1.2% for lobectomies and bilobectomies, and 3.6% (four cases only) for pneumonectomies. Single metastases accounted for 46%, 2–3 metastases (26%), and 4+ metastases (26%). A subset analysis of 1917 patients with pulmonary sarcoma oligometastasis showed that a high relapse (64%) was observed at a median time of 8 months. The actuarial survival rates of sarcoma patients who had complete resections were 31% at 5 years and 26% at 10 years (median 29 months).

A multivariate analysis of the entire cohort suggested that disease-free interval (DFI) (≥36 months vs. <36 months), number of metastases (1 vs. >2–3, vs. 4+), and tumor type were significantly prognostic variables. The European Organisation for Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group ($n = 255$) demonstrated that complete excision of lung metastases from STS is well accepted and should be considered as a first line of treatment if complete resection of all metastases is deemed feasible [91]. The three- and five-year disease-free post-metastasectomy survival rates were 42% and 35%, respectively. Good prognostic factors include complete resection, age under 40, and grade 1–2 sarcomas.

In addition to the above multicenter study reports, several single institutional experiences about metastasectomy of pulmonary oligometastasis were published. In a large retrospective study from the Memorial Sloan Kettering, it was demonstrated that patients ($n = 3149$) treated with complete resection of all lung metastases had improved outcomes compared to those who did not undergo surgery, with a median survival of 33 months compared to 11 months [1]. Casiraghi et al. [92] have reviewed 575 patients who underwent metastasectomy of pulmonary oligometastasis and again demonstrated complete resection and DFI (≥36 months vs. <36 months) and histology as independent prognostic factors. A subset analysis of 80 patients with pulmonary sarcoma oligometastasis showed that OS is 57% at 2 years and 39% at 5 years after complete resection. Canter et al. [17] have reviewed their single institutional experience on 138 patients who underwent pulmonary metastasectomy with a previous history of primary extremity STS between 1990 and 2005 and demonstrated that the median post-metastasis pulmonary PFS was 10 months for patients treated with perioperative chemotherapy and 11 months for patients treated with resection alone, respectively ($P = 0.63$). Multivariate Cox proportional hazards modeling and propensity score analysis revealed no association between perioperative chemotherapy and disease-specific, overall, or pulmonary PFS. Kim et al. [93] described 97 patients who underwent pulmonary resection of metastatic sarcoma between June 2002 and December 2008. Good prognostic factors included complete resection, DFI (≥12 months), number of metastases (1 vs. >2–3 vs. 4+), and completeness of resection. The overall median PFS was 10.9 months. In patients who had undergone a reoperation, the median PFS was 12.9 months compared with 9.1 months for patients who were operated once ($p < 0.028$). The sole good prognostic factor of OS consisted of smaller tumor size (≤3 cm vs. >3 cm). Sarcoma subtypes, histology grade, and the use of perioperative chemotherapy were found to have no effect on survival. Weiser et al. [94] (later updated by Chugdar) reviewed their institutional experience on 141 patients who underwent a second pulmonary metastasectomy. The median OS was 32 months. Longer DFI (>12 months) following the initial metastasectomy, absence of preoperative chemotherapy, and ability to achieve complete resection were associated with better prognosis. Morbidity and mortality rates were similar between patients who underwent one operation and patients who underwent at least one operation.

In summary, although no prospective, randomized trials have evaluated the efficacy of surgical resection of pulmonary metastases from STS, multiple large retrospective studies support the use of metastasectomy including repeated excision in

selected patients with oligometastasis sparing as much of the lung parenchyma as possible. A five-year actuarial survival rate ranges from 15% to 40% after complete resection, and median PFS ranges from eight to ten months. Favorable prognostic factors include complete resection, longer DFI (DFI ≥12 months), number of oligometastasis (1 vs. 2–3 vs. 4+), and tumor size. Other factors, such as prior chemotherapy and tumor grade, were inconsistently associated with prognosis. Even though sarcoma oligometastasis has a poor prognosis, the selected patients' long-term survival justifies the metastasectomy. Current selection criteria for pulmonary metastasectomy generally include controlled disease at the primary site (typically resection or in combination with radiation), good performance status, and no significant comorbidities including good pulmonary function tests. As such, a cohort of patients who are not eligible (technically or medically) for metastasectomy of pulmonary STS oligometastasis might require noninvasive local treatment such as stereotactic body radiation therapy (SBRT).

4.3 Stereotactic Body Radiation Therapy (SBRT) of Oligometastases

With the advent of SBRT and the excellent local control it achieves in non-small cell lung carcinoma [95], its use has rapidly increased in the treatment of pulmonary oligometastases, including those from sarcoma (Table 4.2). Mehta et al. [96] reported a series of 16 patients with high-grade sarcoma and lung metastases treated with SBRT from 2009 to 2011. All 16 patients had prior chemotherapy, and 38% also had prior pulmonary metastasectomy. A total of 25 metastases were treated with histologies such as leiomyosarcoma (28%), synovial sarcoma (20%), and osteosarcoma (16%). Median SBRT dose was 54 Gy (36–54 Gy) in three fractions (3–4). At a median follow-up of 20 months, local control was 94%, and no patient experienced grade ≥2 pneumonitis or any esophagitis. Stragliotto et al. [97] reviewed outcomes of 46 patients with metastatic sarcoma treated with SBRT from 1994 to 2005 at the Karolinska University Hospital. The majority (61%) had STS. A total of 136 metastases were treated, of which 97 (71%) were pulmonary oligometastases. Prescribed doses ranged from 10 to 48 Gy over 1–5 fractions. At a median follow-up of 21.8 months, overall response rate (CR, PR, or SD) was 88% and 34% of the patients survived more than 3 years. No serious acute thoracic toxicity was encountered. Lastly, Dhakal et al. [98] reported outcomes from 15 patients with STS pulmonary oligometastases treated with SBRT from 1990 to 2006 at the University of Rochester. A total of 74 lesions were treated with histologies such as leiomyosarcoma (23%), malignant fibrous histiocytoma (19%), and synovial sarcoma (15%). A median of four lesions (1–16) were treated per patient with the most common dose employed being 50 Gy in five fractions. The three-year local control was 82%. Median survival was 25.2 months. No patients experienced grade ≥3 toxicity. Subsequently, other retrospective studies continued to suggest comparable clinical outcomes (OS and local control) of patients treated with SBRT versus older and current metastasectomy [99–113] (Table 4.2). Overall,

Table 4.2 A summary of studies evaluating the role of localized treatments, surgery, and radiotherapy, for metastatic sarcoma patients

							Overall survival		Local control
First author	Publication year	Patient number	Number of metastases treated	Rx period	Rx type	RT dose fraction	Median (months)	Percent estimates	Percent estimates
Van Geel[91]	1996	255	1 met: 136 2 met: 41 3 met: 28 4 met: 11 >4 met: 39		Pulm Sx			3Y: 54% 5Y: 38%	
Pastorino[90]	1997	5206 (2173 sarcomas)		1991–1995	Pulm Sx			5Y: 30–35%	
Casiraghi[92]	2011	575 (94 sarcomas)		1998–2008	Pulm Sx			1Y: 89% 2Y: 71% 5Y: 43% 10Y: 27%	
Okiror[111]	2015	66	80	2007–2014	Pulm Sx		25.5		
Giuliano[105]	2016	53		1989–2016	Pulm Sx		59.9	1Y: 83% 3Y: 52% 5Y: 28% 10Y: 13%	
Chudgar[101]	2017	539	760	1991–2014	Pulm Sx		33.2		
Gafencu[113]	2017	327	1–3 met: 283 4–9 met: 31 >9 met: 14	1997–2017	Pulm Sx				
Krishnan[106]	2018	43	1 met: 9 >1 met: 34	1998–2015	Mixed Sx		22	2Y: 46% 5Y: 18%	

							Overall survival		Local control
First author	Publication year	Patient number	Number of metastases treated	Rx period	Rx type	RT dose fraction	Median (months)	Percent estimates	Percent estimates
Chudgar[102]	2017	341	1 met: 49.6% 2 met: 14.9% 3 met: 10.6% 4 met: 4.3% 5 met: 0.7% >5 met: 14.2% UNK: 5.6%	1991–2014	Pulm Sx (repeat)		32.4		
Nevala[110]	2019	130	Of the 55 R0: 1 met: 26 2 met: 12 3 met: 7 >3 met: 10	1987–2016	Pulm Sx		22 (R0) 18 (R1/R2)		
Dhakal[98]	2012	15	74	1990–2006	SBRT lung	30–55 Gy in 1–10 fractions	25.2		3Y: 82%
Navarria[109]	2015	28	51	2008–2014	SBRT lung	30–60 Gy in 1–8 fractions		2Y: 96% 5Y: 61%	5Y: 96%
Frakulli[103]	2015	24	68	2010–2014	SBRT lung	30–60 Gy in 3–8 fractions		2Y: 66%	2Y: 86%
Baumann[99]	2016	30	39	2011–2015	SBRT lung	24–50 Gy in 4–5 fractions		1Y: 76% 2Y: 43%	1Y: 94% 2Y: 86%
Franceschini[104]	2017	200 (41 sarcomas)	304	2006–2015	SBRT lung	30–60 Gy in 1–8 fractions		1Y: 89% 2Y: 65%	1Y: 91% 2Y: 85%
Soyfer[112]	2017	22	53	2009–2013	SBRT lung	21–60 Gy in 3–4 fractions		5Y: 50%	5Y: 100%

(continued)

Table 4.2 (continued)

							Overall survival		Local control
First author	Publication year	Patient number	Number of metastases treated	Rx period	Rx type	RT dose fraction	Median (months)	Percent estimates	Percent estimates
Lindsay[107]	2018	44	117	2005–2014	SBRT lung	36–55 Gy in 5–12 fractions		2Y: 82% 5Y: 50%	5Y: 95%
Stragliotto[97]	2012	46	136	1994–2005	SBRT mixed	10–48 Gy in 1–5 fractions	26.3	2Y: 51% 3Y: 34% 5Y: 20%	
Chang[100]	2012	27	32 (10 primary)	2002–2009	SBRT mixed	16–45 Gy in 1–3 fractions	29		1Y: 78% 2Y: 77%
Loi[108]	2018	16	26	2005–2016	SBRT mixed	30–60 Gy in 1–6 fractions	69	4Y: 54%	4Y: 78%
Leeman[115]	2015	88	120	2005–2012	Spine SBRT	18–36 Gy in 1–6 fractions	18.9	1Y: 62%	1Y: 86%
Bishop[114]	2017	48	66	2002–2016	SBRT spine		17	1Y: 81% 3Y: 26%	1Y: 81% 3Y: 61%

pulmonary SBRT studies may achieve local control in 85–100% of the lesions 2–5 years after treatment. Following lung SBRT treatments, a five-year OS ranges from 50 to 65%. Patients treated using mixed SBRT techniques for multi-organ metastases achieve median survivals of 26–69 months. Finally, two studies from Leeman et al. and Bishop et al. reported that patients treated solely using spine SBRT techniques have median survival of 18.9 and 17 months, respectively [114, 115]. Among the 466 patients who reported on toxicities in which 816 lesions were treated using SBRT techniques, there were three grade 3 toxicities (colon perforation, hip contracture, and vertebral insufficiency fracture). There were no grade 4 or 5 toxicities described.

The low rates of toxicity and high control rates seen in these retrospective reviews of SBRT for sarcoma pulmonary oligometastases have been mirrored in other prospective evaluations of SBRT for oligometastases. In a multi-institutional phase I/phase II trial initiated by the University of Colorado, 38 patients with 1–3 solid tumor pulmonary metastases (63 lesions) were treated with SBRT [98]. The cumulative tumor diameter was <7 cm, and they mandated minimum pulmonary function (FEV1 > 1.0 L, DLCO > 40%). Phase I trial enrolled nine patients and escalated the dose from 48 Gy to 60 Gy in three fractions, restricting the percent of the normal lung receiving more than 15 Gy (V15) to <35%. Maximum tolerated dose was not reached, and 29 patients received 60 Gy in three fractions. At a median follow-up of 15.4 months, a 2-year local control was 96%, and median survival was 19 months. Only 7.9% of patients had grade 3 toxicity with no grade 4 or 5 toxicity. Likewise, investigators from the University of Chicago completed a phase I study of 61 patients with 1–5 metastases (113 lesions) treated with SBRT [116]. Dose was escalated from 24 Gy in three fractions to 60 Gy in three fractions. At a median follow-up of 20.9 months, median PFS was 5.1 months. The majority (41/36.3%) of lesions were treated in the lung. Toxicity was limited, with only three patients developing grade 3 toxicity and no instances of grade 4 or 5 toxicity. Correspondingly, the NRG Oncology BR001 phase I trial recruited 36 patients with 2–4 metastases from breast, prostate, or non-small cell lung cancers. SBRT doses ranged from 30 Gy in three fractions to 50 Gy in five fractions (Table 4.3). The study did not find dose-limiting toxicities. However, seven grade 3 adverse events (pneumonitis, pulmonary fibrosis, bronchial fistula, bronchial stricture, gastric ulcer, bone pain, and fracture) that were at least possibly attributable to SBRT were noted in six patients [117]. The above studies culminated in an international phase II randomized study of SBRT applied to patients with controlled primary tumors and 1–5 metastatic lesions. Ninety-nine patients were randomized in this study to either receive standard of care treatment alone (control) or standard of care plus SBRT to all metastatic lesions. Patients who were assigned to receiving SBRT had longer OS than those receiving standard of care alone (median OS 41 vs. 28 months; $p = 0.09$) [118]. Doses of SBRT ranged from 16 Gy in one fraction to 60 Gy in eight fractions, depending on the disease site. Grade ≥2 adverse events occurred in 29% of the patients treated with SBRT compared to 9% in the control arm. Similar randomized trials evaluating the role of SBRT are currently recruiting patients in multiple diseases, but not yet in sarcoma.

Table 4.3 SBRT dose and number of fractions per tumor site used in NRG Oncology oligometastases [117] and the SABR-COMET trials [165]

	NRG Oncology		SABR-COMET	
Site	Dose (Gy)	Fractions	Dose (Gy)	Fractions
Lung—peripheral	45	3	54	3
			55	5
Lung—central	50	5	60	8
Mediastinal/cervical lymph node	50	5	50	5
Liver	45	3	45–60	3–8
			Dose calculated based on normal tissue complication probability of <5%	
Spinal/paraspinal	30	3	30	3
			16–20	1
Osseous	30	3	35	5
Abdominal-pelvic metastasis (lymph node/adrenal gland)	45	3	Adrenal: 60	8
Brain (lesions)	Not included		40	5

Despite good local control and the relative safety of administering SBRT to patients with oligometastatic sarcoma, >60% of patients would subsequently develop new distant lesions, which ultimately lead to death. This suggests that microscopic systemic disease is common among these patient populations. Novel strategies to better select patients for surgery, SBRT, and systemic treatments such as monotherapies or multidisciplinary approaches are critical to improve patient outcome and care based on patient preferences.

4.4 SBRT Technique

SBRT is a radiation technique that allows delivery of a high, potentially ablative, radiation dose to tumors while minimizing the dose to the surrounding organs at risk (OAR). The Canadian Association of Radiation Oncology (CARO) defined SBRT as "the precise delivery of highly conformal and image-guided hypofractionated external beam radiotherapy, delivered in a single or few fraction(s), to an extracranial body target with doses at least biologically equivalent to a radical course when given over a conventionally fractionated (1.8–3.0 Gy/fraction) schedule" [119]. Because of its effective local control and pain relief, SBRT is increasingly used as a tool in the management of oligometastatic disease.

Multiple systems are presently available for treatment delivery of SBRT. Most commonly, treatments are delivered using a linear accelerator (LINAC) that has been modified to include on board image guidance systems. With this system, treatment couches allowing six degrees of freedom (6-DOF) are used to insure precision. *CyberKnife*, a robotic, non-isocentric X-band dedicated radiosurgery linear accelerator system has also been used. In all treatments, motion management and image guidance are an essential part of the radiosurgery treatment.

4.4.1 Spine SBRT

4.4.1.1 Image Guidance

Image-guided radiation therapy (IGRT) allows imaging of the target in a three-dimensional fashion just prior to and during radiation delivery, facilitating the match of the position of the tumor to that at the time of simulation and ensuring secure and proper delivery of treatment. This system allows corrections for any intrafraction variation and maintaining of the 1–2 mm and 1°–2° accuracy aimed for. While the CyberKnife allows for near real-time intrafractional image guidance, LINAC-based treatments need particular immobilization to maintain adequate precision in treatment delivery. A number of devices are utilized to maintain proper immobilization, minimize patient movement, and avoid large shifts from planning position (>2 mm or 2°). For bony lesions involving the cervical spine up to T3, a long thermoplastic mask is used, while lesions located at the T4 level usually necessitate a near-rigid immobilization device, such as BodyFIX (Medical Intelligence), or a custom-made device. Metastases involving non-spine bony tumors will generally be planned in a similar fashion to spine metastases.

4.4.1.2 Treatment Delivery

Dose delivery differs significantly between CyberKnife and LINAC technology. Because the CyberKnife system is a non-isocentric X-band LINAC equipped with circular collimators of fixed diameters ranging from 0.5 to 6 cm mounted on a multi-jointed robotic arm, it allows movement with six degrees of freedom while ensuring maximum target coverage and minimizing OAR irradiation. The system relies on a set of 1–3 beam paths cross-firing from a large number of beam trajectories and angles. The additive effect of the individual beams results in a conformal dose distribution. Modified LINAC-based treatment using MLC (multileaf collimator) for beam shaping and intensity modulation is the most common used technology. Treatment delivery relies on the overlap of multiple beams (approximately 100–300) from a few (approximately 7–11) multiple coplanar and/or noncoplanar beam angles to achieve the desired dose distribution. The latest in MLC-based LINAC radiation delivery is VMAT (volumetric arc therapy). In this technique, the dose rate, gantry speed, and beam openings may be modified in a continuous fashion while treatment is being delivered in a single or multi arc. Because of different optimizations, LINAC-based treatments usually have a more homogeneous dose distribution than treatment delivered with CyberKnife, where intra-tumoral doses can be more significant.

4.4.1.3 Imaging and Planning

Planning for treatments necessitates CT simulation scans with slice thickness not exceeding 2.5 mm [119]. For bone metastasis, and most importantly for spine lesions, MRI images are necessary to ensure proper delineation of not only the tumor itself but also the OAR. MRI imaging of the target vertebrae and at least one or two vertebrae above and below is suggested for accurate definition of the target volumes, OAR, and paraspinal or epidural disease. Axial T1 and T2 sequences are

usually acquired, with gadolinium contrast being used to better visualize paraspinal disease and epidural disease and in the postoperative setting. In the latter treatment of spinal tumors where metal artefacts are prominent and the spinal cord is difficult to visualize, a CT myelogram might be necessary to correctly visualize the cord [120]. In bony metastasis, nuclear medicine imaging such as PET scans may also help in defining target volumes.

4.4.1.4 Target Volumes

Treatment volume guidelines for spinal metastasis have been published by the International Spine Radiosurgery Consortium. In this guideline [121], gross tumor volume (GTV) is to include all gross visible tumors on CT and MRI, including epidural and paraspinal disease. The clinical target volume (CTV) includes the entire vertebral body with extension to the posterior and lateral elements depending on the location of the GTV within the vertebral body. Generally, if the ipsilateral pedicle or lamina and transverse process are included in the GTV, the CTV is extended to include the ipsilateral posterior elements. In a similar fashion, if bilateral involvement of the pedicle, lamina, or transverse process is seen, then bilateral posterior elements are to be included in the CTV. Inclusion of the spinous process is usually limited to the presence of tumor involving such segment or if the laminas are included. As the location of epidural disease can be predictive of local failure [122], when epidural disease is present, a 5 mm anatomic margin is usually necessary within the cranio-caudal direction, and a "donut" circumferential CTV is necessary. In the event of paraspinal disease, a CTV margin of 5 mm is usually added beyond the GTV. Treatment volume delineation in the postoperative setting has been recently proposed [123]. The GTV has been defined as any residual postoperative disease visualized on CT and MRI. CTV should include GTV and account for any infiltration present in the preoperative setting. Any residual paraspinal or epidural disease should be taken into account. However, the surgical material and incision do not have to be included in its entirety but rather should be according to the preoperative tumor location. A margin of 1–3 mm is usually added to the CTV to generate the PTV in spine SBRT. In a similar fashion, a planning organ at risk volume (PRV) is added to a number of OAR, of which the spinal cord is of utmost importance [124].

Delineation of target volumes for non-spine bone metastasis is not as well defined. Many definitions are used in research protocols and in published data (NCT02364557¸ NCT03721341, NCT02685397, NCT03831243), but no guidelines as of yet have defined treatment volumes. What is common to most available literature is the inclusion of the visible tumor, which constitutes the GTV, on diagnostic imaging (MRI scan, PET scan) with a 5–10 mm anatomic expansion to generate the CTV. PTV is usually generated by adding a 3–5 mm margin to the CTV.

4.4.1.5 Patient Selection

Good candidates for SBRT of spinal and bony metastasis are generally patients with oligometastatic or oligoprogressive disease, previously irradiated, or of

radioresistant histology [119, 125]. They have spinal metastasis in three or less contiguous vertebrae. Patients with significant epidural disease, with unstable metastasis, or with a somber prognosis are usually not good candidates for this treatment. For spine metastasis, determining epidural disease and lesion stability is of outmost importance.

Epidural disease extension can be graded using the Bilsky score [126]. A Bilsky grade 0 implies the absence of epidural extension with disease being confined to the vertebral body. Grade 1 disease describes the presence of epidural disease that is abutting the cord but not compressing it, while grade 2 Bilsky score refers to the compression of the spinal cord with visible cerebrospinal fluid (CSF). A lesion with complete cord compression and no visible CSF is defined as a score of Bilsky 3. Although a contraindication to SBRT treatment, patients with complete cord compression could be considered for decompression surgery followed by postoperative SBRT [127]. Data has shown that downgrading a Bilsky grade 2 epidural disease to a grade 0 or even grade 1 increases the local control of tumors, with most failures happening at the epidural level [128, 129]. To maximize dose coverage, a minimal distance of 2 mm should be obtained between epidural disease and the spinal cord [128].

Mechanical instability is scored using the spinal instability neoplastic score (SINS) [130]. It categorizes lesions by taking into account the location of the tumors (junctional vs. non-junctional lesions), posterior element involvement (nonexistent, unilateral, bilateral), presence or absence of vertebral body collapse, lytic or blastic metastases, and vertebral alignment. Lesions being defined as potentially unstable (7–12 points) or unstable (13–18 points) should be evaluated by a surgeon to consider stabilization prior to treatment.

4.4.1.6 Treatment Dose

Currently, there is no consensus concerning the dose to be administered to patients in the treatment of spinal and non-spinal bone metastasis. Mainly retrospective data has shown good local control in patients treated with a high-dose treatment in a single fraction as well as with patients treated in multiple fractions, with a hypofractionated dose treatment [131–135]. However, mainly because of possible increase in the rate of fracture posttreatment of spinal metastasis treated with one fraction radiosurgery, some centers prefer treatment with multiple fractions [136, 137]. No randomized prospective data is available comparing outcomes from single versus multiple fraction spine SBRT treatments.

Thus, possible treatment fractionations include 18–24 Gy in a single fraction, 24 Gy in two fractions, 24–30 Gy in three fractions, and 25–40 Gy in five fractions. Data [128, 138] has alluded that a higher dose per fraction may be a predictive factor of local control when compared to patients received a lower dose per fraction regimen (Fig. 4.1). In the clinical practice, however, dose fractionation will take into account the proximity of the target volume to OAR, the total volume of treatment, and the presence of previous radiation dose.

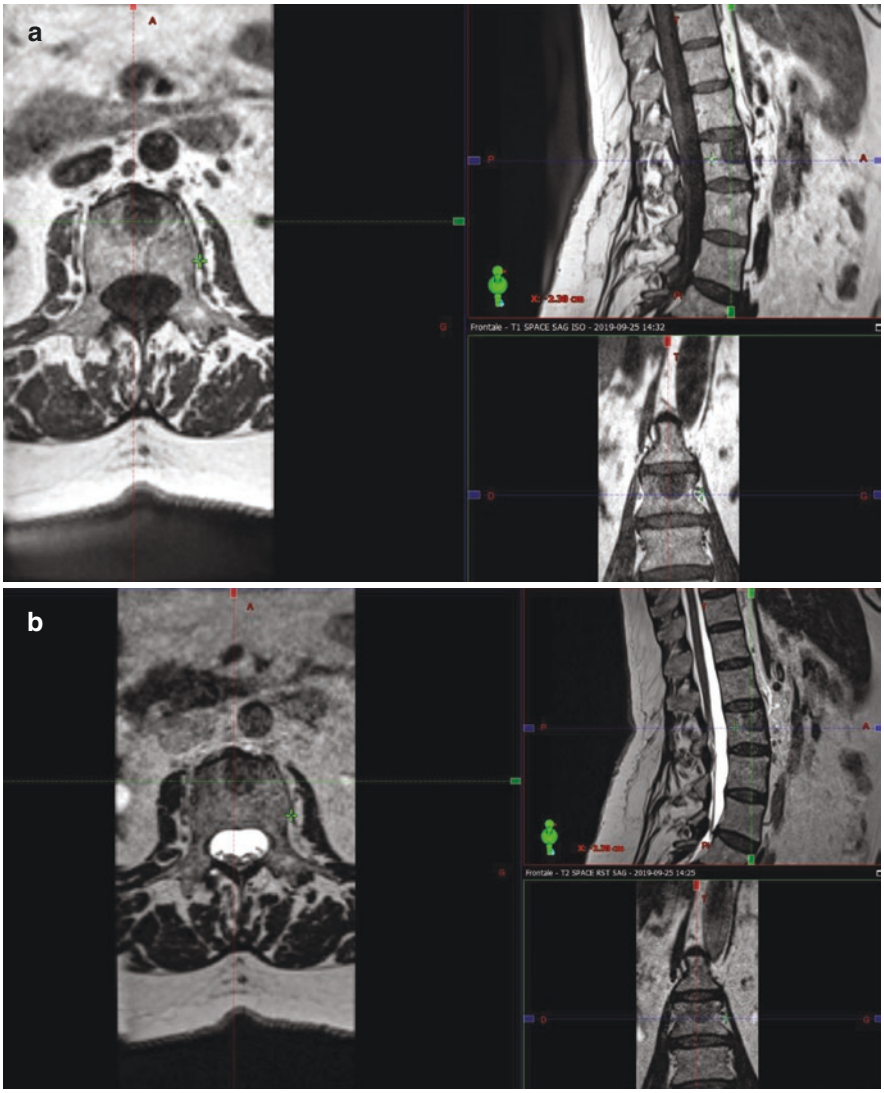

Fig. 4.1 A 52-year-old patient, diagnosed with a sarcoma at the femoral region 7 years ago, presented with back pain in the upper thoracic level. A bone scan revealed a single metastatic disease at the L2 level with degenerative changes. A biopsy of the lesion localized in the anterior body of the vertebrae confirmed the presence of a metastatic disease. Lesion is visible in the anterior part of the vertebral body in T1 and T2 acquired images (**a**) and (**b**), respectively. Target treatment volumes delineated on CT scan (**c**) and MRI (**d**) images with CTV in orange, PTV in green, and the spinal canal in light green. In accordance with the previously stated guidelines, the clinical target volume (CTV) included the whole vertebrae. A 2 mm margin was added to generate the planning target volume (PTV). A dose of 24 Gy in two fractions was administered using a SBRT spine technique. The maximum dose to the spinal canal was limited to 17 Gy in fractions (**e**)

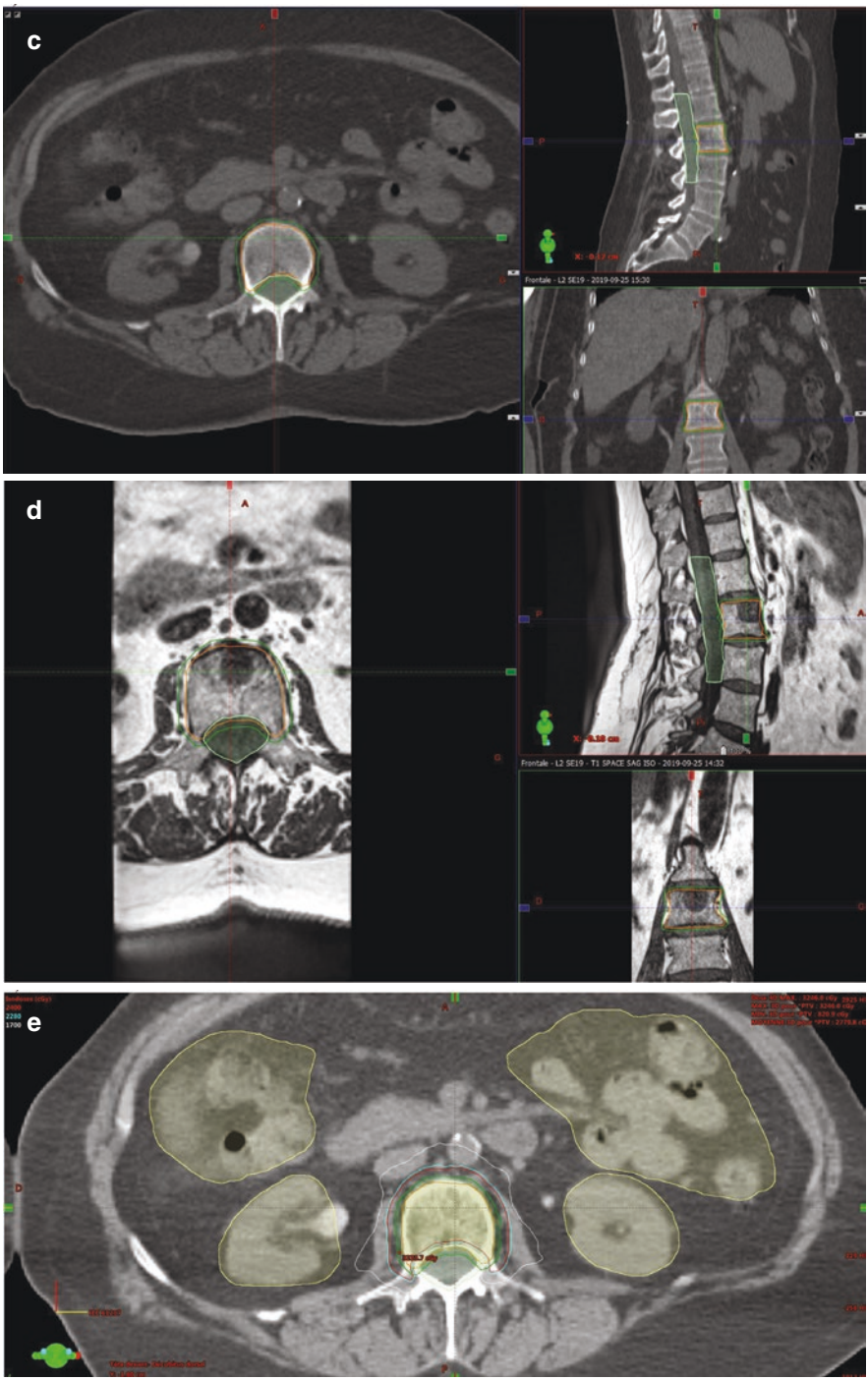

Fig. 4.1 (continued)

4.4.2 Lung SBRT

The use of stereotactic body radiotherapy (SABR) is an effective treatment option in small pulmonary lesions in patients with oligometastatic disease, achieving local control of 90% [107, 112, 139–141]. Although lung SABR is typically recommended for lesions typically ≤5 cm, treatment of selected lesions beyond 5 cm can achieve acceptable local control but at the cost of higher toxicity [142]. Treatment can be delivered using several possible technologies, including conventional linear accelerator, arc therapy accelerator, and robotic linear accelerator (CyberKnife). While each technology may have specific advantages in particular situations, a previous meta-analysis has suggested similar cancer control outcomes across platforms [143].

4.4.2.1 Simulation

Patients planned for lung SABR are typically positioned supine in a comfortable and reproducible position, to minimize movement. Several immobilization systems may be used, including vacuum systems, thermoplastic shells, stereotactic body lock frame, cradle systems, or any other customized approach to achieve near-rigid immobilization [144]. Additionally, compression or breath-hold devices (see Sect. 2. Motion Management) may be added. A free breathing planning CT using a slice thickness ≤2 mm is desirable [145]; the use of intravenous contrast should be considered for optimal delineation of central tumors. An end-exhalation breath-hold CT is obtained in patients treated with robotic tracking [146]. In addition, a planning four-dimensional computed tomography (4DCT) is required to assess the specific motion of each patient's tumor in all three coordinate axes [147].

4.4.2.2 Motion Management

Individualized selection of respiratory motion management strategy is critical for optimal dose delivery in lung SABR. Selection of optimal strategy is based on multiple factors, including tumor and organ at risk location, breathing excursion, patients' tolerability, and technologies available at each institution [148]. As a general rule, when respiratory tumor excursion is ≤1 cm, standard strategy involves the use of an internal target volume (ITV), generated from the 4DCT (using selected respiratory phases of the 4DCT, the average CT, and/or the maximal intensity projection CT) [149]. The purpose of this strategy is to ensure that the tumor remains within the target volume during the entire breathing cycle. Tumors presenting respiratory excursion >1 cm (frequently located in the lower lung lobes) should be considered for additional motion management strategies, including abdominal compression, breath hold, and respiratory gating or tracking [150]:

- *Abdominal compression* consists in the application of a constant upper abdominal pressure using a compression belt device or a stereotactic frame. This method has been shown to effectively minimize tumor excursion during breath-

ing by several millimeters and therefore can result in significantly reducing the ITV [140, 151]. Patients considered for this method should have good lung function for tolerance of the device at simulation and during treatment delivery. A drawback of this method is the patients' discomfort caused by the pressure, which may induce involuntary motion and reduce reproducibility that could offset the benefit of the breathing reduction in poorly selected patients [152].

- *Breath-hold technique and respiratory gating: Breath-hold technique* consists in planning and delivering treatment on a particular phase of 4DCT, frequently in mid- or end-expiration (which has the advantage of being more reproducible) or in deep inspiration (which has the advantage of decreasing lung dose) [150]. This method involves active patient participation, including the use of spirometry to measure respiratory levels and patient coaching; the *active breathing control* system is one of such systems allowing for visual feedback to the patients. In addition to good respiratory function, this approach also requires optimal patient cooperation. *Respiratory gating* consists in delivering radiation during only over a portion of the respiratory cycle, with a typically optimal gating window of 40% [153]. In opposition to breath hold, patients undergoing respiratory gating breathe freely, while the beam is periodically on during the predetermined respiratory window. Both breath-hold and respiratory gating are associated with reduction of the ITV but at the cost of significant prolongation of treatment delivery time [154].
- *Tumor tracking:* When a robotic linear accelerator is available, tracking technique is another method to account for motion, using either fiducial markers or direct soft tissue tracking (Xsight Lung) [155]. Tracking can be achieved using fiducial markers (typically three) as surrogates. These markers can be placed under transthoracic CT guidance, endobronchial, or endovascular techniques, at least 7 days before simulation to ensure the stability of their position. Risk of pneumothorax, tumor position, and low pulmonary function tests can preclude the feasibility of fiducial marker placement. Xsight Lung technique can be used for large and dense tumors that can be visualized in the in-room orthogonal X-rays [156].

4.4.2.3 Image Guidance

The use of high-dose per fraction requires strict image guidance before each fraction. For both conventional- and arc-based linear accelerator techniques, volumetric imaging (such as cone beam CT) should be acquired before each SABR fraction [157]. Manual soft tissue registration (through translation and rotation) should be applied, and impact on constraints to critical organs at risk should be assessed [158]. In the context of robotic tracking, bilateral orthogonal X-rays obtained at 45° on each side of the patient, taken at regular intervals during treatment, are used to track in near real time either fiducial markers or the tumor directly, if visible (Xsight Lung) [156]. The fiducials and tumor are tracked by correlation of these X-ray images with the set of digitally reconstructed radiographs extrapolated from the planning CT scan [156].

4.4.2.4 Target Volumes

The gross tumor volume (GTV) is generally drawn using CT lung window width and level, but mediastinal windows can also be used usefully when delineating central tumors or lesions in proximity to the chest wall or atelectasis [159]. An ITV (sometimes also called IGTV) should be created by combining visible tumor on all phases of the 4DCT. No additional margin for CTV is recommended. The PTV is typically generated with a 3–5 mm uniform expansion from the ITV [159].

In the case where a robotic *tumor tracking* technique is used, the GTV is drawn on the end-expiration breath-hold CT images. The 4DCT can be used in order to correct for tumor rotation and deformation during the respiratory cycle, since only translational motion is taken into account during tracking. The PTV is typically generated with a 3–5 mm uniform expansion from the ITV [159]. The PTV is then generated with a 3–5 mm uniform expansion from the GTV.

4.4.2.5 Dose

The optimal radiation dose and fractionation for the treatment of lung metastasis remain unclear. Unless delivered in the context of concurrent systemic therapy, most reports of metastatic lung SBRT have used similar dose/fractionation regimen to those used in primary lung SABR, but the use of more practical single fraction approach is currently being investigated for pulmonary oligometastases [160]. Optimal local control is thought to be achieved with biologically effective doses (BED10) beyond 100 Gy to the PTV [161–163]. The most frequently used dose/fraction regimen in peripheral lesion is 54 Gy in three fractions on alternate days [159], but several equivalent regimens have been reported. Central lesions (i.e., lesions within 2 cm of the proximal bronchial tree) are at higher risk of severe toxicity given the proximity to critical organs at risk and should be treated with more protracted dose regimen (50–60 Gy in five fractions or 60 Gy in eight fractions are frequently used). The safety of SABR for the treatment of ultra-central tumors (i.e., when the target volume touches critical structures such as the tracheobronchial tree or esophagus) is currently being investigated [164].

4.5 Concluding Remarks

The oligometastatic state of STS was one of the first cancer histologies in which the use of aggressive local treatment was included in standard patient management following careful selection of patients. An increasing number of radiation centers are prepared to treat patients using various SBRT techniques. As prospective trials involving oligometastases are completed, the safety and indications of SBRT will likely improve and expand. Despite metastasectomies and SBRT providing high local control, many patients soon develop distant recurrences. Whereas there is accumulating phase II evidence hinting at a benefit of SBRT in oligometastatic patients, this needs to be properly validated via ongoing phase III trials. With accumulating data, better prognostication may guide physicians and patients in making better treatment decision between localized therapies versus systemic treatments or a combination of both.

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Radiotherapy for Pediatric Sarcomas

5

Molly Blau, Stephanie K. Schaub, and Ralph P. Ermoian

Contents

5.1 Introduction

The incidence of pediatric cancer is low compared to adult cancer. Each year, there are about 14,000 children (age 15 or less) in the United States who are diagnosed with tumors, compared to about 1.6 million adults [1].

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Whereas the most common adult tumors are breast cancer, prostate cancer, and lung cancer, the most common pediatric cancers are leukemias, lymphomas, and central nervous system (CNS) neoplasms. While sarcomas and bone tumors are not among the top ten adult cancers, they represent about one out of eight pediatric tumors [2]. The most common pediatric bone and soft tissue sarcomas are osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, and non-rhabdomyosarcoma (NRSTS, which includes a variety of histologies). By their nature, these tumors can arise out of bones and soft tissues throughout the body, and their presentations are varied.

Fortunately, the prognosis for patients with these sarcomas has improved over decades. For patients with rhabdomyosarcoma, the four-year event-free survival (EFS) of low-risk patients is nearly 90%. For patients with high-risk disease with metastases, there are long-term survivors with the EFS between 15% and 35%, depending on histologic subtype [3]. In Ewing sarcoma, patients with localized disease have about a two-thirds chance of cure, while in patients with isolated lung metastases, the EFS is about 30%, and those with more widespread disease have less than 15% chance of cure [4]. In osteosarcoma, the three-year disease-free survival (DFS) for patients with localized resectable disease is 60–70%. For patients with metastatic disease, the two-year overall survival (OS) is 10–20% [5].

Mindful of concerns about late effects and the improvements in systemic therapy, the use of radiation in treating pediatric malignancies has decreased over decades [6]. Nonetheless, radiotherapy remains a critical component of curative multimodality care for Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma, and occasionally osteosarcoma. With modern radiotherapy techniques, patients are increasingly cured with fewer late effects. Radiotherapy also can be a helpful component of palliative care for patients who will not be cured.

5.2 Management Principles

The management of pediatric malignancies is fundamentally a multidisciplinary effort. Typically the medical oncologist is the primary oncology provider but works in partnership with not just surgeons and radiation oncologists but also child life specialists, social workers, nurses, anesthesiologists, and many other providers.

5.2.1 Workup for Pediatric Sarcomas

The workup of all patients with bone and soft tissue sarcoma includes characterizing the primary site of disease and assessing for metastases. In each of these diseases, the most common sites of metastases include the lungs and bones. The primary site is assessed using a combination of radiographs, computed tomography (CT) imaging, and magnetic resonance imaging (MRI). Then, a biopsy is obtained, optimally performed by a surgical oncologist and/or interventional radiologist with insight into the eventual planned surgical resection to include the biopsy tract and to minimize the risk of tumor contamination of uninvolved anatomic compartments.

The staging is completed with a CT chest and bone scintigraphy and/or positron emission tomography-CT (PET-CT). In Ewing sarcoma and rhabdomyosarcoma, most patients will also undergo a bone marrow biopsy. In patients with parameningeal disease or other diseases abutting the CNS, MRI of the brain and spine with lumbar puncture is indicated to assess for local extension of the CNS and metastases. The workup will also include laboratory and other studies to assess the patient's fitness for chemotherapy.

5.2.2 Staging for Pediatric Sarcomas

Patients with Ewing sarcoma are most commonly staged as simply having localized or metastatic disease. Sometimes the American Joint Commission on Cancer (AJCC) bone tumor staging system is used and is shown in Table 5.1. Extraosseous Ewing (EOE) tumors are staged differently. They are staged like soft tissue sarcomas. Information about soft tissue sarcoma staging can be found in Sarcoma—Adult Soft Tissue Cancer—as described in non-rhabdomyosarcoma below [7].

The staging for rhabdomyosarcoma is complicated. It involves the stage, the group, and the risk categorization which comes from the International Rhabdomyosarcoma Studies and is shown in Table 5.2. The *stage* is dependent largely on the site but also includes the size and nodal involvement and whether there are metastases (Table 5.2A). If the site is favorable (i.e., orbit, head, and neck (non-parameningeal), GU (non-bladder/prostate), biliary tract) and non-metastatic, then all are simply considered Stage I. Whereas, if the site is unfavorable, to be considered Stage II, the size must be ≤5 cm and N0. The *group* depends on the extent of residual disease involvement at the time of starting chemotherapy (after initial biopsy or resection). For example, a patient with upfront unresectable disease, who then undergoes a gross total resection (GTR) after induction chemotherapy, is still considered

Table 5.1 American Joint Committee on Cancer bone tumor staging system

Stage	Tumor	Nodes	Metastases	Grade
IA	T1	N0	M0	G1 or Gx
IB	T2	N0	M0	G1 or Gx
IIA	T1	N0	M0	G2 or G3
IIB	T2	N0	M0	G2 or G3
III	T3	N0	M0	G2 or G3
IVA	Any T	N0	M1a	Any G
IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

T: TX, primary tumor cannot be assessed; T0, no evidence of primary tumor; T1, ≤8 cm; T2, >8 cm; T3, discontinuous tumors at primary site

N: NX, nodes and lymph nodes cannot be assessed; N0, no regional lymph node metastases; N1, regional lymph nodes involved

M: M0, no distant metastases; M1a, lung metastases; M1b, bone or other distant sites

G: GX, grade cannot be assessed; G1, well differentiated, low grade; G2, moderately differentiated, high grade; G3, poorly differentiated, high grade

Table 5.2 Rhabdomyosarcoma staging

A

Stage	Site	Size	Nodes	Metastases
1	Favorable sites: Orbit/eyelid, head and neck (excluding parameningeal), non-bladder/ non-prostate GU	Any	Any	No
2	Unfavorable sites: Bladder/prostate, extremity, parameningeal, other (trunk, retroperitoneal, etc.)	<5 cm	N0	No
3	Unfavorable sites: Bladder/prostate, extremity, parameningeal, others (trunk, retroperitoneal, etc.)	<5 cm ≥5 cm	N1 Any	No
4	Any distant metastases	Any	Any	Yes

B

Group	Description
I	Localized disease, completely resected
II	(a) Gross totally resected with microscopic margins (b) Gross totally resected with lymph node involvement (even if gross nodes resected) (c) Gross totally resected with microscopic margins and lymph node involvement
III	Incomplete resection of gross disease
IV	Metastatic disease

C

Risk group	Stage	Group	Histology	% of cases	Long-term EFS%
Low, subset 1	1	I–II	ERMS	27	85–95
	1	III (orbit)	ERMS		
	2	I–II	ERMS		
Low, subset 2	1	III (non-orbit)	ERMS	5	70–85
	3	I–II	ERMS		
Intermediate	2–3	III	ERMS	27	73
	1–3	I–III	ARMS	25	65
High	4	IV	ERMS	8	35
	4	IV	ARMS	8	15

Abbreviations: ERMS Embryonal rhabdomyosarcoma, *ARMS* Alveolar rhabdomyosarcoma

Group III (Table 5.2B) because the patient started chemotherapy with gross disease. The *group* is critically important for the radiation oncologist because it drives the indications and dosing for radiotherapy. The *risk* classification is based on the combination of the stage and *group* to inform on prognosis (Table 5.2C) and guides recommendations for systemic therapy and the timing of therapy [3].

Patients with non-rhabdomyosarcoma tumors are staged according to the AJCC eighth edition staging system, as shown in Table 5.3 [7].

Table 5.3 AJCC eighth edition soft tissue sarcoma staging system

Stage	Tumor	Nodes	Metastases	Grade
IA	T1	N0	M0	G1 or Gx
IB	T2, T3, T4	N0	M0	G1 or Gx
II	T1	N0	M0	G2 or G3
IIIA	T2	N0	M0	G2 or G3
IIIB	T3, T4	N0	M0	G2 or G3
IV	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Grade is by FNCLCC (Fédération Nationale des Centres de Lutte Contre Le Cancer) histologic grade
T: TX, primary tumor cannot be assessed; T0, no evidence of primary tumor; T1, ≤5 cm; T2, 5–≤10 cm; T3, 10–≤15 cm; T4, 15 cm or larger in greatest dimension

Table 5.4 Musculoskeletal Tumor Society (MSTS) staging system

Stage	Tumor	Metastases	Grade
IA	T1	M0	G1
IB	T2	M0	G1
IIA	T1	M0	G2
IIB	T2	M0	G2
III	T1 or T2	M1	G1 or G2

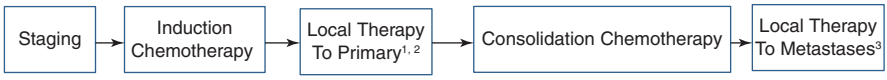
T: T1 intracompartmental; T2 includes extracompartmental

Like patients with Ewing sarcoma, osteosarcoma patients are typically staged as either with localized or metastatic disease. Sometimes the Musculoskeletal Tumor Society (MSTS) staging system is employed, shown in Table 5.4.

5.2.3 Treatment Algorithm for Pediatric Bone and Soft Tissue Sarcoma

The treatment algorithms vary by disease. However, with the exception of some non-rhabdomyosarcoma histologies, patients start with induction chemotherapy after staging (including biopsy) is complete (Fig. 5.1). The rationale for this sequencing includes the following:

- Upfront treatment of subclinical disease, because these patients have potential for developing metastatic disease.
- It can facilitate the local and regional therapy in patients who have a response to induction chemotherapy by improving the resectability of primary tumors and/or reducing the size the radiation fields, at least for the higher-dose radiation boost phase.
- Radiation fields can sometimes be extensive and necessitate treating large volumes of the bone marrow, so it delays myelosuppression that may interfere with chemotherapy.



[1]For Rhabdomyosarcoma: delayed primary excision + chemoradiation, or definitive radiation
[2]For Ewing Sarcoma, Surgery +/-adjuvant chemoradiation
[3]Typically radiation alone

Fig. 5.1 Ewing sarcoma and rhabdomyosarcoma general treatment schema

There are several critical treatment strategies and controversies for the four main types of pediatric bone and soft tissue tumors.

5.2.3.1 Ewing Sarcoma

Ewing sarcoma is considered a "small round blue cell tumor" that arises from the bone or soft tissue, associated with the classic t(11,22) EWS-FLI1 translocation (86–90%) and t(21;22) (5–10%) and is considered fairly radiosensitive [8]. The treatment schema for Ewing sarcoma is shown in Fig. 5.1. The general treatment paradigm includes induction chemotherapy of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VAC + IE) for 6 cycles, local control at week 13, and consolidative chemotherapy of VAC + IE for 11 cycles with postoperative radiation therapy (if indicated) starting with cycle 1 of consolidation (doxorubicin held during radiation), followed by metastasis local control (if indicated) as shown in Fig. 5.1.

Reasonable choices for local therapy include surgery alone, surgery followed by radiation, or radiation alone, depending on the lesion. Retrospective analyses from the Childhood Cancer Survivor Study show that the most common cause of late mortality is late disease recurrence, but the second most common cause is treatment-related conditions, including very high rates of second malignancies, cardiac conditions, and musculoskeletal problems, all of which can be caused by radiotherapy [9]. Therefore, the preferred method of local control is surgery when feasible and not excessively morbid. In general, Ewing sarcoma involving "expendable bones" such as the ribs, fibula, clavicle, distal scapula, metatarsals, metacarpals, and small iliac wing and pubic bone lesions receive surgery alone for local control.

Retrospective studies have examined the local control rates between surgery, surgery plus radiation, and radiation alone. Typically, surgery is associated with higher rates of local control compared to surgery plus radiation, highlighting the selection bias associated with analyses of these treatment modalities. In a pooled analysis of three recent international trials, the five-year cumulative incidence of local failures showed a trend toward higher local failures for radiation alone (26%) compared to surgery (13%) and surgery plus radiation (0%). The local control rates varied by disease site, with spine having the lowest local failure rates (0–5.6%, depending on local therapy modality), pelvis having the highest (3.9–22.4%, depending on modality), and extra-skeletal tumors, extremity tumors, and non-spine axial tumors in-between [10]. In a large single institution trial, all local failures in the radiation-only group occurred infield, with a trend toward a decreased incidence of local recurrence (17% vs 28%, $p = 0.61$) for those who received radiation doses ≥56 Gy. The potential benefit for dose escalation, particularly for unresected tumors >8 cm at

diagnosis, is supported by Phase 2 data demonstrating a 0% ten-year cumulative local failure rate and remains an ongoing area of investigation [11].

Implicit in this question is whether relatively small differences in local control affect OS. Data from the German Paediatric Oncology and Haematology (GPOH) trials in the 1980s and 1990s show that among all Ewing sarcoma patients, even in patients with localized disease at diagnosis, the vast majority of recurrences are distant metastases-only so long as patients received some form of local control [12]. Further, Dubois et al. showed that it is unclear whether differences in local control strategies affect OS when accounting for propensity bias [13].

An additional very rare and highly-aggressive malignant round cell soft tissue tumor seen in children is a CIC-rearranged (most commonly CIC-DUX4) soft tissue tumor that harbors morphologic features similar to Ewing sarcoma. While there is no standard therapy for this disease, consideration for treatment using an Ewing sarcoma treatment algorithm may provide more appropriate aggressive systemic and locally directed therapy until further prospective data is available [14].

Finally, there is a question of treating metastatic disease sites. Not surprisingly, there is evidence that treatment of metastatic disease with definitive doses of radiation therapy is associated with excellent local control of the treated lesions [15, 16]; it is less clear that treating metastases is associated with better survival. For patients with pulmonary-only metastatic disease at diagnosis, following consolidative chemotherapy, either whole lung irradiation (WLI) or busulfan-melphalan high-dose chemotherapy with autologous stem cell rescue without WLI has demonstrated similar OS (HR = 1.00, $p = 0.99$) with similar eight-year EFS (43.1% vs 52.9%, $p = 0.16$) based on the R2Pulm Phase 3 trial [17].

5.2.3.2 Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common pediatric soft tissue sarcoma, with a locally-invasive nature, an overall 15% risk of lymph node metastases, and is considered one of the most radiosensitive sarcoma histologies. Molecular-based classification is replacing histological classification due to the improved prognostic significance of PAX-FOXO1 fusion status (seen in approximately 80% of alveolar RMS); patients where patients with fusion-negative alveolar RMS had overall similar five-year OS compared to embryonal RMS (89% and 82%, respectively) with both showing improved OS compared to fusion-positive alveolar RMS (64% for PAX3-FOXO1) patients [18, 19].

The treatment schema for RMS is similar to that of Ewing sarcoma and is also shown in Fig. 5.1. For RMS, the backbone chemotherapy regimen is VAC-based chemotherapy (vincristine, dactinomycin, cyclophosphamide) for three cycles (starting week 1), local control typically at week 13 (protocol-dependent), followed by further VAC-based consolidative chemotherapy. Radiation therapy is recommended for all *groups* of RMS for local and regional therapy in the postoperative or definitive setting, with the exception of Group I embryonal RMS where radiation has shown no benefit. Even among patients with Group III RMS (those with gross disease at the start of chemotherapy), radiation is associated with local control rates of greater than 80% in most disease sites [20]. While radiation fields traditionally

only encompass the known sites of disease and involved lymph nodes, their effectiveness (and the terrible outcomes associated with recurrence) has prompted some to recommend using radiation prophylactically to treat apparently high-risk but uninvolved draining lymph nodes [21, 22].

The effectiveness of radiotherapy has to be balanced with its late toxicity because of young age of most RMS patients. The most challenging patient populations are infants and toddlers. Recognizing radiation oncologists' appropriate concerns about disfiguring bone hypoplasia, decreased soft tissue development, heart disease, neurocognitive effects, and other concerns, some Children's Oncology Group trials have allowed patients under 2 to be treated at variance from protocol without citing deviations. However, when patients receive less than the standard recommended therapy, they have a marked increase in the five-year local failure rate (35% vs 16%; $p = 0.02$) and decrease in EFS (55.6% vs 77.5%; $p = 0.04$), which supports the overall important role that radiation plays for RMS [23].

Interactions between radiation and chemotherapy are important both in terms of efficacy and toxicity. After induction chemotherapy, radiotherapy is usually delivered with concurrent chemotherapy, where the chemotherapy regimen is continued without dactinomycin. The synergism between radiotherapy and chemotherapy has recently been highlighted in articles observing higher local failure rates on recent trials compared to the Intergroup RMS Study Group (IRS)-IV trial. In IRS-IV, the total cumulative cyclophosphamide dose was 26.4 G/m^2, whereas on the subsequent D9802 and ARST0331 trials, the cyclophosphamide dose was decreased to 0–4.8 G/m^2, respectively, owing to the concern about hematologic and reproductive toxicity (male-predominant), while maintaining similar radiation therapy doses. With this cyclophosphamide dose reduction, recurrence rates at low- and intermediate-risk sites including the orbit were higher than historical studies [24–26]. This highlights that the radiation oncologist must be aware of the chemotherapy agents being delivered to optimize the dose of radiotherapy to match the chemotherapy.

Historically, surgical resection was completed prior to the start of chemotherapy. However, more recent trials have started with induction chemotherapy, partly due to the role of radiotherapy for all *groups* of patients, except Group I embryonal RMS in which an upfront R0 resection can be achieved. The definitive dose of radiation (with the possible exception of the orbit) is at least 50.4 Gy for Group III patients. There is concern that patients with tumors initially greater than 5 cm should receive more radiation, perhaps as high as 59.4 Gy (as is currently being studied on COG ARST1431). This is in contrast to patients with Group II disease who should receive 36–41.4 Gy. In a growing child, the differences in these dose levels have long-term impacts. Therefore, the concept of "delayed primary excision" after induction chemotherapy to achieve at least an R1 resection has been studied and appears effective to potentially allow for radiation therapy dose reduction [27]. The concept of delayed primary excision is being further studied on COG ARST1431, where resectability is assessed at the week 9 evaluation.

The timing of radiotherapy has been largely consistent on recent Children's Oncology Group trials, at week 13 following induction chemotherapy. A controversial subset of patients are those with parameningeal tumors who are at risk of intracranial extension. Spaulding et al. showed that for those patients without neuroforamen base of skull bone remodeling, cranial neuropathies, or radiographic evidence of intracranial extension, there is not an increased risk of CNS recurrences with delaying therapy from week 4 (as was done on IRS-IV) to week 13 (as was done on COG D9803) [28]. However, there are two other analyses that suggest that all parameningeal RMS patients are at increased risk of CNS recurrence if radiotherapy does not commence near the beginning of chemotherapy [22, 29].

The same questions about treating metastases in Ewing sarcoma patients also apply to RMS patients; treating them with definitive doses reduces risk of the treated metastases recurring or progressing but may not change overall disease outcomes [15, 16]. For patients with lung metastases at the time of diagnosis, whole lung irradiation is indicated after completion of consolidative chemotherapy [30].

5.2.3.3 Non-RMS Soft Tissue Sarcoma

Non-RMS soft tissue sarcoma (NRSTS) encompasses varying other histologies, with the most common reported of synovial sarcoma (26%), malignant peripheral nerve sheath tumor (MPNST) (11%), and undifferentiated sarcomas (11%) as per the recent NRSTS ARST0332 trial [31]. Surgery remains the primary local treatment modality for this disease; radiation therapy is not thought to be an adequate substitute for resection of gross disease [32]. The role of chemotherapy depends on the tumor histology, the stage, and the presence of metastatic disease.

Radiation therapy plays multiple roles in NRSTS management including the following:

- Adjuvant treatment of resected disease with positive margins.
- Neoadjuvant treatment to improve resectability of disease. Depending on the histology, this may be done with concurrent chemotherapy.
- Adjuvant treatment of involved draining lymph nodes.
- Definitive treatment of metastases.

The Children's Oncology Group ARST0332 study provided results that help define the role of radiation therapy for NRSTS. The treatment schema for the study is in Fig. 5.2. Patients with gross totally resected nonmetastatic low-grade lesions of any size were observed regardless of whether there were microscopically positive margins, and patients with small (<5 cm maximal tumor diameter) high-grade lesions with negative margins were also observed. The only patients in this "low-risk" stratum to receive adjuvant radiation therapy (to a total dose of 55.8 Gy) were patients with small (≤5 cm) high-grade lesions resected with microscopically positive margins, with initiation of radiation within 42 days after surgery. This "low-risk" cohort did exceedingly well with five-year EFS of 89% and OS of 96% [31].

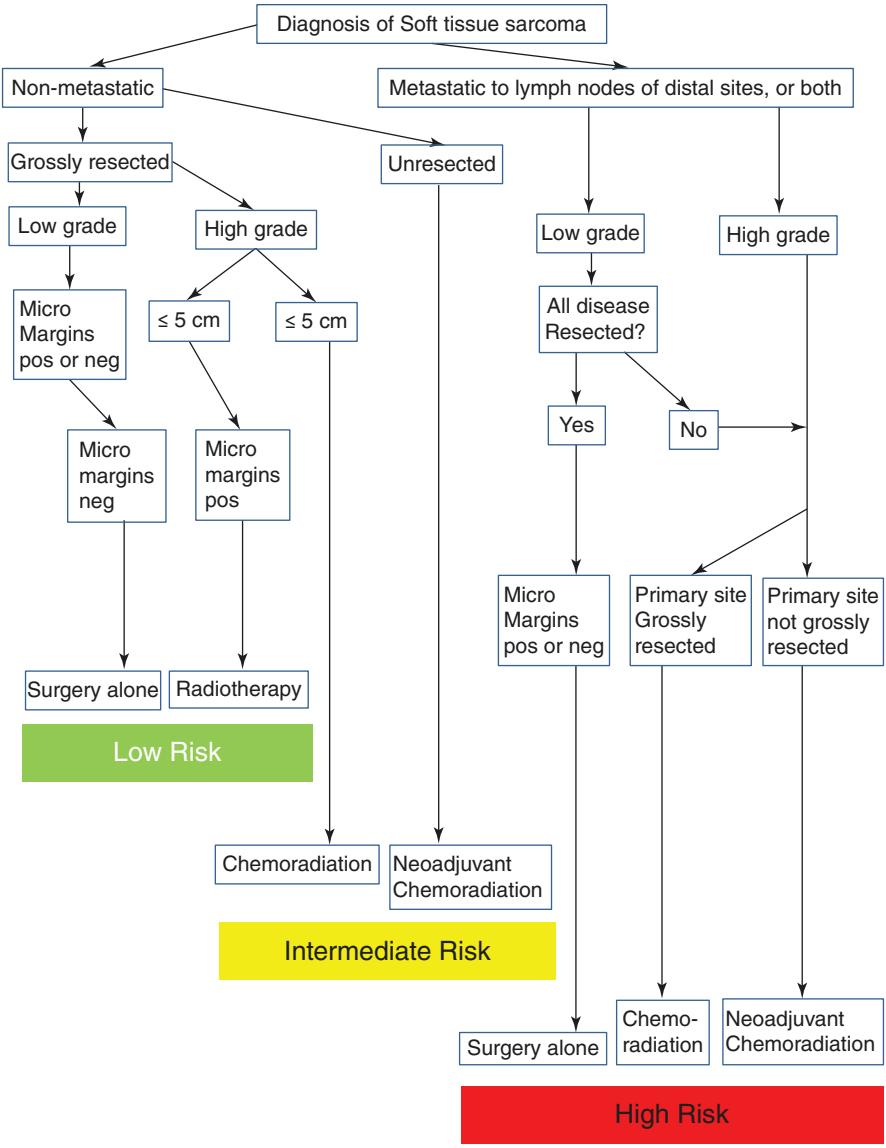


Fig. 5.2 Schema of COG ARST0332 risk-adaptive protocol for non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) patients under age 30 years

"Intermediate-risk" patients included two subgroups of patients who did not have metastatic disease. One subgroup included patients with high-grade tumors >5 cm who had microscopic margins. These patients received adjuvant chemoradiation therapy to a total dose of 55.8 Gy with a total of six cycles of ifosfamide and five cycles of doxorubicin, with initiation of RT at week 4 (holding

doxorubicin). The other subgroup was patients with unresectable gross disease or high-grade >5 cm lesions where assessment of delayed primary excision was planned, who were treated with preoperative chemoradiation to a total dose of 45 Gy at week 4 with neoadjuvant chemotherapy of ifosfamide/doxorubicin for two cycles followed by two cycles of ifosfamide alone. For patients treated with neoadjuvant chemoradiation therapy, there was an option for a postoperative boost of 10.8 and 19.8 Gy for microscopically or grossly positive margins, respectively, at week 13. The five-year EFS and OS in these patients were 65% and 79%, respectively [31].

The "high-risk" group had involved lymph nodes or metastatic disease. Similar to the "low-risk" cohort, patients with low-grade tumors who had gross total resection (with or without microscopically negative margins) of the primary site and all gross disease were observed. Patients with low-grade histology with residual disease or high-grade histology regardless of residual disease had assessment of the resection status of the primary tumor to inform if they should receive adjuvant chemoradiation therapy (if resectable) or neoadjuvant chemoradiation therapy (if unresectable), as above. The five-year EFS and OS in these "high-risk" patients were 21.2% and 35.5%, respectively, indicating that there remains a need for improved treatment algorithms [31].

COG ARST1321 examined the addition of pazopanib to preoperative chemoradiation or preoperative radiation regimens for intermediate- and high-risk NRSTS patients. This data (abstract-only) from this study showed that pazopanib increased the rate of near pathologic complete response of tumor specimens compared to controls, often thought to be an early prognostic surrogate for local control [33].

5.2.3.4 Osteosarcoma

Osteosarcoma is the most common primary bone tumor in children [34]. Although the tumors can develop in nearly any bone, nearly half of osteosarcomas arise in femurs or tibias [35].

As with Ewing sarcoma and RMS, most patients undergo induction chemotherapy (methotrexate, doxorubicin, and cisplatin; MAP), followed by local therapy and then adjuvant chemotherapy. Surgery is the preferred local therapy option for patients with osteosarcoma both because osteosarcoma is relatively less radiosensitive than other bone tumors and concerns about radiation effects [36]. Nonetheless, five-year local control rates of 75% have been reported in children receiving chemoradiation for definitive local therapy. Better OS was associated with smaller tumor size, lack of metastases at presentation, and concurrent chemotherapy [37]. The Massachusetts General Hospital has also reported treating with a preoperative dose of approximately 20 Gy in a subset of their patients [38]. Radiation can also be considered for treating patients with positive margins on the resection bed where a second surgery is not recommended [36].

5.2.4 Radiation Therapy Techniques and Planning

5.2.4.1 Preparing to Treat the Patient

The treatment algorithms for pediatric sarcoma are described above. Except in the case of some NRSTS, local therapy typically follows induction chemotherapy.

Early involvement of the radiation oncologist in formulating the treatment plan is necessary, ideally being part of multidisciplinary discussions about the approach to the patient's care before tumor-directed therapy has started. Critical opportunities to optimize care can be lost when the radiation oncologist does not learn about a patient until aftercare has started and radiation is "due."

The radiation oncologist should not only be part of tumor board discussions but also see the patient for consultation. He/she will assess and counsel what if any role radiation would play, the timing of radiation, the modality of radiation, the dose and fractionation, and the side effects and risks. Early consultation also will facilitate optimal radiotherapy in other ways, including the following:

- Cancer predisposition syndromes. Does the patient have a family history suggestive of a cancer predisposition syndrome such a Li-Fraumeni syndrome? If so, does the patient need genetic counseling? If the patient does have a cancer predisposition syndrome, should the local therapy plan be changed to avoid radiation?
- Anesthesia. Will the patient tolerate simulation and treatment without anesthesia?
- Reproductive health. With the location of the tumor, would radiation therapy be associated with risks of infertility or reproductive endocrinopathy? Should the patient undergo fertility preservation? Can some of the risks be mitigated by the bladder being full or empty during simulation/radiation? Should the ovaries or testes be transposed?
- Discussions with referring medical oncologists, surgeons, social workers, and child life experts and other progressions about other considerations such as whether active breathing control would be used during radiation and whether the patient could tolerate it.
- Consideration of unique family dynamics and situations. Which parents and guardians must sign consent? In what parts of the consultation should the patient participate? Are there particular cultural or other considerations?

5.2.4.2 Simulation

An excellent radiation plan relies on an optimal simulation for the patient. Because sarcomas can occur in nearly every part of the body, it is beyond the scope of this chapter to describe in detail each site setup. However, the general principles of simulation of pediatric patients are applicable.

Reproducibility. The patient's position should be set up with ease and patient comfort each day, with as little interfraction variability as feasible. Masks, cradles, and other devices are often helpful. Critically important in establishing this is the radiation oncologist and therapist encouraging the child to be forthright about his/

her comfort during simulation and confirming that comfort before proceeding with simulation imaging.

Minimizing intrafraction movement. Targets subject to physiologic movement require interval target volumes (ITVs) created with the use of a four-dimensional computed tomography (4DCT) scan and which necessitate more normal tissue irradiation. Active breathing control and other advanced simulation and treatment techniques can decrease the intrafraction movement but may not be as well tolerated in children. The radiation oncologist can assess these advanced techniques in simulation with the assistance of other professionals involved in the child's care.

Anesthesia. Many patients are simply too young to stay adequately still for simulation and treatment and therefore require anesthesia for treatment. The decision to use anesthesia comes with a number of considerations, including the following:

- It requires a patient to fast each day before treatment, with associated effects on nutrition. For this reason, children treated with anesthesia are often treated in the morning, so some of the fasting time can be when they are sleeping.
- It requires the expertise of an anesthesiologist with pediatric expertise.
- Repeated anesthesia has been associated with late side effects and risks (including neurocognitive effects) separate from radiotherapy [39].
- If one starts treatment with anesthesia and later finds the patient can be treated without it, the ITVs may change.
- The use of anesthesia will require additional vault time and personnel time to assist with induction and emergence from anesthesia.

If anesthesia is employed, the radiation oncologist should partner with the anesthesiologist to plan the patient positioning prior to simulation.

Position to minimize normal tissue exposure. Survivors of pediatric cancer may have decades to experience the risks and effects of their therapies. Thus, the radiation oncologist must be aware of the potential late side effects and risks of radiation in children and take all reasonable steps to mitigate those risks in simulation and planning.

When treating sarcoma, particularly in the extremities, there are ample opportunities to lower normal tissue radiation exposure by optimally positioning the patient. This is best achieved with the input of the dosimetrist and/or physicist who will be looking ahead to anticipate radiation planning. Some considerations include the following:

- Empty or full bladder to affect the positioning of the uterus, ovaries, and bowel.
- Positioning upper extremity tumors away from the trunk, head, or other normal tissues so they receive as little "low-dose bath" of radiation as feasible.
- In the lower extremity, rotating the affected extremity to make the target amenable to beam angles (often AP and PA) that minimize exposure of the contralateral lower extremity.

- One can also flex/extend, rotate, or abduct one hip relative to the other to further allow entrance and exit of beams with minimal risk of secondary malignancies on the contralateral extremity.
- In males, one can use a mesh, a sheet, or other materials to gently pull the scrotum and testicles away from the affected thigh targets. Depending on anticipated beam arrangement, the penis can be positioned to one side.

5.2.4.3 Target Definitions

As in all disease sites in radiation oncology, scrupulous attention to detailed tumor and target volume definition is essential for good outcomes.

Gross tumor volume (GTV) accounts for all clinically apparent diseases by any imaging modality and physical examination. Although plain film, CT, and PET imaging are all useful in delineating disease, in sarcoma, MRI is usually the imaging modality of choice for the defining the GTV. It is important for the radiation oncologist to look at multiple sequences of MRI imaging, including both the T1 imaging with contrast and the T2, the latter particularly for assessing invasion into surrounding tissues. In tumor originating from or invading the bone, sometimes plain film and CT scan can clarify how extensively the tumor is infiltrating the bone.

In modern treatment planning systems, radiation oncologists typically perform "fusions" of diagnostic imaging to radiation planning studies to help define the GTV. In many sarcoma disease sites, the fusions can be very challenging if the patient is positioned for treatment differently from when she/he had his/her diagnostic imaging. This is particularly the case in the extremities where rotations in the shoulders and hips can particularly complicate alignment. There are instances where one must rely on cognitive registration using anatomical landmarks to "interpret" the extent of disease more than relying solely on the fused images.

Clinical target volume (CTV) accounts for the gross disease plus the surrounding tissues that might harbor microscopic disease. It can be limited by normal tissues into which tumor is unlikely to invade. However, great care must be taken to examine all imaging before determining how to anatomically limit the CTV expansion into a surrounding structure, for example, sometimes a soft tissue sarcoma will invade into an abutting bone or at least in a small space between bones. The size of the anatomically limited expansion from GTV to CTV is generally larger in adult sarcomas than in pediatric sarcomas. In adult sarcomas, the CTV expansion is typically at least 2–3 cm in longitudinal planes and 1.5 cm radially, with additional expansion to encompass any T2 edema.

In Ewing sarcoma, the recently reported Euro-Ewing99/COG AEWS0331 trial used 1.5 cm GTV to CTV expansions on initial volumes and 1 cm expansions on boost volumes [10]. St. Jude reported excellent local control using 1 cm GTV to CTV expansions [11]. The most recent COG trial for localized disease, AEWS1031, used a 1 cm margin, but the results have only been presented in abstract. Recent trials target the extent of disease at time of presentation for the initial 45 Gy volume, followed by a boost to the post-induction chemotherapy extent of disease. Importantly, for bone tumors, only the soft tissue extent of the GTV is changed after induction chemotherapy; the extent of bone involvement is not decreased.

For RMS, recently reported COG Trials ARST0431 (high risk) and ARST08P1 (high risk), ARST0531 (intermediate risk), and ARST0331 (low risk) all used GTV to CTV expansions of 1 cm [40–43]. Further, St. Jude reported excellent outcomes also using 1 cm GTV to CTV expansions [44]. As with Ewing sarcoma, recent reported trials have allowed for a cone-down of target volumes to post-induction volumes after 36 Gy, when the radiation oncologist can be confident the tumor border represented a "pushing margin" rather than infiltrating surrounding tissues.

For NRSTS, the recently reported COG ARST0332 used 1.5 cm GTV to CTV expansions on initial volumes and 1 cm expansions on boost volumes [31]. St. Jude recently reported their excellent local control outcomes with treating NRSTS with (mostly) 1.5 cm margins [45].

In the case of osteosarcoma, the GTV to CTV expansion is commonly 2 cm [37]. Recent COG protocol AOST06P1 used a 1.5 cm GTV to PTV expansion, but the preceding study AOST0331 used 2 cm expansions on GTV for axial tumors and 4 cm on ependymal tumors.

Interval target volumes (ITVs) and planning target volumes (PTVs) are highly variable and site specific and vary by institution and image-guided radiation therapy options.

Target volume delineation guidelines are summarized in Table 5.5. An example of target volume delineation is shown in Fig. 5.3.

5.2.5 Curative Dose Recommendations

5.2.5.1 Ewing Sarcoma

The Euro-Ewing 99/COG AEWS0331 trial and COG AEWS1031 patients are generally treated to 50.4 Gy for microscopic disease and 55.8 Gy for gross disease. Table 5.4 provides an approximate summary of the doses on these two studies, although there are further complexities depending on overlapping extent of disease such as a chest wall tumor with positive pleural cytology.

At the time of this publication, COG AEWS1031's results have only been presented in abstract and have not been reported in a peer-reviewed publication; the treatment algorithm should be considered investigational.

The doses summarized in Table 5.6 are from studies of patients with localized disease. For patients with lung metastases, one can also treat the lungs with 15 Gy in ten fractions (1.5 Gy per fraction) (or 12 Gy in eight fractions if ≤6 years old).

5.2.5.2 RMS

The most recent reported COG trials use the doses shown in Table 5.7.

There are concerns that tumors larger than 5 cm have poorer local control. Therefore, on the ongoing COG ARST1431 trial, these patients receive 59.4 Gy in 33 fractions, which is a study question. There have also been questions about whether 45 Gy is sufficient for patients with Group III embryonal RMS when paired with low-risk RMS chemotherapy [24].

Table 5.5 Target volume delineation adapted from Children's Oncology Group (COG) trials

Structure	Target volume definitions
Gross tumor volume (GTV)	**GTV1** "pretreatment tumor volume," tumor based on exam and imaging (CT + contrast, MRI T1 + gad), including any pathologically involved nodes and including all infiltrative diseases at diagnosis and all areas of the initially involved bone.[a–d] It excludes extension beyond patient or into anatomically uninvolved cavities that were compressed and re-expanded following treatment **GTV2** "posttreatment tumor volume," tumor based on exam and imaging (CT + contrast, MRI T1 + gad) after surgery and/or induction chemotherapy and all areas of the initially involved bone[a–d] **GTV2,** none, if GTR or complete response to chemotherapy **GTV1,** GTV2 if no reduction to chemotherapy and/or interval growth **Post-op osteosarcoma GTV** includes operative bed, residual gross tumor defined by exam, CT, and MRI but does not need to cover operative tract or scar if not at risk
Clinical target volume (CTV)	**CTV1** "microscopic at-risk disease," GTV1 + 1[a, b]–1.5[c, d] cm and includes any edema most commonly visualized on MRI T2 and FLAIR, pathologically involved nodes[e]. For extremity osteosarcoma, 1.5 cm radial and 2 cm longitudinal margin **CTV2** "cone-down microscopic at-risk disease," GTV2 + 1[a–c]cm excluding anatomic barriers as above **CTV2,** GTV1 +/− margin, if GTR or complete response to chemotherapy **Post-op osteosarcoma CTV,** GTV +1.5 cm around the operative bed and tissue initially infiltrated by tumor
Internal target volume (ITV)	**ITV** "internal motion," CTV + internal motion, based on magnitude of internal motion as determined by imaging (4DCT) Not always indicated, considered for pelvic, retroperitoneal, chest, lung, and mediastinum sites
Planning target volume (PTV)	**PTV1** "initial extent of disease," CTV1 (or ITV1) + institutional specified margin based on daily set-up accuracy and uncertainty of immobilization, margin typically 0.3–0.7 cm **PTV2** "cone-down," CTV2 (or ITV2) + institutional specified margin **PTV** for proton planning is based on beam-specific robustness
• All CTV volumes exclude extension beyond patient or into normal uninvolved tissues (bone, muscle if fascial anatomic barriers exist) or previously displaced, non-invaded organs.	

Abbreviations: GTR Gross total resection
[a]Ewing sarcoma (adapted from COG AEWS1031)
[b]RMS (adapted from COG ARST0531 and 1431)
[c]Non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) (adapted from COG ARST0332)
[d]Osteosarcoma
[e]For RMS provider discretion regarding prophylactic coverage of adjacent or draining nodal basin if there is a high suspicion for involvement

5.2.5.3 Non-RMS Soft Tissue Sarcoma

The recently reported COG ARST0332 effectively establishes dose standards. The preoperative dose of radiation is 45 Gy in 25 fractions, with postoperative boosts of 10.8 Gy in 6 fractions for microscopic margins and 19.8 Gy in 11 fractions for gross residual disease. The study only included patients either with resected disease or

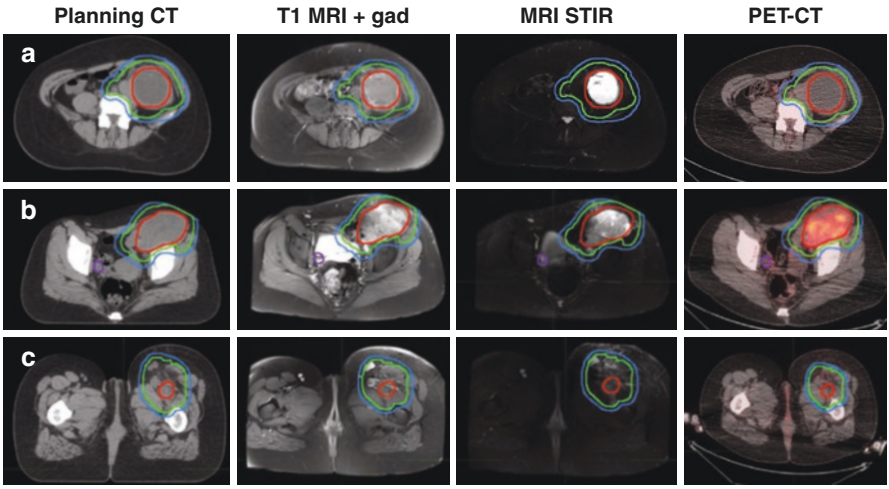


Fig. 5.3 Example of target volumes in a girl with left pelvis NRSTS

Table 5.6 Radiation dose recommendations for Ewing sarcoma

	Dose in Gy[a], including cone downs	
Clinical situation	Euro-Ewing-99/COG AEWS0331	COG AEWS1031
Vertebral body	45	50.4
Preoperative RT	45	36
Postoperative, after pre-op with microscopic margins	10.8	14.4
Postoperative, after pre-op with gross margins	10.8	19.8
Postoperative with microscopic margins	50.4 (45 + 5.4)	50.4
Definitive osseous disease	55.8 (45 + 10.8)	55.8 (45 + 10.8)
Definitive extraosseous site with complete response	50.4 (45 + 5.4)	50.4
Definitive extraosseous site with less than complete response	55.8 (45 + 10.8)	55.8 (45 + 10.8)
Lymph nodes resected	50.4	50.4
Lymph nodes unresected	55.8 (45 + 10.8)	55.8 (45 + 10.8)
Whole abdomen for malignant peritoneal ascites or diffuse peritoneal involvement		24
Hemithorax radiation for chest wall tumors with positive pleural cytology	15[b] if >6 yo 12[b] if ≤6 yo	15[b] if >6 yo 12[b] if ≤6 yo

[a]In 1.8 Gy fractions unless otherwise specified
[b]In 1.5 Gy fractions

Table 5.7 Dose recommendations for RMS

Group	Dose[a]
I Embryonal histology[b]	0 Gy
I Alveolar histology[b, c]	36 Gy in 20 fractions
IIA Microscopically positive margins	36 Gy in 20 fractions
IIB Lymph nodes with no residual disease	41.4 Gy in 23 fractions
III Gross residual disease at start of induction chemotherapy	50.4 Gy in 28 fractions
III Gross residual disease at start of induction chemotherapy (orbital primary)	45 Gy in 25 fractions
Whole lung irradiation if disease present at initial staging	15 Gy[d] in 10 fractions 12 Gy[d] in 8 fractions (if less than 8 yo)

[a]In 1.8 Gy fractions unless otherwise specified
[b]The alveolar vs embryonal distinction is being replaced with PAX-FOXO1 fusion positive vs negative on current trials
[c]If the patient has an amputation and margins clearly negative, then no adjuvant radiation
[d]In 1.5 Gy fractions

anticipated surgery after neoadjuvant therapy [31]. In the European Pediatric Soft Tissue Sarcoma Study Group trial EpSSG NRSTS 2005, the definitive dose of radiation used concurrently with ifosfamide was 59.4 Gy in 33 fractions [46].

5.2.5.4 Osteosarcoma

Because radiation is used less frequently in this disease, the prescribed doses are less well established. Osteosarcoma is considered a relatively radio-resistant sarcoma. St. Jude reported using definitive radiation doses of approximately 60 Gy in conventional fractionation when treating children [37]. A Massachusetts General Hospital osteosarcoma case series reported using greater than 70 Gy in a majority of patients treated with curative intent, including a subset of patients who received 19.8 Gy in the preoperative setting [38].

5.2.6 Treatment Planning Considerations

The first planning consideration is whether radiation therapy can be omitted. However, as indicated above, radiation therapy is often necessary.

When radiation therapy is required, the imperative is not just limiting radiation to organs at risk but aiming to maximize the amount of the normal tissue receiving no radiation. As noted above in the introduction, survivors of pediatric sarcoma diseases have high risks of second tumors that are associated with late mortality.

Reducing normal tissue exposure begins with simulation but is particularly critical in dosimetry. Modern treatment techniques increase the conformality of radiation around target volumes but can increase the volume of the tissue receiving a "low-dose bath" of radiation. When reviewing a child's treatment plan, the radiation oncologist must "turn on" the low-dose isodose lines in the treatment planning software to assess this.

The focus of the radiation oncologist is most naturally on the "tissue tolerance," particularly with respect to critical organs such as the kidney, liver, spinal cord, heart, and lungs. However, in children, there are additional concerns that cannot be overlooked. Some examples include the following:

- Bone hypoplasia can occur with doses as low as 10 Gy. For this reason, when skeletally-immature patients are treated, attention is paid to trying to avoid sharp gradients across vertebral bodies, thus reducing the risk of scoliosis. Growth plates should be identified, and minimizing radiation dose to them should be prioritized. Handwrist radiographs can be ordered to assess skeletal maturity.
- Radiation also can cause decreased soft tissue development between 10 and 15 Gy of radiation exposure, affecting not just muscle development but other soft tissues (including the breast tissue) with important cosmetic and functional implications.
- As discussed above, the gonads are very sensitive to radiation, and even low doses of radiation can affect a child's future reproductive and hormonal functions. Males can become infertile with as low as 1–2 Gy of radiation, and girls can become infertile with as low as 2–4 Gy of radiation.
- Sometimes sarcomas—particularly in the head and neck and parameningeal regions—can abut the central nervous system. The developing brain is very sensitive to radiation therapy and dose to it—and particularly critical substructures such as the temporal lobes and hippocampi should be minimized. Survivors of pediatric tumors who received radiation to the head are also at risk of endocrinopathies, increased risk of strokes/vascular problems, dry eyes, cataracts, vision impairment, and sensorineural hearing loss (particularly high frequencies).
- Radiation to the heart can increase risk of ischemic heart disease and congestive heart failure. Mulrooney et al. showed that mean heart dose >15 Gy increased the relative hazard of congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities by twofold to sixfold compared to non-irradiated survivors of Hodgkin lymphoma [47]. In another analysis, coronary artery disease was more closely correlated with the left circumflex artery V20 and left anterior descending artery V5 than mean heart dose [48].

In short, while minimizing radiation exposure to organs at risk is important in all patients, it is particularly critical in children.

Bone marrow is an organ at risk that should not be overlooked. When suppressed, the patient can be fatigued and at increased risk of infection, require transfusions, and unable to receive critical concurrent chemotherapy. There is suggestion from treating central nervous system tumors that decreased blood counts are not just the result of treating the bone marrow but also due to irradiation of the circulating blood pool [49]. The concern about myelosuppression is greatest when treating in the pelvis and long lengths of the spine, but present whenever radiation therapy is delivered.

There can be trade-offs between conformality and increased low-dose exposure. One example is volumetric-modulated arc therapy (VMAT) in which radiation is constantly delivered as the linear accelerator treatment head is rotated around the

patient, allowing very conformal high-dose isodose lines for the radiation plan. However, one can imagine how without constraining the arc, treating a patient with a lower extremity tumor will result in at least some exposure to the contralateral lower extremity. VMAT plans are faster to deliver, which is particularly advantageous in a child who might be marginally able to stay still for treatment without anesthesia. However, in spite of these advantages of VMAT, a static field intensity-modulated radiation therapy (IMRT) plan and a three-dimensional conformal radiation plan (3D CRT) may be superior because they might spare more normal tissues of receiving any radiation.

In contrast to the above, recent feasibility and dosimetry studies highlight benefits of using advanced planning techniques such as IMRT and VMAT radiation when treating whole lung irradiation (WLI) for lung metastases in patients with sarcomas and other diseases such as nephroblastoma. In this case, historical anterio-posterior three-dimensional conformal plans do not prevent low-dose to normal tissues. The whole lung irradiation technique includes obtaining a 4DCT scan in the supine treatment position with the arms placed above the head using immobilization. Then using the average scan, CTV bilateral lung volumes are generated, which are adjusted to the ITV based on the phases of respiratory gating (which can use minimum intensity projection to aid in the generation of the ITV with confirmation based on direct visualization of each respiratory phase). Coverage includes the bilateral hila and lymph nodes from the sternal notch to 1.5 cm inferior to the carina with vertebral coverage necessary for uniform bone development in skeletally-immature patients (approximately age <15 years). PTV expansion is a uniform 1 cm limited to the patient. Planning is performed using heterogeneity corrections. The use of advanced planning techniques IMRT for WLI allows for excellent coverage of the lungs while reducing radiation to the whole heart and cardiac substructures [50].

Finally, because many of these tumors are sensitive to radiation and treated with conformal radiation plans, the radiologist must assess during on-treatment visits and with onboard imaging whether a tumor response allows for replanning.

5.2.7 Modalities of Radiation

The above discussion almost exclusively refers to conventionally fractionated radiation (typically 1.8 Gy per fraction), which until recently was mostly delivered with photon therapy.

Proton therapy is a rapidly approaching photon therapy as the most common modality of radiation for pediatric malignancies. By 2016, nearly 50% of pediatric patients with RMS, medulloblastoma, ependymoma, Ewing sarcoma, and atypical teratoid rhabdoid tumors were receiving proton therapy [51]. With its lack of exit dose, it is associated with decreased integral dose to organs at risk distal to the targets, with anticipated decreases in acute and late effects. Because the targeting, dose, and fractionation are almost always the same between photons and protons in pediatric cancer, the disease outcomes are expected to be the same. The clinical

evidence supporting the use of proton therapy includes retrospective studies regarding Ewing sarcoma [52–54] and RMS [55–57].

There has never been a randomized controlled trial between photon and proton radiation therapies in children. It is unclear if such a trial could accrue if families were to be informed about the differences in dose distribution associated with the plans between which their child would be randomly assigned. Most COG trials (with notable exceptions of diffuse intrinsic pontine glioma and leukemia trials) allow for proton therapy at the discretion of the treating physician.

Figure 5.4 shows a proton radiation plan for the patient whose target volumes were delineated in Fig. 5.3.

Stereotactic body radiotherapy (SBRT) is an extraordinarily precise hypofractionated radiation therapy using five or fewer fractions delivered with the intent of ablating the targeted tissue. It has been shown to be effective in treating sarcoma metastases and spine primaries in case series [58–60]. Its feasibility for treating Ewing sarcoma metastases was examined on COG AEWS1221 in which metastases were treated to 40 Gy in five fractions. The study is closed to accrual but results have not been reported. On COG ARST1431, stable or partially responding metastatic lesions can be treated to 35 Gy in five fractions. That study remains open at the time of this writing.

Finally, perhaps the most conformal but largely underutilized form of radiation therapy for pediatric sarcoma is brachytherapy. It is used extensively in some European centers as well as a few US centers including the St. Jude Children's Research Hospital [11, 45] and Memorial Sloan Kettering Cancer Center [61]. Most COG sarcoma protocols allow for its use, and it can be particularly important in treating girls with vaginal and vulvar RMS [62, 63].

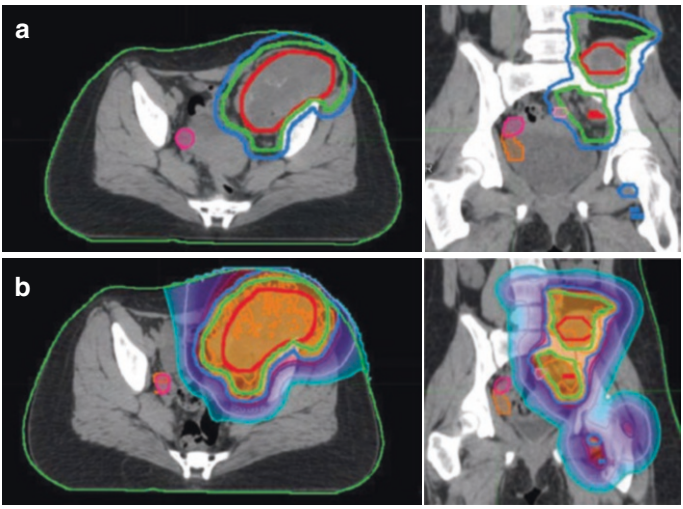


Fig. 5.4 Example of proton plan in a girl with left pelvis NRSTS, bladder full in (**a**) and empty in (**b**)

5.2.7.1 Physics/Quality Assurance

In addition to the same medical physics and quality assurance integral to excellent treatment of adults, pediatric radiation oncology programs have additional quality assurance elements.

The radiation oncologist must focus on reducing all radiation exposures, including onboard imaging. Daily onboard imaging is usually necessary to use the smallest target volumes. Cone beam CT (CBCT) settings can be adjusted by medical physics to account for the smaller sizes of pediatric patients, thus reducing the radiation exposure. More importantly, the radiation oncologist should work with his or her team to decide if KV imaging can be used in place of daily CBCTs in some cases to ever further reduce exposure.

Even more important is that the pediatric radiation oncology program be integrated with the rest of the pediatric oncology team and prepared for unexpected events. Questions that need to be considered include the following:

- Are there providers trained in Pediatric Advanced Life Support (PALS)?
- If the radiation facility is in an adult hospital and the code team is called, are they prepared to care for a small child?
- Are nurses prepared to assist the anesthesiologists?
- When pediatric patients come from a children's hospital, is there daily sign-out of the patient to and from the hospital?
- Is it clearly defined whether the radiation oncologist will prescribe medications to treat symptoms, or will only the medical oncology team do so?
- Is it clear to the patient which provider to call in the case of urgent questions?
- How is daily radiation paired with concurrent chemotherapy that is often delivered with multiple-day hospitalizations, such as with ifosfamide and etoposide?
- Are there robust mechanisms for transmitting imaging and records both to and from the radiation oncology center?
- Is there a shared quality assurance program between the other pediatric oncology providers and the radiation oncology center?

Finally, because many patients with pediatric cancers become long-term survivors at risk of late effects, the radiation oncologist must take extra steps in treatment summaries and follow-up notes to communicate (ideally with images) where radiation was delivered, doses to critical organs at risk, and recommended follow-up by providers other than medical oncologist.

5.3 Summary

Radiotherapy plays an essential role in managing many patients with pediatric sarcomas in part because the tumors are sensitive to radiation. In treating these pediatric patients, the radiation oncologist's focus must be on minimizing dose to not just critical organs at risk but exposing all tissues to as little radiation as feasible. An outstanding pediatric radiation oncology program is partnered and integrated with the rest of the pediatric oncology providers.

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Concurrent Chemoradiation Therapy for Soft Tissue Sarcoma

6

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Contents

6.1 Introduction

Many patients with extremity soft tissue sarcoma (STS) are treated with wide local excision. Radiotherapy and/or chemotherapy may be added before or after surgery in order to increase local control. Numerous studies have elucidated high-risk

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patient and tumor factors that are associated with increasing rates of local and distant disease recurrence [1–4]. These include larger tumor size and higher FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer) grade (i.e., AJCC (American Joint Committee on Cancer) stage) as well as positive surgical margin status and certain histologic types, such as malignant peripheral nerve sheath tumor (MPNST) [5]. Trials testing adjuvant chemotherapy have consistently demonstrated that patients with large (i.e., ≥5 cm) and/or high-grade tumors have experienced disease recurrence rates of 40–50%.

Several prior studies have attempted to intensify treatment for patients with large, high-grade STS using concurrent chemoradiotherapy (CRT) [6]. CRT seeks to achieve dual goals of improving local control and introducing early systemic therapy to address potential micrometastatic disease in patients with de novo localized soft tissue sarcoma [6]. Multiple strategies have been used. Early strategies utilized large two- or three-dimensional (2D or 3D) planned radiotherapy fields with cytotoxic chemotherapy and observed excellent disease control but high rates of toxicity. Modern approaches are using smaller radiotherapy fields and intensity-modulated radiation therapy (IMRT) plus cytotoxic chemotherapy or combined with immune or targeted systemic agents (NCT03217266, NCT03092323). These modern paradigms are expected to improve toxicity compared with past CRT regimens and are currently under prospective evaluation.

6.2 Concurrent Radiotherapy with Anthracycline-Based Chemotherapy

One strategy developed by DeLaney and colleagues [7] includes three cycles of preoperative mesna (22 mg/m^2/d, days 1–4), doxorubicin (20 mg/m^2/d, days 1–3), ifosfamide (2000 mg/m^2/d, days 1–3), and dacarbazine (250 mg/m^2/d, days 1–4) (MAID (medical assistance in dying)) chemotherapy interdigitated with radiotherapy. Radiotherapy is delivered to 44 Gy in 22 daily fractions using a split course of 22 Gy in 11 daily fractions delivered after completion of cycles 1 and 2 of MAID. Following MAID CRT, patients undergo wide local excision followed by three more cycles of MAID. This CRT regimen was tested in a single-arm phase II institutional study for patients with FNCLCC grade 2 or 3 STS ≥8 cm. This CRT regimen resulted in excellent patient outcomes with long-term follow-up [8]. Seven-year actuarial rates of local control, disease-free survival (DFS), and overall survival (OS) are 90%, 81%, and 79%, respectively. The PFS (progression-free survival) and OS associated with CRT on this phase II trial were significantly higher than seen in similar patients treated off-trial without tri-modality therapy during the same time period (50% and 45%, respectively, both $p < 0.005$). The authors reported that the regimen was well tolerated. Eighty-three percent of patients received all six prescribed cycles of MAID, and all patients were able to undergo wide local excision. Interestingly, the MAID regiment has not been widely implemented by institutions across the country.

This regimen was subsequently tested in a single-arm phase II multi-institutional study, RTOG 95-14 [9]. Unfortunately, the authors reported substantial toxicity

associated with MAID CRT in this setting. Eighty-four percent of patients experienced a grade 4 toxicity, almost all of which were hematologic (78%). Twelve patients had non-hematologic toxicity including four patients experiencing grade 4 cutaneous toxicity. Three patients (5%) died from treatment. Eighty-nine percent of patients received the prescribed radiotherapy dose, and 79% of patients completed all three cycles of neoadjuvant CRT. Only 61% completed all three cycles of prescribed postoperative chemotherapy. The limited ability for patients to complete the protocol therapy may have contributed to inferior outcomes observed during RTOG 95-14 compared with the MGH (Massachusetts General Hospital) study. With a median follow-up of 7.7 years, 5-year rates of local control, DFS, and OS were 87.8%, 56.1%, and 71.2%, respectively [10]. The substantial toxicity and marginal improvement in outcomes associated with MAID CRT demonstrate that this regimen offers a narrow therapeutic window, and this dampened enthusiasm for this regimen despite a recognized need for improved treatment strategies for this high-risk cohort [11].

6.3 Improvements in Concurrent CRT

The quality of radiotherapy and chemotherapy delivery has significantly advanced since these initial studies were completed. Three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and image-guided radiotherapy (IGRT) can be used in the preoperative setting to substantially reduce the volume of the normal tissue receiving high dose. RTOG 95-14 radiotherapy utilized substantial fields delivered using two-dimensional (2D) techniques: ≥2 cm radial and 9 cm proximal-distal field margins off the primary gross tumor volume (GTV). In contrast, RTOG 0630 used 3DCRT and IMRT to deliver 2 cm radial and 3.5 cm proximal-distal clinical target volume (PTV) expansions off the GTV [12]. CT-based planning also allows for additional shrinkage of radiotherapy fields along anatomic barriers compared with two-dimensional planning techniques.

Supportive care with chemotherapy and radiation therapy has additionally improved substantially over the last two decades. Due to the intensity of several systematic chemotherapy regimens used for the treatment of many STS, the introduction of growth colony-stimulating factors (G-CSF) led to a decrease in hematologic toxicities and an increase in the number of patient able to maintain the desired dose and frequency of these high intensities of regimens. It is important to note that the use of G-CSF in CRT has not been studied in clinical trials. In terms of G-CSF, support delivery mechanisms, such as on-body injectors, should be avoided for patients undergoing radiation therapy. Radiation therapy can cause potential damage to the on-body device and cause it to malfunction.

Other improvements in prevention and treatment include treatment for chemotherapy, and radiation induced nausea and vomiting, which has improved patient tolerance and increased their ability to receive planned doses of chemotherapy and radiation. When radiation is used in combination with antineoplastic agents, antiemetic prophylaxis is determined by emetogenic risk of the antineoplastic agents

being used. The National Comprehensive Cancer Network (NCCN) (https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf) and American Society of Clinical Oncology (ASCO) offer evidenced-based recommendations.

It is therefore not surprising that recent studies of CRT demonstrate reduced toxicity and improved patient outcomes. One single-institution retrospective study evaluated patients with large (≥5 cm), high-grade STS of the extremity who received MAI CRT with modernized radiotherapy delivery from 2008 to 2016 [13]. This was similar to the RTOG regimen (Fig. 6.1), but without dacarbazine, patients received mesna (600–750 mg/m^2 given before and after ifosfamide), ifosfamide (2000–2500 mg/m^2/d, days 1–3), and doxorubicin (30–37.5 mg/m^2/d days 1 and 2) for three cycles interdigitated with radiotherapy prior to surgery and three cycles after surgery. Radiotherapy was delivered using 3DCRT or IMRT and CTV margins of ≤2 cm radially and ≤5 cm in the proximal-distal dimension. The authors reported the results for 23 patients with a median follow-up of 47.3 months (minimum 14.7 months). There were no local recurrences, one patient experienced a regional nodal failure (3.8%), and nine patients developed metastatic disease (34.6%). Three-year locoregional recurrence-free survival, DFS, and OS were 95%, 64%, and 94.4%, respectively. Eighteen patients (69.2%) experienced a grade 4 acute hematologic toxicity (almost all neutropenia), and two patients (7.7%) experienced a grade 4 non-hematologic toxicity, one neurological toxicity attributed to ifosfamide and one late infield fracture requiring internal fixation. The toxicity associated with the modified MAI CRT regimen is considerable but improved compared with the RTOG regimen, and it is associated with excellent outcomes in this retrospective study. Prospective testing of this regimen should be considered in patients with high-risk STS (Table 6.1).

Another model of preoperative CRT was developed at the Oregon Health and Science University (OHSU) [14]. This regimen utilizes epirubicin (30 mg/m^2/day, days 1–4) and ifosfamide (2.5 g/m^2/day, days 1–4) for three 21-day cycles. Radiotherapy begins concurrently with cycle 2 and consists of 28 Gy in eight daily fractions of 3.5 Gy each delivered using 3DCRT. Three cycles of epirubicin and ifosfamide were delivered after surgery. The investigators reported on 25 patients with high-risk sarcoma treated using this regimen in a phase II clinical trial and 51 subsequent patients treated off-trial identified from retrospective chart review. With a median follow-up of approximately 4 years, the estimated five-year rates of OS, distant disease-free survival, and local recurrence-free survival were 70.4%, 55.9%, and 87.2%, respectively. Most patients (95%) were able to complete all chemoradiation therapy cycles, but only 64% completed all six planned chemotherapy

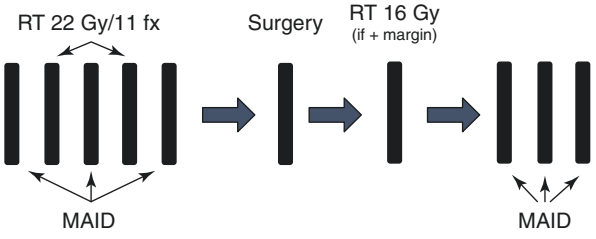

Fig. 6.1 Chemoradiation Regimen tested in RTOG 95-14. MAID = mesna (22 mg/m^2/d, days 1–4), doxorubicin (20 mg/m^2/d, days 1–3), ifosfamide (2000 mg/m^2/d, days 1–3), and dacarbazine (250 mg/m^2/d, days 1–4)

Table 6.1 Modern approaches to chemoradiation for soft tissue sarcoma of the extremity

Citation	Radiotherapy	Chemotherapy	Study type	Outcome
Chowdhary et al. [13]	• 50 Gy in 25 fractions • 16 Gy for + margin	• Mesna (600–750 mg/m^2, before and after ifosfamide). • Doxorubicin (30–37.5 mg/m^2/d days 1 and 2). • Ifosfamide (2000–2500 mg/m^2/d, days 1–3)	Retrospective	• 3-year LRFS 95% • 3-year OS 94.4%
Lu et al. [14]	• 28 Gy in 8 fractions	• Epirubicin (30 mg/m^2/day, days 1–4). • Ifosfamide (2.5 g/m^2/day, days 1–4).	Prospective + retrospective	• 5-year LRFS 87.2% • 5-year OS 70.4%
Sarc032 (NCT03092323)	• 50 Gy in 25 fractions • 16 Gy for + margin	• Pembrolizumab (200 mg IV Q3 weeks)	Prospective	• Ongoing
NRG-DT001 (NCT03217266)	• 50 Gy in 25 fractions	• AMG-232 (120 mg PO in escalating doses, up to five times per week)	Prospective	• Ongoing
Concurrent chemoradiation with taxol (cutaneous angiosarcoma only, NCT03921008)	• 50–50.4 Gy in 25 fractions	• Paclitaxel (80 mg IV weekly, 6-week induction followed by 5–6-week chemoradiation)	Prospective	• Ongoing

cycles. Wound complications were observed in 32% of patients, but the wound healing complication rate was only 7% in the upper extremity versus 32% in the lower extremity. Acute toxicities related to chemotherapy were not reported, but there were two late deaths attributed to systemic therapy-related myelodysplasia/acute myeloid leukemia 7 years after completion of therapy.

6.4 Concurrent Radiotherapy and Immunotherapy

Immune checkpoint antibodies, such as anti-PD-1 antibody pembrolizumab or nivolumab, have generated much excitement in oncology. Studies across cancer types demonstrate that some patients can achieve excellent and durable responses to checkpoint blockade. Moreover, the immunotherapies are generally well tolerated compared with systemic chemotherapy.

Prior work demonstrates that the expression levels of immune checkpoint molecules such as PD-L1 are prognostic in soft tissue sarcoma [15], and therefore it is hypothesized that anti-PD-L1 antibodies are potentially therapeutic. However, it is likely that the immune infiltrate and the role of specific immune subpopulations

differ across sarcoma histotypes ([16]) [17]. One study retrospectively analyzed the tumor tissue from 81 patients with STS to quantify PD-1 and PD-L1 expression in different sarcoma histotypes. This study found very high expression of PD-1- and PD-L1-positive infiltrates and tumor cells in undifferentiated pleomorphic sarcoma, leiomyosarcoma (MRCL), and well-differentiated/dedifferentiated liposarcoma compared with myxoid/round cell liposarcoma and synovial sarcoma (SS) [18]. The authors also demonstrated that higher-grade tumors were associated with higher PD-1 and PD-L1 expression compared with lower-grade tumors across tumor types. Further, they analyzed TCR-Vβ complementarity and found that in addition to greater PD-1/PD-L1 expression, UPS (undifferentiated pleomorphic sarcoma) and leiomyosarcoma (LMS) expressed a more oligoclonal T-cell repertoire than liposarcoma, SS, and MRCL, reflecting a more robust and focused T-cell response.

The finding of differential immune cell infiltration for different sarcoma histotypes is consistent with the findings of two multicenter randomized trials that evaluated pembrolizumab in patients with metastatic STS. The first study, SARC028, was a multicenter open-label, phase II study of pembrolizumab monotherapy for adult patients with metastatic or unresectable soft tissue sarcoma of the following common subtypes: leiomyosarcoma, poorly or dedifferentiated liposarcoma, and synovial sarcoma [19]. Of note, patients 12 years or older with bone sarcomas were also eligible. Patients received 200 mg pembrolizumab every 3 weeks until disease progression or unacceptable toxicity and the primary end point were objective response rates by RECIST 1.1. The study was overall negative as pembrolizumab was associated with an objective response in only 7/40 (18%) patients with STS. A 12-week progression-free survival was only 55%. The second study, Alliance A091401, was a noncomparative randomized phase II trial of nivolumab with or without ipilimumab in adult patients with metastatic or unresectable STS [20]. This study found a poor overall response rate in patients in both arms: 5% for patients receiving nivolumab monotherapy and 16% for patients receiving dual immunotherapy. The median PFS was an only 1.7 months and 4.1 months in the monotherapy and dual immunotherapy arms, respectively. However, as may be expected based on retrospective data, subgroup analysis demonstrates promise for immunotherapy in specific subtypes of STS including UPS, LMS, myxofibrosarcoma, and angiosarcoma.

Other researches evaluating immunotherapy suggest that radiotherapy may potentiate the effects of immunotherapy in sarcomas and other cancer types. This concept is supported by preclinical and clinical data and is well reviewed in an editorial by Drs. Formenti and Demaria [21]. As new cancers form, they are sensed by the innate immune system and tissue microenvironment changes, such as an increase in interferon gamma, and encourage antitumor activities of infiltrating leukocytes. The cytotoxic activities of these infiltrating cells cause the release of tumor-associated antigens which are processed by dendritic cells, which activate tumor-specific CD4 and CD8 T-cell populations. However, if tumor cell kill is incomplete, surviving cells can mutate due to genetic instability and then escape immune surveillance. The immune system still engages the tumor, which can limit disease progression, but it is ultimately unable to eliminate all tumor cells. It is felt that this

equilibrium state can persist subclinically for a long time and that at the time of presentation, tumor cells can already be highly resistant to immune rejection. However, radiotherapy, which has been shown to lead to immunogenic tumor cell death, can promote the release of new tumor antigens and allow for expansion of tumor-specific leukocyte populations that can enhance the tumoricidal effects. Therefore, it is hypothesized that radiotherapy can be combined with immunotherapy to overcome the dominant immunosuppressive state that characterizes most tumors.

The combination of radiotherapy and immunotherapy is being evaluated prospectively in the randomized, prospective phase II clinical trial SARC032 (NCT03092323). This trial is seeking to enroll patients with clinically localized and resectable, grade 2–3 undifferentiated pleomorphic sarcoma or liposarcoma of the extremity. Enrolled patients will be randomized to receive standard of care neoadjuvant radiotherapy to 50 Gy in 25 fractions with or without 3 cycles of concurrent pembrolizumab 200 mg IV given every 3 weeks and adjuvant pembrolizumab at the same dose given every 3 weeks for up to 1 year. The primary outcome is disease-free survival, and the secondary outcomes are locoregional recurrence-free survival, distant disease-free survival, overall survival, and the safety of combination radioimmunotherapy in this cohort. Exploratory objectives will evaluate the peripheral and intra-tumoral immune response to combination immunoradiotherapy in order to identify predictors of response.

6.5 Concurrent Radiotherapy and MDM2 Inhibitor, AMG-232

A novel systemic therapy target is the interaction between MDM2 and p53, which is critical for radiotherapy-induced cell death. Activation of p53 in response to DNA damage drives a downstream transcriptional response that leads to cell senescence and death. MDM2 downregulates p53 activation by enhancing protein degradation, and therefore high levels of MDM2 inhibit the tumoricidal DNA damage response in patients with wild-type p53. While p53 is one of the most common mutations in all cancers, recent studies demonstrate that p53 mutations are present in less than half of soft tissue sarcomas.

An ongoing NRG single-arm, phase I trial (NCT 03217266) is evaluating the MDM2 inhibitor AMG-232 with concurrent radiotherapy in two cohorts: extremity and chest wall STS and retroperitoneal STS. A key feature of the trial is that requires next-generation sequencing of the tumor tissue in order to demonstrate a p53 wild-type state. AMG-232 is an oral systemic therapy that is given with a one-week lead-in followed by AMG-232 with preoperative radiotherapy. AMG-232120 mg is given orally twice weekly during the lead-in, and then dose escalated 1 day per week over 3 weeks starting with radiotherapy with a cap of daily with radiation (i.e., five times per week).

Another important feature of the study is a focus on radiotherapy quality, including centralized review of the local radiotherapy treatment planning process for the

retroperitoneal sarcoma cohort (NCT 03217266). Target delineation using diagnostic contrast-enhanced MRI and daily image-guided radiotherapy is required. Intensity-modulated techniques are recommended for the extremity cohort and required for the retroperitoneal cohort. The extremity cohort receives 50 Gy in 25 daily fractions with NRG standard CTV cranio-caudal expansions of 3 cm for high-grade and 2 cm low-grade STS (consistent with RTOG 0630). The retroperitoneal cohort receives 45 Gy in 25 fractions prescribed to a 1.5 cm PTV (1.0 cm CTV) with a simultaneous integrated boost to 50 Gy in 25 fractions prescribed to the GTV.

The study is currently enrolling 46 patients. The primary outcome is the median tolerated dose of AMG-232 at 4 weeks after concurrent AMG-232 and radiotherapy treatment completion. Secondary end points will evaluate pCR and rates of local failure, DFS, and OS at 2 years.

Early results from a European open-label phase I study tested trabectedin with neoadjuvant radiation therapy suggesting promise for the combination. This study enrolled 14 patients with clinically localized myxoid liposarcoma (ML). Patients received 45 Gy in 25 daily fractions with concurrent trabectedin with a 24-h infusion every 3 weeks. Radiotherapy started within 1 hour of initiation of the chemotherapy infusion. The trial had a 3 + 3 design with escalating dose levels of T and found that the ceiling dose level of 1.5 mg/m^2 was safe. All patients competed radiotherapy, and there were low frequencies of grade 3 or 4 toxicities (7–14%). Twenty-five percent of patients achieved a pathologic complete response. At a minimum follow-up of two years (median 26 months), local recurrence-free survival, disease-free survival, and overall survival were 92%, 86%, and 93%, respectively. This phase I study clearly demonstrates promise for combination trabectedin (1.5 mg/m^2 given Q3 weeks) and radiotherapy (45 Gy in 25 fractions).

6.6 Concurrent Radiotherapy and Taxanes for Angiosarcoma

Multiple studies have demonstrated significant activity of taxanes against angiosarcoma. Several retrospective analyses have demonstrated the effectiveness of paclitaxel against angiosarcoma [22, 23]. For instance, a European Organization for Research and Treatment of Cancer (EORTC) study of 32 patients with angiosarcoma found that the overall response rate was 62% and 75% in angiosarcomas of the scalp [23]. Most recently, the ANGIOTAX phase II study of weekly paclitaxel in patients with metastatic and/or unresectable angiosarcoma demonstrated efficacy with a nonprogression rate of 74% at 2 months [24]. Additionally, the regimen was well tolerated with manageable expected toxicity. Of note, prior work further suggests that paclitaxel may be especially effective in angiosarcomas of the head and neck. Fata and colleagues reported objective responses in eight of nine patients with head and neck angiosarcoma treated with paclitaxel [25].

Concurrent chemoradiation with taxanes has been tested in randomized trials in multiple diseases including gastric/esophageal cancer [26–28], non-small cell lung cancer [29–32], and head and neck cancer [33, 34]. In angiosarcoma, one

retrospective study suggests that chemoradiotherapy with a taxane is promising [35]. In this Japanese study, 28 patients were treated with either chemoradiotherapy with a taxane (docetaxel or paclitaxel) or surgery plus radiotherapy. This study found that patients treated with chemoradiotherapy had improved survival compared with patients treated with surgery followed by radiotherapy. While promising, this study is limited by its retrospective nature.

Concurrent chemoradiation therapy with paclitaxel is currently being tested for patients with clinically localized cutaneous angiosarcoma in a prospective phase II trial (NCT03921008). Eligible patients are treated with weekly induction paclitaxel at 70 mg/m^2 for six cycles (i.e., weeks 1–6) followed by weekly paclitaxel at the same dose concurrent with external beam radiotherapy to 50–50.4 Gy in 25–28 fractions. Patients then undergo surgical resection after 3–8-week break.

Unlike STS of the extremity and chest wall, protocol preoperative radiotherapy requires a 4 cm CTV expansion off the original GTV, which reflects the infiltrative nature of this disease. Importantly, clinical responses to paclitaxel are common, so detailed documentation of the original extent of disease is essential. The protocol also requires wide local excision of the original GTV plus a 4 cm circumferential margin if possible.

6.7 Adjuvant Chemotherapy for Resectable Soft Tissue Sarcomas (STS)

The role of adjuvant chemotherapy in high-grade localized STS has been a subject of controversy, particularly as regards to improving survival rates. Though there is a very clear survival benefit with neoadjuvant/adjuvant chemotherapy in young adults with rhabdomyosarcoma, Ewing's sarcoma, and osteosarcoma (likely related to their highly aggressive biology, propensity for metastases, and exquisite chemosensitivity), systemic chemotherapy in the adjuvant and metastatic setting for other high-grade sarcomas shows much lower response rates. The impact on survival, if any, is likely to be small in absolute magnitude [36–39]. Previous studies of adjuvant chemotherapy have been limited by tumor heterogeneity, inclusion of low-risk tumors, and various chemotherapy regimens [38, 40]. Still, some support the use of adjuvant chemotherapy in high-risk, chemosensitive extremity or trunk lesions. Retrospective analyses in risk-stratified STS patients have demonstrated survival benefit with adjuvant combination chemotherapy [41, 42].

6.8 Systemic Therapy in Advanced/Metastatic STS

Systemic treatments, including cytotoxic chemotherapy (single agent and combination) and targeted therapies, are the mainstay of treatment in STS with disseminated metastases. Limited metastases involving only one organ should be considered for resection to improve survival (e.g., pulmonary metastasectomy for patients with limited lung disease) [43].

While most single agents studied in STS have response rates of ≤10%, doxorubicin and ifosfamide have response rates on the order of 20–35%. Other single-agent options that demonstrate clinical activity include dacarbazine, epirubicin, gemcitabine, ifosfamide (with mesna), and paclitaxel (for angiosarcoma) [44, 45].

Doxorubicin has been used for decades in the treatment of STS and is one of the most effective chemotherapeutic agents against multiple subtypes of sarcomas. A dose response curve has been described, with higher doses to 60–75 mg/m^2 producing response rates of 20–37% [46]. More recent studies show response rates of 14% in the frontline setting, which likely reflects more stringent tumor response definitions in newer trials [47]. A different formulation of doxorubicin, a pegylated liposomal doxorubicin, prolongs circulation time. The changed pharmacokinetics result in less myelosuppression and cardiotoxicity, though it has significant dose-limiting mucocutaneous toxicities [48]. Clinical activity of pegylated doxorubicin versus doxorubicin is unclear, though a phase II study showed similar response rates [49].

A combination of an anthracycline and alkylating agent (doxorubicin/ifosfamide) has been a cornerstone of STS chemotherapy for decades, though its value over single-agent doxorubicin is still debated. Results from a large, prospective phase III RCT (randomized controlled trial) (EORTC 62012) of full-dose doxorubicin/ifosfamide compared to doxorubicin alone showed no significant difference in OS (14.3 vs 12.8 months, $P = 0.076$). However, PFS (7.4 vs 4.6 months, $P = 0.003$) and overall response rate (26% vs 14%) were significantly higher with the combination, though with the caveat of increased toxicity. Therefore, it is reasonable to consider this combination in fit patients when higher response rates are desired (e.g., to improve symptom control via tumor cytoreduction) and in histologies with selective sensitivity to alkylating agents, such as synovial sarcoma [47].

The decision for combination chemotherapy should be individualized and take into account age, performance status, and organ function. These regimens may require prophylactic growth factor support given their greater associated toxicities. Importantly, there has been no demonstrated survival advantage over single agents. Examples of combination chemotherapy regimens include the following:

- AIM (doxorubicin, ifosfamide, and mesna)
- AD (doxorubicin and dacarbazine)
- Gemcitabine and docetaxel (especially in leiomyosarcoma)

6.9 Progression After First-Line Chemotherapy for Metastatic Disease

After failure of first-line chemotherapy, agents approved for subsequent lines of treatment include pazopanib (for all subtypes except liposarcoma), trabectedin (for leiomyosarcoma and liposarcoma), and eribulin (for liposarcoma).

The phase III PALETTE trial demonstrated significantly prolonged median PFS with pazopanib, a multitargeted tyrosine kinase inhibitor, compared to placebo in

metastatic non-lipogenic STS refractory to anthracycline-based chemotherapy [50]. Trabectedin, an alkylating agent, was assessed in comparison to dacarbazine in the ET743-SAR-3007 randomized phase III trial, which showed improvement in PFS (4.2 vs 1.5 months) but relatively similar OS (13.7 vs 13.1 months) [51]. Eribulin improved OS compared to dacarbazine in previously treated or advanced STS with subgroup analysis indicating a significant benefit restricted to liposarcoma patients [52].

Additionally, drugs, such as ifosfamide or gemcitabine, may be used as single agents sequentially at the time of recurrence or progression. Notably, none of these agents increase OS, so clinical trials are certainly an appropriate option. Gemcitabine is active in refractory STS and has more clinical activity in leiomyosarcoma and angiosarcoma [53]. Other histologic preferences include paclitaxel in angiosarcoma (which can be used as first-line or salvage therapy) and ifosfamide in synovial sarcoma.

6.10 Summary

- Patients with high-risk STS of the extremity or body wall (i.e., size ≥5 cm and FNCLCC grades 2–3) should be considered for intensified treatment with CRT.
- Modern radiotherapy approaches with cytotoxic chemotherapy regimens (i.e., MAI) are associated with improved toxicity profiles compared to older regimens.
- Supportive care, such as G-CSF and antiemetics, had advanced the ability for patients to tolerate intensive regimens.
- Radiotherapy recommendations are provided in Table 6.2.

Table 6.2 Chemoradiotherapy recommendations

Dose regimens	• 50–50.4 Gy in 25–28 fractions • 28 Gy in 8 fractions
Technique	IMRT preferred
Image guidance	• Daily required • kV-kV may be used daily • CBCT (cone beam computed tomography) at least weekly
Target volumes	• GTV, gross tumor as defined by T1 contrast-enhanced MRI • CTV, 1–1.5 cm radial and 2–3 cm cranio-caudal expansion off GTV • PTV, 0.5–1 cm using daily image guidance
Organ at risk constraints	
Long bone (i.e. femur)	• V40 Gy <64% • Mean <37 Gy • 50 Gy isodose line does not encompass 100% of circumference of the bone
Skin strip	V20 Gy <50%
Joint	V50 Gy <50%

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Particle Therapy for Head and Neck Sarcomas

7

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Contents

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Abbreviations

CIRT	Carbon ion radiotherapy
IMCT	Intensity-modulated CIRT
IMPT	Intensity-modulated proton radiotherapy
KPS	Karnofsky performance scale
MFO	Multifield optimization
PBRT	Particle beam radiation therapy
PBS	Pencil beam scanning
PFS	Progress-free survival
SFO	Single-field optimization

7.1 Introduction

- Surgery is the most important modality of the treatment of sarcoma. Complete resection with sufficient margin(s) is one of the most important prognostic factors for long-term control of the disease. Radiation therapy plays an important role in the management of inoperable/unresectable as well as incompletely resected sarcomas. In addition, pre- or postoperative radiation therapy can improve local control for soft tissue sarcoma if clinically indicated.
- Many histological types of bone and soft tissue sarcomas are relatively resistant to photon radiotherapy. However, substantial escalation of radiation dose is usually not feasible due to the dose constraints of the surrounding organs at risk (OARs). Among all the regions, bone and soft tissue sarcomas occurring in the head and neck, retroperitoneum, and paraspinal area pose the most challenges to radiation oncologists due to their complex anatomy. Long-term control after conventional RT for unresectable sarcomas of these regions is uncommon [1, 2]. Although intensity-modulated radiation therapy (IMRT) may improve the therapeutic ratio, significant improvement in local control and overall survival as compared to three-dimensional conformal radiotherapy (3D-CRT) for sarcoma patients has not been confirmed.
- Accelerated charged particle (e.g., proton and carbon ion) beams have physical and biological characteristics that may benefit patients with resistant malignancies such as sarcoma that are not amenable to complete resection due to their complex anatomical background. Six different ions have been used for cancer treatment, but most patients have been treated with proton and carbon ions.
- Clinical evidence on the use of proton or carbon ion beam for sarcoma treatment is limited due to the rarity of the disease as well as the limited facilities available. In the past decade, the results of a few studies, most in retrospective fashion, have been published for sarcomas of the head and neck regions. Data on the use of PBRT for sarcomas occurring in other regions such as retroperitoneum, extremities, and paraspinal region are scarce. Therefore, this chapter will focus on the bone and soft tissue sarcomas of the head and neck regions. The indica-

tions covered include osteosarcoma, chordoma, and chondrosarcoma for which photon radiotherapy has limited application while PBRT has proven efficacy, as well as soft tissue sarcomas that need definitive or adjuvant radiotherapy.
- Although proton therapy has been widely used in the treatment of pediatric tumors, the use of carbon ion radiotherapy (CIRT) has not been proven safe and effective in pediatric patients. As such, discussion on rhabdomyosarcoma, largely a pediatric malignancy, is limited to proton therapy only.

7.2 Essentials of Particle Beam Radiotherapy

7.2.1 Characteristics of Charged Particle Beams

- The physical properties of accelerated charged particle (e.g., proton, helium, and carbon ion) beams offer several advantages for their use in cancer treatment: (1) the low entrance dose and minimal dose distal to the target and (2) the dose gradients at the distal and lateral sides of the targets are higher than with photon radiotherapy. Both features are important and result in a bigger dose gradient as compared to photon-based IMRT (Fig. 7.1). In addition, the relative biological effectiveness (RBE) of heavy ion (such as carbon ion with 12× mass of proton) increases with increasing depth; thus, treatment target(s) receive higher RBE dose than the tissues on the beam path. Both lateral and distal penumbra of carbon ion beams are sharper than those of proton beams because their larger mass results in less scatter.
- In addition to the physical properties, heavy ion beams have higher linear energy transfer (LET) and greater relative biological effectiveness (RBE) as compared to those of both photon and proton beams [3, 4]. The RBE of proton is estimated at 1.1–1.3 of photon, and ICRU (International Commission on Radiation Units and Measurements) 78 report is recommended to use a constant RBE of 1.1 for proton. Heavier charged particles are considered high-

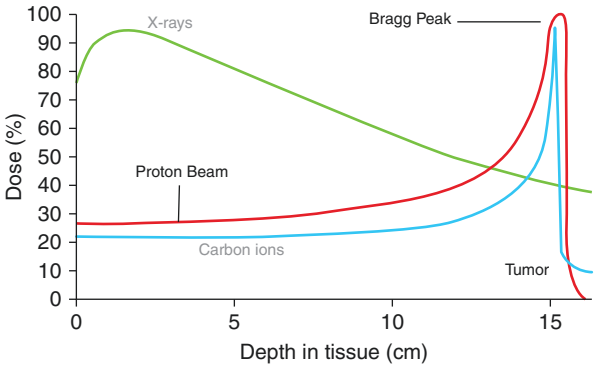

Fig. 7.1 Proton and carbon ion beam dose in the tissue. Dose release is low and nearly minimal before and after the "Bragg peak" for both proton and carbon ion beams

LET radiation. The calculation of RBE of carbon ion is far more complex, and ranges between 2 and 5 depend on factors such as cell/tissue types and fraction dose [5, 6]. Results from in vitro studies showed that up to 70% of the cell damage are induced by double-strand break after carbon ion radiotherapy (CIRT). Theoretically, PBRT is more biologically effective for radioresistant tumors such as chordoma, chondrosarcoma, and certain histological subtypes of soft tissue sarcomas.

- Both physical and biological features are important in the treatment of sarcomas especially those that occur in complex anatomical regions.
- Doses of PBRT are measured by Gy relative biological equivalents (Gy [RBE]) to account for the RBE differences of proton therapy or CIRT compared to photon-based radiation.

7.2.2 Delivery Technologies of PBRT

- Passive scattering (PS) is a conventional technology of PBRT and creates a large PBRT field size by scattering a focused particle beam. The details of the PS technologies such as single and double scattering or uniform scanning are out of the scope of this chapter.
- Pencil beam scanning (PBS) technology has become the new standard of PBRT technology and is capable of delivering highly conformal dose to any three-dimensional (3D) shape. PBS provides intensity-modulated PBRT by varying the position of each pencil beam and the number of particles delivered. Compared to passive scattering, PBS is capable of true three-dimensional dose painting and delivering conformal dose to a target volume in a single beam. In the treatment of head and neck malignancies, for example, it reduces target dose heterogeneity caused by significant tissue heterogeneity.
- There are two main approaches to PBS planning and delivery. In the single-field optimization (SFO) (a.k.a. single-field uniform dose [SFUD] in ICRU 78), each individual field uniformly covers a target. In the multifield optimization (MFO), the target coverage is achieved by the combination of all the fields (usually 2–4) included in the optimization. Both technologies can be used in the treatment of sarcomas of various parts of the body. The SFO delivers more robust plans, and MFO produces highly conformal plans but is also highly sensitive to motion and setup errors.

7.3 Registration and Planning

7.3.1 Patient Registration and Immobilization

- Patients with head and neck tumors are usually registered and immobilized in the supine position with individualized thermoplastic masks for PBRT. Planning CT scans without intravenous contrast from the vertex to the inferior margin of cla-

vicular heads should be performed at 1.5 mm slice thickness. It is important to use MRI-CT fusion for all patients prior to target volume delineation, as MRI is more superior than CT for defining soft tissue mass.

7.3.2 Definition and Delineation of Target Volumes

- For soft tissue sarcomas including rhabdomyosarcoma, the gross tumor volume (GTV) is defined as the gross tumor discovered on clinical examination or imaging studies. Definition of the clinical target volumes (CTVs) is similar to those of photon-based IMRT. For patients who received surgery and/or chemotherapy, the pretreatment tumor bed should be included for the CTV of high risk. The use of elective nodal irradiation (ENI) depends on the biological behavior of the histology diagnosis and the lymphatic drainage of the involved anatomical regions. However, most literatures do not recommend neck dissection or radiation unless necessary, that is, in patients with clinical adenopathy.
- For chordoma and chondrosarcoma patients, the GTV is defined as the gross tumor discovered on clinical examination or imaging studies. The CTV covering GTV (CTV_{gross}) include gross tumor with an expansion of 3–5 mm. A second CTV covering high-risk regions ($CTV_{high\ risk}$) should include all volumes at risk for microscopic disease, including any sites of residual microscopic disease and the tumor bed after surgery. The third CTV for lower risk ($CTV_{low\ risk}$) covers all areas at risk for microscopic disease. If the tumor invades the clivus, the entire clivus should be included in $CTV_{low\ risk}$. If the lower clivus is involved, inclusion of C1 can be considered in $CTV_{low\ risk.}$
- The planning target volume (PTV) of PBRT should consider both setup errors and range uncertainties of the particle beams. The lateral expansion of 2–3 mm is usually sufficient for setup errors. An additional margin of 2.5–3.5% of the beam range and an extra 1–3 mm is added to the distal and proximal edges of the CTV for range uncertainties. It is important to note that MFO fields are collectively considered for uncertainty mitigation.

7.3.2.1 Beam Directions

- Tissue inhomogeneity issues are significantly worse in particle beams than photon beam.
- Despite of the sharp distal penumbra and minimal dose distal to the target, one should avoid directing the beam toward any critical OARs, that is, PBRT field cannot range out into a critical structure. Moreover, anterior or anterior/oblique beams pass through the nasal cavity, or paranasal sinuses should be avoided if possible due to the heterogeneity of the structure and potential variation in air/fluid contents. Therefore, lateral and posterior/oblique fields are often used in PBRT for head and neck malignancies to avoid ranging into the brain stem and spinal cord.

7.3.3 Dose and Fractionation of PBRT

7.3.3.1 Soft Tissue Sarcoma and Osteosarcoma

- The dose/fraction regimen used in proton therapy for head and neck soft tissue sarcoma is similar to those used in IMRT. Definitive dose typically used ranges between 60 and 70 Gy (RBE) in conventional fractionation depending on the status of surgical margin and other prognostic factors. Higher dose is usually required for osteosarcoma (e.g., 70–75 Gy [RBE]).
- Due to the different facility and biological models used, the CIRT dose/fraction regimens used for both soft tissue sarcoma and osteosarcoma varied significantly among institutions. Two main regimens including 70.4 Gy (RBE) in 16 fractions (4 fractions per week) based on the MKM model and 63–70 Gy (RBE) in 18–20 fractions (5 daily fractions per week, using LKM) based on the LKM model have been suggested for most subtypes of soft tissue sarcomas of the head and neck.

7.3.3.2 Rhabdomyosarcoma

- Rhabdomyosarcoma is a relatively radio- and chemosensitive condition. The recommended dose of proton therapy for rhabdomyosarcoma of the head and neck is 54 Gy (RBE) in conventional fractions.

7.3.3.3 Chordoma and Chondrosarcoma

- For proton therapy for chordoma and chondrosarcoma, conventional fractionation is commonly used (i.e., 2Gy [RBE]/daily fraction), and the doses to CTV_{gross} and $CTV_{high\ risk}$ = 70–74 Gy (RBE) and $CTV_{low\ risk}$ = 54–60 Gy (RBE) are recommended. If complete resection is achieved, $CTV_{high\ risk}$ and $CTV_{low\ risk}$ can be treated to 66 and 54 Gy (RBE), respectively.
- Non-consensus on the CIRT dose has been concluded for chordoma and chondrosarcoma. The following dose/fraction regimens can be considered for CIRT under LEM: $CTV_{gross/high\ risk}$ = 70 Gy (RBE) and $CTV_{low\ risk}$ = 60 Gy (RBE) in 20 fractions using SIB technique can be considered for patients with incomplete resection. And $CTV_{high\ risk}$ = 63 Gy (RBE) and $CTV_{low\ risk}$ = 54 Gy (RBE) in 18 fractions can be considered for patients who achieved R1 resection.

7.3.4 Dose Constrains for Organs at Risk (OARs)

- The most important vital OARs in PBRT for head and neck tumors involve the central nervous system (CNS). Among them, optical nerve and chiasm, brain stem, spinal cord, and temporal lobes are of the most importance.
- The dose constrains for these organs and tissues are listed in Table 7.1 for both proton and carbon ion beam therapies. It is important to note that the dose/fractionation of CIRT used in the treatment of head and neck sarcomas differs significantly from center to center. Most of the Japanese particle therapy centers use a hypofractionation scheme (i.e., 16 fractions or less at ≥3.2 Gy [RBE]/daily

Table 7.1 Dose constrains of vital organs at risk involved in PBRT for head and neck tumors [7]

OAR	Clinical manifestation	Dose in Gy (RBE) for proton therapy[a]	Dose in Gy (RBE) for CIRT[a]
Each optic nerve and chiasm	Visual impairment	$D_2 < 60$	$D_2 < 40$
Brain stem	Radiologic or clinical evident adverse effects	$D_{surface} < 63$ $D_{center} < 50$	Dmax < 40
Spinal cord	Same as above	$D_{surface} < 67$ $D_{center} < 55$	No specific data Dmax < 30[b]
Temporal lobe	MRI evident necrosis	$D_2 < 71$	$D_{2cc} < 68.8$

Abbreviations: D_2 Dose to the 2% of the volume, D_{surfae} Dose to the surface of the structure, D_{center} Dose to the center of the structure, D_{max} Maximum dose

[a]Conventional fractionation (at 1.8 or 2 Gy RBE) is the standard for proton therapy; hypofractionation (at >3 Gy RBE) is commonly used for CIRT

[b]Dose constraint used at the NIRS and SPHIC

fraction, 4 fractions/week, MKM model). However, the centers in China, Germany, and Italy (all with LEM model) use 3.0 Gy (RBE)/daily fraction and five fractions/week. As such, the listed dose constraints should be used with caution, and clinical judgment should be applied in practice.

7.3.5 Reirradiation

- For patients who failed previous radiation therapy, the old plans need to be obtained, and the doses to the organs at risk (OARs) should be identified. Recovery from previous radiation therapy (≥1 year prior to the recurrence) can be set at 70%, regardless of the latent time between the two courses of radiation [8].
- Salvage PBRT for locally recurrent sarcomas usually covers only the GTV with an expansion (e.g., 3–5 mm) to generate a CTV_{gross} without prophylactic irradiation to the subclinical areas.
- Proton therapy to a total dose of >60 Gy (RBE) in conventional fractionation can be considered for both chordoma/chondrosarcoma and soft tissue sarcomas (rhabdomyosarcoma excluded). CIRT to 63 Gy (RBE) in 21 fractions have been reported with few severe adverse effects and acceptable disease control and patient survival. However, no consensus has been reached for salvage CIRT re-irradiation.

7.3.6 Setup Verification

- Setup accuracy can be confirmed with daily orthogonal X-ray using bony landmarks as reference. We recommend weekly verification CT scans typically started after the second week of the radiation course to assess for changes in anatomy and decide on the need of replanning.

7.4 The Use of Chemotherapy with PBRT

- Whether chemotherapy should be used in concurrent with PBRT has not been investigated in a prospective fashion. Due to the similarity of RBE between proton and photon beams, the use of concurrent chemotherapy with proton therapy can follow the current protocols of IMRT for individual sarcoma subtypes.
- Currently, no evidence supports the use of chemotherapy in concurrent with CIRT for any types of bone or soft tissue sarcoma. Patients should be encouraged to participate relevant clinical trials if available.

7.5 Clinical Outcomes

7.5.1 Soft Tissue Sarcomas and Osteosarcoma

- Only few retrospective studies reported the outcomes of head and neck sarcomas after definitive PBRT. The results of a single-arm perspective study of 24 patients from the NIRS, Japan, CIRT to 70.4 Gy (RBE) in 16 fractions (4 fractions per week) produced 3−/5-year local control and overall survival rates of 91.8/80.4% and 74.1/57.6% for patients with osteosarcoma and soft tissue sarcomas [9]. In our experience of 51 patients with soft tissue and bone sarcomas, 17 patients had soft tissue sarcomas other than rhabdomyosarcoma. The two-year OS and LC for radiation-naïve patients were 100% and 83%, respectively [10]. Toxicities reported in both studies for radiation-naïve patients were acceptable.
- A retrospective study from the Massachusetts General Hospital on proton therapy for osteosarcoma used 68.4 CGE for 55 (including 27 head and neck osteosarcoma) patients. The five-year local control and overall survival rates were 72% and 67%, respectively. Severe toxicities (grades 3–4) were observed in 30.1% of the patients [11]. A few additional reports on CIRT for soft tissue sarcoma and osteosarcoma of various anatomical regions used doses ranged from 52.8 to 73.6 Gy (RBE). The 3−/5-year local control and overall survival rates of 68–73%/65–79% and 46–60%/46–52% were reported [12–14].
- A typical treatment plan (a patient with locally advanced pleomorphic sarcoma of the nasopharynx) is shown in Fig. 7.2.

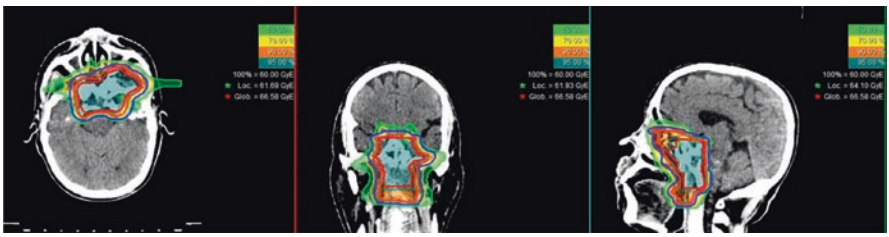

Fig. 7.2 A typical intensity-modulated CIRT treatment plan of a patient with locoregionally advanced soft tissue sarcoma of the nasopharynx

7.5.2 Rhabdomyosarcoma

- Dosimetry study that compared proton vs. IMRT revealed more superior OAR spearing by proton therapy [15]. According to the two recently published experiences, the reported five-year local control rates approached 80%, and the five-year overall survival rates ranged between 75 and 80% in patients treated with proton therapy using PBS technology [16, 17]. Furthermore, treatment-associated toxicity after proton therapy is moderate, and less than 20% of patients experienced grade 3 late toxicities.
- The abovementioned outcomes appeared to be improved than the historically reported five-year OS rate of 65% after conventional treatment.

7.5.3 Chordoma and Chondrosarcoma

- Approximately one-third of the chordoma and chondrosarcoma cases originate from the head and neck (base of the skull and cervical spine), and surgery is the primary modality for their treatment. However, due to the complexity of the anatomy, en bloc resection which is usually required for long-term disease control is challenging. Patients with R1 or R2 resection usually suffer from local or regional recurrence after surgery.
- Results after photon-based IMRT adjuvantly to surgery are suboptimal due to, at least in part, insufficient radiation dose to the tumor volume(s) as well as the relative radioresistance of the disease. The vital OARs close to the disease foci including the spinal cord, brain stem, optic nerve, and chiasm substantially limit the potential of escalation of radiation dose required for disease control.
- Both proton and carbon ion beam radiotherapies have been investigated for the management of chordoma and chondrosarcoma of the base of the skull and cervical spine. Although all studies were of retrospective nature, the local control and overall survival after adjuvant or definitive PBRT showed substantial improvement as compared to histological data. Based on the literatures published in the past decade, the five-year local control and overall survival rates range between 75–80% and 75–90%, respectively, for chordoma after either proton therapy or CIRT [18–27]. And those rates for chondrosarcoma were universally >90% for both five-year LC and OS after PBRT [18–22, 28–32].
- Unfortunately, for patients who experienced recurrence after surgery, especially after previous course of adjuvant radiotherapy (e.g., IMRT or gamma knife), the local control is nearly halved after salvage PBRT. Therefore, it is highly recommended to provide adjuvant PBRT as part of the initial effort of definitive therapy.
- The efficacy of proton vs. carbon ion beam for chordoma or chondrosarcoma has not been addressed in any prospective clinical trials, although no difference was reported in retrospective studies [32, 33]. A randomized clinical trial is currently ongoing at our institute to compare the effectiveness of proton vs. carbon ion beams for chordoma/chondrosarcoma patients with residual gross disease.

7.6 Future Direction

- PBRT may improve the therapeutic ratio in the treatment of head and neck bone and soft tissue sarcomas due to its physical and biological advantages. However, due to the limited available clinical evidence, future research, preferably in the prospective fashion, should be performed to understand the efficacy of PBRT, the difference between CIRT and low-LET radiation modality (e.g., proton therapy), and the use of combined chemo-PBRT in the management of head and neck sarcomas.
- In addition, the optimal dose/fraction regimens of CIRT for various subtypes of sarcomas should be a focus of investigation as well, especially in the radioresistant subtypes.

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Desmoid Tumors

8

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8.1 Introduction

Desmoid tumor, also known as aggressive fibromatosis or formerly as fibrosarcoma grade I of the desmoid type, is a locally aggressive neoplasm caused by mesenchymal hyperplasia with locally infiltrative capacity. It accounts for approximately 3% of all soft tissue tumors with an incidence of 2–4 per million per year [1]. It can be localized or multicentric and can involve any mesenchymal tissues including those of mesentery and retroperitoneum, the breast, bone, meninges, and central nervous system. Common sites include the trunk and abdominal wall, extremities, and abdomen. Symptoms can vary depending on the location and disease extent. Most present as a deeply seated, slowly growing tumor with minimal symptoms. Intra-abdominal tumors, however, can present with serious intestinal complications. Although desmoid tumors are benign with negligible metastatic potential, they can cause significant morbidity due to infiltration of nearby organs, mass effect, and a high rate of local recurrence.

The majority of desmoids are sporadic and associated with a *CTNNB1* mutation [2]. The *CTNNB1* gene encodes a protein called β-catenin, and its mutation was identified in 92.4% (133 of 144) of sporadic desmoid tumors in a genetic sequencing study [3]. Non-sporadic or hereditary-type desmoids constitute 5–15% of desmoids and are commonly attributed to familial adenomatous polyposis (FAP), an autosomal disorder caused by mutation of the *APC* gene. Approximately 15% of individuals with Gardner's syndrome, a subgroup of FAP, are found to develop desmoids. The cumulative risk of developing desmoids in FAP patients is 20.6% at age 60, and most FAP-associated desmoids arise in the abdominal wall or within the abdomen [4, 5]. Other risk factors include history of antecedent trauma such as surgery at the tumor site and family history. High estrogen state during and after pregnancy has also been suggested as a risk factor, especially for intra-abdominal desmoids, although controversial given antecedent trauma caused pregnancy and delivery is a confounder [6, 7].

Nearly all desmoids show increased β-catenin expression although the exact molecular mechanism is still under investigation. Inactivation of *APC* gene, for example, leads to accumulation of intracellular β-catenin [8]. An overexpression of β-catenin alone was able to cause desmoids in a mouse model [9]. Increased expression of β-catenin during wound healing may therefore explain the mechanism of antecedent trauma as a major risk factor. The *Wnt*/β-catenin signaling pathway is known to play the most crucial role in the molecular pathogenesis of desmoids. Molecular studies have shown that overexpression of *WISP2* of *Wnt*/β-catenin signaling pathway and *NOTCH1* and *HES1* of the Notch signaling pathway may be linked in pathogenesis of desmoid tumors [10–12]. In addition, JAK/STAT, PI_3 kinase/AKT, mTOR, hedgehog, and the estrogen growth regulatory pathways, as well as genetic alterations including mutations in *AKT1*, *BRAF*, *TP53*, trisomies 8 and 20, chromosomal loss of 6p, loss of 5q, and gain of 20q, have been associated with pathogenesis of desmoids [13, 14].

Treatment options include observation, local therapy, and systemic therapy. Surgery has been the primary therapeutic modality for treatment of desmoids, and

radiation therapy has played an important role both as an adjuvant therapy to improve local control and as a definitive therapy for inoperable or incompletely resected cases. When both surgery and radiation therapy are not an option due to comorbidities or nearby critical structures, cryoablation as a local therapy or systemic therapy can be considered [15]. Systemic therapy has traditionally played a limited role and includes hormonal, nonsteroidal anti-inflammatory drugs (NSAIDs), cytotoxic chemotherapy, and targeted therapies. Targeted therapies such as imatinib and sorafenib have shown some efficacy and are becoming an important modality with emerging insight into the molecular pathogenesis of desmoid tumors [16].

8.2 Management Principles

8.2.1 Workup

Workup needs to be tailored depending on patient presentation and the location of the tumor. History and physical examination should screen for symptoms and signs of local invasion, mass effect, and FAP or Gardner's syndrome. CT or MRI is needed to assess the extent of the tumor before determining optimal management. MRI is preferred over CT for its superior soft tissue delineation to better assess surgical resectability or delineate target and normal tissues for radiation therapy. MRI is particularly helpful for desmoids of the extremity and trunk. Desmoids appear hypo- or isointense to the muscle on T1-weighted sequences, mildly enhance with gadolinium, and mostly appear hyperintense to the muscle on T2-weighted sequences. Desmoids appear hypoechoic to the fat and adjacent muscle on ultrasound, and areas with a high amount of collagen show a fibrillar hyperechoic pattern. Ultrasound may confer additional information particularly for desmoids of the chest or abdominal wall.

Regardless of imaging of choice, there are no pathognomonic radiologic features of desmoids, and histopathologic confirmation is necessary to distinguish from malignant soft tissue tumors. Incisional biopsy provides greater amount of the tissue than core needle biopsy, increasing the probability of histologic accuracy. However, it should be performed by a surgeon with experience with soft tissue tumors to avoid contamination of tissue planes. Fine needle aspiration cytology can provide a tentative diagnosis and can be used when invasive biopsy is contraindicated. Desmoids display a monoclonal fibroblastic proliferation as a group of spindle cells in fibrous stroma. Desmoid cells show infiltrative appearance of the connective tissue without nuclear characteristics of malignancy such as high nuclear-cytoplasmic ratio. Immunohistochemistry often shows a strong positivity to nuclear β-catenin, vimentin, and smooth muscle actin and negativity to desmin, cytokeratin, and S-100. PCR (polymerase chain reaction) sequencing for detection of *CTNNB1* mutation has shown high sensitivity when immunohistochemistry is insufficient to distinguish desmoids from other diagnoses. Differential diagnoses include superficial fibromatosis, reactive fibrous lesions secondary to inflammation, leiomyoma, solitary fibrous tumor, gastrointestinal stromal tumor, fibrosarcoma, and synovial sarcoma.

Colonoscopy should be considered to screen for FAP for patients with an intra-abdominal desmoid or risk factors based on family history. Multidisciplinary tumor board discussion is recommended for evaluation and management for all cases if possible and particularly for complex tumors, unfavorable sites, and recurrences.

8.2.2 Observation

Desmoids show a wide range of clinical behaviors from spontaneous regression to rapid extensive local growth with invasion of adjacent organs. Both retrospective and prospective studies have shown 20–30% rate of spontaneous regression, and one retrospective study showed that 16% of those on surveillance had complete resolution without any treatment [17–19]. Watchful waiting can therefore be recommended for asymptomatic patients with radiologically stable tumors, especially if high surgical burden is anticipated. Watchful waiting can be either observation alone or with tamoxifen and/or NSAIDs. A recent population-based study which looked at 111 patients without FAP showed that only 42% of those who underwent watchful waiting progressed with median progression-free survival of 10 months (median follow-up: 35 months) [20]. The outcome was similar for the subgroup of abdominal wall desmoids, although there was a trend toward decreased recurrence after surgery.

8.2.3 Surgery

Wide local excision with adequate negative margin is the historical standard treatment for progressive or symptomatic desmoids. However, up to half of patients with surgery alone develop local recurrence and may require additional treatment [21, 22]. For example, a retrospective review of 122 surgery alone cases showed a relapse rate of 34% and 38% at 5 and 10 years, respectively [23]. High recurrence rate is often attributed to difficulty in achieving wide margin for cosmesis and/or preservation of function. Although multiple studies have identified positive margin as a predictor of local failure, adjuvant therapy is not routinely recommended with resection with negative or close margins due to lack of level 1 evidence [24, 25].

Function-sparing or incomplete resection can be performed if excessive morbidity is anticipated to achieve complete resection and adjuvant radiation can be offered or with a palliative intent in the setting of mass effect. Re-resection should be considered, if technically feasible, for grossly residual or recurrent tumor before proceeding with adjuvant or salvage radiation therapy.

8.2.4 Radiation Therapy

Radiation therapy is an effective primary and adjunct therapeutic option and can be recommended for desmoid tumors of the extremity, superficial trunk, or head and neck. Radical radiation therapy is indicated in the setting of inoperable tumor, poor

surgical candidacy, or patients who decline surgery. Neoadjuvant radiation therapy can be utilized to improve resectability by cytoreduction and to improve local control and can be especially beneficial for extra-abdominal desmoids. Unlike neoadjuvant radiation therapy for soft tissue sarcoma, neoadjuvant radiation therapy for desmoids has not been associated with an increased risk of wound dehiscence or other acute wound complications [26].

Both radical and adjuvant radiotherapies have been used to treat primary and recurrent desmoids for decades with good long-term outcome of approximately 78% of local control per a systematic review [27]. Interestingly, several studies have shown that there is no statistically significant difference in the rate of local control between definitive RT and combination of surgery and radiation therapy [28–30]. For example, a retrospective study of 115 patients treated with radiation therapy with a 10.1 years of median follow-up showed that there was no significant difference in local control rate between the two groups, 75% and 74% at 5 and 10 years, respectively [28]. Radiation was given to a median dose of 56 Gy for those who received radiation therapy alone and 50.4 Gy for those who underwent combination of surgery and radiation therapy. A recent meta-analysis showed a local control benefit of adjuvant radiation therapy for positive or indeterminate margins for both primary and recurrent tumors (RR 1.54 and 1.60 for primary and recurrent setting, respectively, treated with surgery alone versus surgery and adjuvant radiation therapy) [31].

Dose response of desmoids has been an area of controversy, and although 56 Gy is commonly used for definitive RT, an optimal dose in this setting remains a question to date. Some retrospective studies observed a positive dose response with a superior local control of greater than 80% with doses 60 Gy or higher, whereas others have reported that a dose of greater than 56 Gy was associated with increased toxicity with no difference in local control [22, 28, 32, 33].

8.2.5 Systemic Therapy

There is no established role for routine use of systemic therapy either in the setting of primary or recurrent desmoids due to lack of high-level evidence. Conventional chemotherapy, such as doxorubicin, methotrexate, and vinblastine, has showed some efficacy in unresectable or recurrent cases when other modalities have failed [34–36]. Hormonal therapies such as tamoxifen +/− sulindac, toremifene, and progesterone have been associated with tumor control in approximately 50% of patients and have been used in the setting of watchful waiting or recurrent disease [37, 38]. Other agents that have shown some benefit in retrospective studies include nonsteroidal anti-inflammatory drugs such as celecoxib; low-dose chemotherapy regimens such as methotrexate, vinblastine, methotrexate, and vinorelbine; doxorubicin-based regimens; immunotherapy such as interferons; and targeted agents such as imatinib and sorafenib. For example, results from the French Sarcoma Group following 62 patients showed 1.6% and 19.4% complete and partial responses, respectively, with the median follow-up of 71.3 months. There was a higher rate of

response with anthracycline-containing regimens, methotrexate and vinblastine being the most common regimens [39].

Imatinib is a tyrosine kinase inhibitor that has shown efficacy for multiple mesenchymal neoplasms in addition to chronic myelogenous leukemia and gastrointestinal stromal tumors. It has been tested for unresectable and recurrent desmoids for nearly two decades. A phase II trial evaluating the efficacy of imatinib initiated by the Sarcoma Alliance for Research through Collaboration showed an objective response rate of 6% and 1-year progression-free survival of 66% among 51 patients with unresectable desmoids [40]. A long-term follow-up of another phase II trial by the French Sarcoma Group in the setting of unresectable and progressive desmoids showed objective responses at a short-term follow-up, and the two-year progression-free survival was 55% [41]. Another phase II trial by the German Interdisciplinary Sarcoma Group showed that imatinib treatment was associated with 65% progression arrest rate after 6 months and that the progression arrest rate after 6 months of imatinib treatment was higher in patients with *CTNNB1* mutations [42, 43]. Patients who progress on imatinib treated with nilotinib showed a progression arrest rate of 88% at 3 months.

Sorafenib was compared to placebo in a randomized double-blind phase III trial of 87 patients with progressive, symptomatic, or recurrent desmoid tumors. At a median follow-up of 27.2 months, progression-free survival was 81% in the sorafenib group versus 36% in the placebo group. The objective response rate was 33% with sorafenib versus 20% with placebo [44].

8.2.6 Follow-Up Guidelines Based on Recurrence Patterns and Prognosis

Follow-up assessment should include monitoring of symptoms and functional status with multidisciplinary approach involving occupational and physical therapy. Imaging can be repeated every 3–6 months for the first 2–3 years and every 6–12 months afterward. Time to regression after RT is often protracted, and regression may take several years [45]. The role of long-term follow-up beyond 5 years is controversial given the small difference between the recurrence rates at 5 and 10 years [23, 28].

8.2.7 Management of Recurrent Disease

As discussed above, recurrence is observed in up to 50% of desmoid patients who undergo surgery alone and in approximately 20% of patients who receive definitive or adjuvant radiation therapy. Apart from positive surgical resection, young age, male gender, size, and extremity location were shown as negative prognostic factors [19, 46]. Treatment options should be discussed at a multidisciplinary sarcoma tumor board. Management of choice for recurrence would depend on the previous treatment; tumor characteristics including location, extent, and natural history; nearby normal tissues; and patient comorbidities. If feasible without significant risk of morbidity, repeat resection can be considered as the first step. If not previously

irradiated, re-resection followed by radiation therapy or salvage radiation therapy to 50–56 Gy can be offered and may confer a higher rate of local control than surgery alone. For retractable recurrence or recurrence after radiation therapy, systemic therapy or enrolling on a trial can be considered.

8.3 Radiation Therapy Techniques and Planning

8.3.1 Simulation

Whether delivered as primary therapy or as an adjunct to surgery, the principles of radiation therapy simulation/setup are similar to those for soft tissue sarcomas. The treatment area should be immobilized in as reproductible a position as possible, taking into consideration motion, rotational variation, and the possibility of radiation exposure to other normal structures (such as an unaffected limb for extremity tumors). For extremity tumors, setup devices may include a Vac-Lok or alpha cradle. Contralateral limbs should also be immobilized in a reproducible position to ensure that they do not move into the path of treatment beams. Distal extremity tumors can be immobilized using a supporting device such as a customizable headrest paired with covering device (such as an Aquaplast mask). This limits rotational setup variation. Thoracic and abdominal tumors may be immobilized with the arms raised to move them away from the treatment field.

8.3.2 Treatment Volumes

There is no established standard for target volume definition. Most radiation therapy series describe the use of wide margins to prevent a marginal recurrence. Early papers describe margins on the order of 5–7 cm. The authors recommend contouring GTVs based on a combination of CT and MRI with CTV expansions of 2.5–4 cm. Tumors often enhance with IV (intravenous) contrast and can be

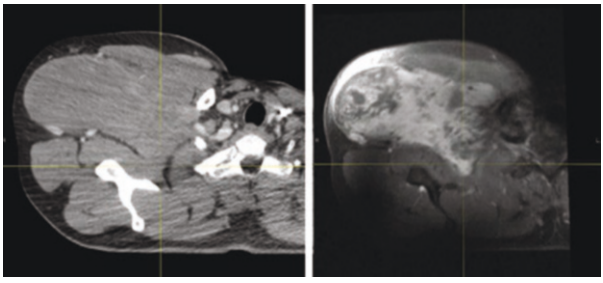


Fig. 8.1 Axial CT- and T1 gadolinium-enhanced images of an unresectable right shoulder desmoid tumor involving the brachial plexus. MRI was performed in treatment position and fused to the planning CT to assist with target delineation. The medial borders of the enhancing tumor are more clearly visible on the MR images

visualized on contrast-enhanced CT- and T1-weighted MR sequences. Image fusion with MRI is helpful in delineating tumor margins (see Fig. 8.1). In general, CTV expansions do not need to extend through fascial planes although the fascial plane itself should be included as desmoids may grow along these planes.

8.3.3 Treatment Techniques

Radiation therapy treatment techniques will vary based on anatomic considerations of the target volume. For well-lateralized lesions, three-dimensional conformal radiation therapy may be appropriate. For tumors in close proximity to normal structures, IMRT (intensity-modulated radiation therapy) may be appropriate. Specialized techniques such as proton therapy may be used in unusual cases involving prior radiation.

8.3.4 Dose

Radiation therapy may be delivered as an adjunct to surgery (either pre- or postoperatively) to a dose of 50–50.4 Gy in 1.8–2 Gy fractions. When delivered as definitive therapy, radiation is typically delivered to a dose of 56 Gy with conventional fractionation [32].

8.3.5 Dose Constraints

Radiation therapy dose constraints for adjacent organs at risk follow standard QUANTEC guidelines. Treatment of abdominal wall desmoids may require consideration of dose to intra-abdominal organs such as the bowel, bladder, liver, and kidneys. Additionally, for patients of reproductive age who wish to preserve fertility, consideration should be given to means of limiting dose to the uterus, ovaries, or testes (see Fig. 8.2). For extremity tumors, a normal tissue strip should be spared to

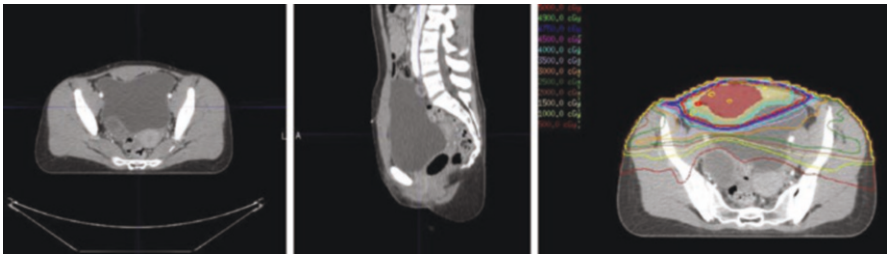
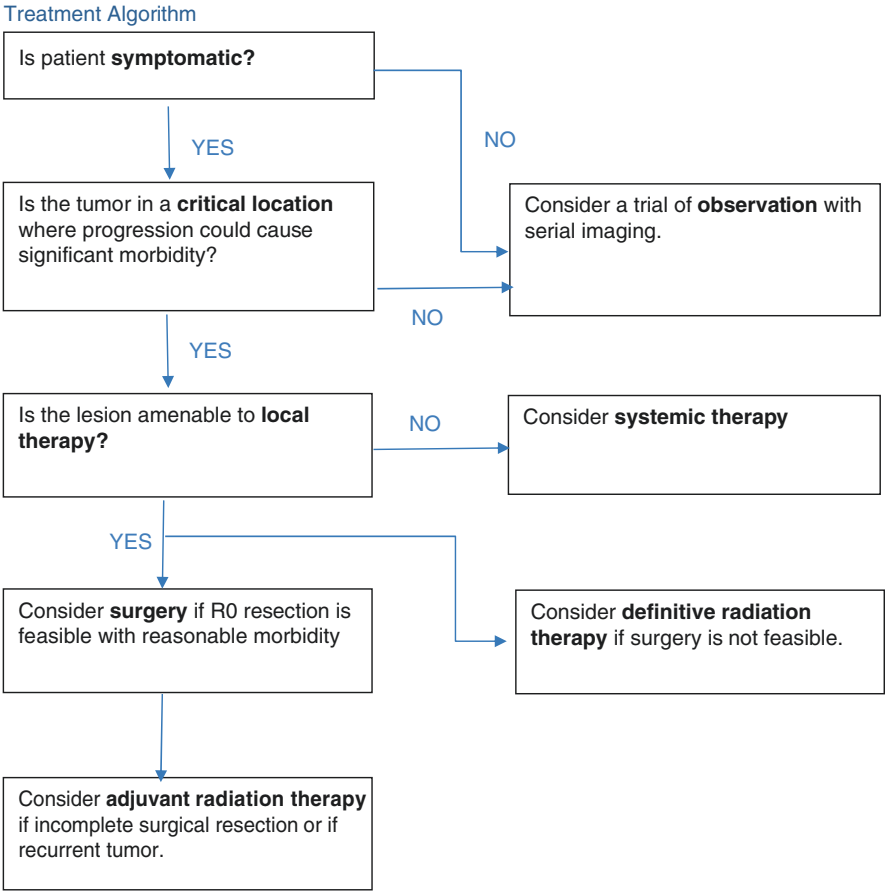


Fig. 8.2 This is a premenopausal woman who received radiation therapy and surgery for a recurrent abdominal wall desmoid tumor. The patient was instructed to drink a set volume of water 1 h prior to radiation every day to maintain a full bladder to displace the uterus and ovaries posteriorly to preserve fertility. The patient was able to become pregnant several years after completing treatment

reduce the risk of lymphedema. Similarly, the contralateral limb should be contoured and immobilized in a stable position that minimizes dose to the nontarget tissue.

8.4 Treatment Algorithm



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Solitary Fibrous Tumors/ Hemangiopericytoma

9

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9.1 Introduction

Solitary fibrous tumors (SFTs) are a rare histopathologic entity characterized as spindle cell mesenchymal neoplasms [1] and account for <2% of soft tissue sarcomas [2]. This class of tumors is comprised of both benign and malignant neoplasms found in three classic locations: (1) intrathoracic/pleural, (2) intracranial/meningeal, and (3) extrathoracic/soft tissue [3]. However, SFTs may occur in any part of the body and have been identified all throughout, including within the pleura, lung, mediastinum, sella, meninges, pelvis, retroperitoneum, abdomen, and head and neck. Included in the classification of SFTs is hemangiopericytoma (HPC), which is defined as a type of benign neoplasm derived from the pericytes lining the endothelium of smaller vessels. HPCs were initially regarded as a separate subgroup of fibrous-type tumors; however, in the updated 2016 World Health Organization (WHO) classification system, they became included as a type of SFT after it was noted that their behavior mimicked that of other solitary fibrous tumors [4]. At present, the term SFT is preferred [5, 6] to describe this class over tumors over simply "hemangiopericytoma" given the evolving changes in nomenclature, with SFTs as a tumor incorporating HPCs within their definition. The differences in clinical manifestations, diagnostic evaluation, and treatment of SFTs are guided largely by their anatomic location.

9.1.1 Nomenclature and Historical Perspective

The first well-documented case of SFT was in 1931 by Klemperer and Rabin, who noted a distinct entity of pleural-based tumors felt to be of mesothelial origin [7]. Following this initial conception, SFTs have historically been regarded with names implying a mesothelial line of differentiation, such as "solitary fibrous mesothelioma" and "submesothelial fibroma." As SFTs were increasingly studied using immunohistochemical staining and analyses, it became increasingly apparent that SFTs largely originate from fibroblastic cells, many of which reside in tissue lacking in mesothelium. SFT is now recognized to occur anywhere in the body, including soft tissue and viscera, albeit with an unusual predilection for body cavity sites/deep soft tissues, including the pleura, peritoneum, and dura of the meninges. Later on in 1942, the term "hemangiopericytoma" was coined by Stout and Murray and described as a highly vascular and malignant soft tissue tumor arising from "Zimmerman's pericytes" and affecting the retroperitoneum and gluteal area [8].

Thirteen years later in 1954, Begg and Garrett identified the first intracranial hemangiopericytoma (HPC), which had previously been regarded as an "angioblastic meningioma" [9]; however, the reclassification of "angioblastic meningiomas" to intracranial HPCs did not officially take place until a WHO revision in 1993.

9.1.2 Epidemiology and Clinical Manifestations

Although SFTs may arise at any age, they are most common in the fifth to seventh decades. Meningeal tumors arise in slightly younger patients (fourth decade), while pleural SFTs often present in older patients (sixth to seventh decade, median age at diagnosis 56–60) compared with SFTs arising intraabdominally or in soft tissue [5, 6, 10]. Both male and female genders are affected with equal frequency except for intracranial SFT/HPC that exhibits a slight male predominance. There is no known association with environmental exposure to radiation, tobacco, asbestos, or other toxicants and no known inherited, predisposing risk factors.

9.1.2.1 Pleural/Intrathoracic SFTs

In contemporary series, approximately 30% of cases arise in the thoracic cavity (including pleura, lungs, and mediastinum). Intrathoracic SFTs may arise in the pleura, mediastinum, or lung parenchyma. Pleural SFTs are benign in approximately 80% of cases and typically affect adults age 50–70 with an equal predominance of males and females affected [3]. The visceral pleura is more commonly affected than the parietal pleura, following a 2:1 ratio [3]. Unlike other thoracic tumors such as primary bronchogenic carcinomas or mesothelioma, there is no established relationship between the development of SFTs and exposure to classic environmental risk factors, such as tobacco or asbestos [3]. Patients will typically manifest with symptoms of cough, dyspnea, and pleuritic chest pain at the time of diagnosis, which is how the intrathoracic SFT is generally discovered. Rarely, an intrathoracic SFTs causing airway compression may manifest with symptoms of obstructive pneumonitis or hemoptysis. Additional clinical manifestations of intrathoracic SFTs are sequelae of their associated paraneoplastic syndromes, as paraneoplastic syndromes are most commonly associated with intrathoracic/pleural SFTs; these include pulmonary osteoarthropathy (Pierre-Marie-Bamberger syndrome) and paraneoplastic hypoglycemia (Doege-Potter syndrome) [11, 12].

Pierre-Marie-Bamberger syndrome is characterized by disabling arthralgias/arthritis with possible additional findings of digital clubbing, tubular bone periostosis, and synovial effusion development [11]; this syndrome is associated with other pulmonary diseases, including bronchogenic carcinoma and pulmonary tuberculosis, and is felt to be mediated by increased production of hyaluronic acid [13]. Doege-Potter syndrome is characterized by life-threatening hypoglycemia mediated by increased production of insulin-like growth factor II (IGF-2) by the SFT [12]. Reports have historically indicated that the incidence of Pierre-Marie-Bamberger syndrome is about 7–20% among intrathoracic SFTs, with Doege-Potter syndrome being less common and having an incidence around 2% [14]. However, updated

literature has found that the incidence of Doege-Potter syndrome among SFTs may be higher than previously published and ranges from 5–10% [12]. Paraneoplastic syndromes are more likely to manifest in patients afflicted with malignant SFTs than benign SFTs [15].

Local recurrence and distant metastasis rates for intrathoracic SFTs depend largely on whether the tumor is benign or malignant, and this, in turn, is largely determined by the tumor's histopathologic features, including Ki-67 proliferative index and presence of fibroblast growth factor (FGF) [16]. (Tumor histopathology will be discussed in greater detail in the diagnostic evaluation portion of this chapter.) It is estimated that 15–20% of patients will develop local recurrence, and even benign tumors may recur locally and transform into malignant tumors [17]. Studies have estimated overall local recurrence rates at several-year follow-up ranging 3–5% for stage 0/1, 14–52% for stage II, and 63–71% for stage III disease [18, 19]. The metastasis rate has been reported to range 35–45%, with metastases sometimes occurring up to 20 years following curative intent therapy [20]. Clinicians reporting these recurrence and distant metastasis rates have suggested that differences in recurrence patterns were more often attributed to histopathologic features and extent of R0 resection rather than anatomic pattern or location [18].

9.1.2.2 Hemangiopericytoma

Hemangiopericytomas (HPCs) may be found in any tissue but have been most frequently studied and described within the central nervous system (CNS). CNS hemangiopericytomas account for <1% of intracranial tumors and about 2.5% of meningeal tumors [21, 22]. These neoplasms commonly affect individuals in their 40s, with the two most frequently identified patient populations being males younger than age 45 and older females [23]. HPCs are most commonly identified as dural-based and supratentorial tumors [24]; the most common locations identified, in order of decreasing incidence, are the tentorium cerebelli, frontal convexity, cerebellopontine angle, ventricles, and falx cerebri [25]. Symptoms associated with these tumors occur secondary to mass effect with compression of nearby structures or increased intracranial pressure and may include headache, gait abnormalities, sensorimotor deficits, cranial nerve dysfunction, nausea/emesis, and altered mental status/confusion.

Intracranial HPCs are automatically classified as WHO grade II (low grade) or WHO grade III (high grade, if anaplasia is noted on pathology), as they tend to be more aggressive given their increased tendency to recur locally as well as spread distantly [24]. Among intracranial HPCs, even lower-grade tumors (grades I–II) may demonstrate high local recurrence rates following gross total resection [26], and meta-analysis data has demonstrated a significantly higher risk for local recurrence as opposed to distant intracranial metastases and extracranial metastases [23]. Even then, the distant metastatic rate at 15 years has been reported to be as high as nearly 65% [22]. The most common sites of distant metastases reported include the lungs, bone, liver, subcutaneous tissues, and pleura [23]. The mean time to distant metastases reported in the literature is about 7.5 years, indicating that the tumor often spreads late in its disease course, and some patients may experience the

development of distant metastases at 10–15 years following their initial course of curative intent therapy [23].

9.1.2.3 Extrathoracic/Soft Tissue SFTs

While most frequently identified within the thorax or skull, SFTs may be diagnosed anywhere throughout the body and affect all mesenchymal tissues. Other common sites of extrathoracic and extracranial SFTs, in decreasing order of frequency, are the lower extremities, pelvis, and head and neck [16]. SFTs in these locations most commonly present as a painless mass and otherwise are diagnosed based on the onset of symptoms secondary to local invasion of nearby structures (e.g., development of hematuria in the setting of a renal HPC or facial pain in a patient with newly diagnosed SFT of the head and neck). Similar to intrathoracic and intracranial SFTs, extrathoracic/soft tissue SFTs have a predilection toward local recurrence and late distant metastases. Studies on extrathoracic SFTs have been mostly limited to single-institution case reports, often reporting an incidence of <100 cases over 15 years of the described tumor [27, 28].

9.2 Diagnosis

9.2.1 Initial Evaluation

There is a broad differential for SFTs based on their anatomic location, as clinical manifestations and symptoms are frequently triggered by mass effect of the lesion as it grows in its respective tissue. Pleural SFTs should be considered in the differential diagnosis of intrathoracic tumors in elderly adults, particularly those with no known smoking history or other environmental risk factors for the development of other thoracic neoplasms. For patients experiencing headache, neurologic deficits, or other symptoms suggestive of the presence of an extra-axial lesion yielding mass effect, the differential diagnosis includes intracranial HPC as well as meningioma, dural metastasis, dural lymphoma, neurosarcoidosis, and gliosarcoma [25]. As with diagnosing any neoplasm, diagnostic workup begins with a thorough history focusing on character and duration of symptoms followed by a comprehensive physical exam. Pertinent history includes the patient's personal medical and surgical history, including discussion of any history of exposures or environmental risk factors, as well as family history to identify any genetic syndromes that may be linked to the development of a neoplastic process. The clinical encounter should include a complete review of systems to allow for early identification of any sites of metastatic disease, and the physical exam should include nodal assessment and may also include a genitourinary exam, depending on both proximity of the primary tumor in question and index of suspicion of involvement. For patients experiencing a head and neck SFT, flexible nasolaryngoscopy must be performed to identify any other occult sites of disease. Following a thorough initial encounter, further evaluation with imaging studies is performed, and a pathologic diagnosis is often required to formally diagnose an SFT.

9.2.2 Imaging

As with many other soft tissue tumors, SFTs are generally well-circumscribed in appearance on imaging, and imaging may be a helpful adjunct in clinical management for purposes of assessing location and displacement of adjacent normal tissue as well as evaluating potential resectability. Imaging obtained in the diagnostic evaluation of patients with SFTs includes imaging studies ordered in the evaluation for any patients with soft tissue tumors, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT). CT and PET-CT are particularly useful imaging studies for diagnosis and surveillance of SFTs arising from within the thorax, abdomen, or soft tissue, whereas MRI with contrast allows for better detection of intracranial HPCs.

On CT, intrathoracic SFTs are described as "well-defined, homogeneously hyper-dense masses that form obtuse angles with the pleura" associated with heterogeneous contrast enhancement [29]. SFTs are felt to be hyper-dense, owing to their relatively high percentage composition of collagen; however, larger tumors may be increasingly heterogeneous-appearing and demonstrate variability in their contrast-enhancement patterns due to calcification, hemorrhage, cystic degeneration, and necrosis [30]. Pleural-based SFTs that are benign are more likely to demonstrate mobility and deformability that allows them to change shape and migrate in location when followed on subsequent scans; on the other hand, malignant tumors are more likely to demonstrate chest wall invasion and pleural effusions [30]. SFTs arising from the mediastinum are also more likely to demonstrate invasive features and may be initially misdiagnosed as lymphoma, thymoma/thymic carcinoma, or malignant mesothelioma [29]. SFTs arising from within the parenchyma may appear as well-circumscribed pulmonary nodules of round or ovoid shape, akin to an early-stage primary bronchogenic carcinoma. When feasible, it is helpful to obtain a contrast-enhanced CT scan to help delineate soft tissue tumor from adjacent vasculature that may be encased by tumors exhibiting more locally aggressive behavior.

On MRI, SFTs are re-demonstrated as a well-defined mass; they exhibit low-to-intermediate signal intensity on T1-weighted sequences and heterogeneous but potentially high signal intensity on T2-weighted sequences [31]. This variability is accounted for by the degree of cellularity of the tumor; hypocellular tumors (which often have a lot of collagens, such as intrathoracic SFTs) tend to exhibit a low signal on T2-weighted imaging, whereas tumors that are hypercellular and/or highly vascular (such as intracranial HPCs) tend to exhibit high signal intensity on T2 [32, 33]. A gadolinium-enhanced T1-weighted image showing an enhanced mass lesion (intracranial HPC) with enhanced corkscrew artery and a dural tail sign is shown in Fig. 9.1. Due to its superior soft tissue delineation, MRI is more effective than CT for evaluating tumor origin, extent, and invasion into adjacent structures. MRI brain with contrast is especially useful for imaging evaluation of intracranial HPCs. The diagnosis of intracranial HPC is suggested by the presence of a (most commonly extra-axial) tumor with increased "corkscrew" vascularization and associated extensive edema along with irregular/lobulated borders [34]. Both meningiomas and

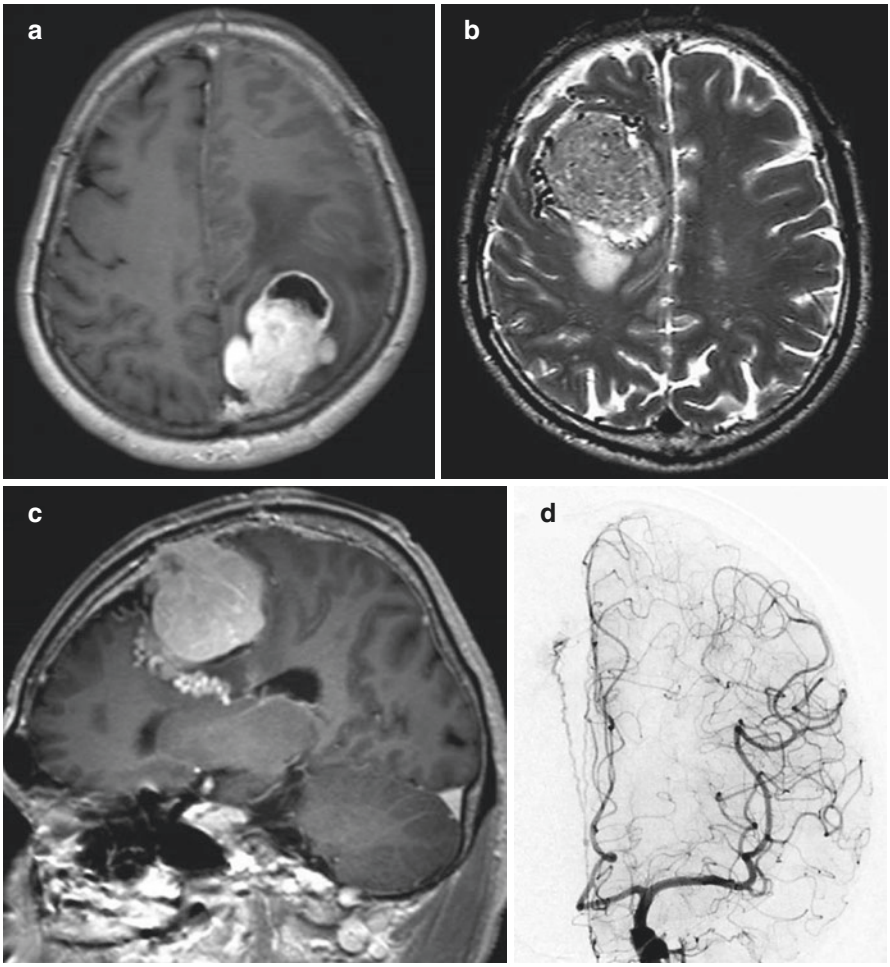

Fig. 9.1 Neuroimaging findings. (**a**) Gadolinium-enhanced T1-weighted image showing an enhanced tumor with cystic lesion. (**b**) T2-weighted image showing slightly high intensity mass lesion with flow void and perifocal edema. (**c**) Gadolinium-enhanced T1-weighted images showing an enhanced mass lesion with enhanced corkscrew artery and dural tail. (**d**) Corkscrew finding on angiography
Reference: Yamashita, D., Suehiro, S., Kohno, S. et al. Intracranial anaplastic solitary fibrous tumor/hemangiopericytoma: immunohistochemical markers for definitive diagnosis. Neurosurg Rev. (2020). https://doi.org/10.1007/s10143-020-01348-6 (Reproduced with permission)

intracranial HPCs may exhibit a dural tail sign; however, whereas meningiomas are often associated with thickening of the adjacent bone, intracranial HPCs often may have eroded the adjacent bone, and this serves as a distinguishing feature between these two extra-axial tumors [25].

PET-CT has been frequently utilized for staging, restaging, and surveillance of extracranial SFTs [16]. Reports have indicated that ^{18}F-FDG uptake that is similar

to that of the mediastinal blood pool [29]. Larger tumors may be associated with heterogeneously low FDG uptake due to the aforementioned characteristics of hemorrhage, necrosis, etc. associated with increased size. While PET-CT is useful in detecting the presence of tumor, it has not yet demonstrated utility in predicting for benign versus malignant SFTs [29]. The FDG uptake associated with SFTs is moderate compared to other neoplasms, and intense FDG avidity should prompt clinicians to consider alternative diagnoses [30, 35].

9.2.3 Pathology

On gross appearance, SFTs are soft and lobulated and may range from subcentimeter to several centimeters (>50 cm) in widest dimension. Tumors are often associated with a fibrous pseudocapsule or may be encompassed by serosal lining [15]. Intrathoracic, visceral pleural-based tumors are often pedunculated and associated with a narrow pedicle containing vasculature that supplies the tumor, while parietal pleural-based tumors are often larger, with a broad-based attachment. HPCs in particular are notorious for being highly vascularized tumors [15]. As aforementioned, the tumor may grossly be associated with changes of cystic degeneration, hemorrhage, calcification, or necrosis, especially if it is larger in size.

Under the microscope, SFTs demonstrate a wide gamut of histopathologic features. Intrathoracic, pleural-based SFTs are frequently characterized by a "hypocellular" phenotype associated with significant collagenation (which is what allows for these SFTs to appear hyperdense on imaging), and these tumors are typically considered to behave in a benign fashion. This is in contrast to HPCs, which are more classically "hypercellular" and marked by greater biological aggressiveness [24]. HPCs are very vascular and associated with clusters of dilated, branching blood vessels in a pathognomonic "staghorn" pattern [24]. Another prominent microscopic feature of HPCs is the presence of a basal lamina layer characterized by thick collagen bands; these may become more evident when collagen IV staining is performed, as this allows for intracranial HPCs to be distinguished histopathologically from meningiomas [24].

Histopathologic features are important for characterizing SFTs as benign versus malignant; debate over the criteria for distinguishing benign SFTs from malignant SFTs has spurred the development of multiple risk stratification and staging schemes (reviewed in "Risk Stratification and Staging"). One such scheme to characterize malignant SFTs established by England et al. in 1989 included major criteria of mitoses (>4/10 HPFs), tumor necrosis/hemorrhage, nuclear pleomorphism, and metastasis. Minor criteria for classifying an SFT as malignant were large tumor size (>10 cm) and cellular atypia [15].

Furthermore, anaplasia is another feature of great histopathologic significance; with regards to intracranial HPCs, tumors with evidence of anaplasia are automatically upgraded from WHO grade II to WHO grade III. Research has

demonstrated that HPC-predominant morphology is associated with significantly higher rates of cellularity, pleomorphism, and mitotic activity and that meningeal SFTs are found to have a greater ratio of HPC-predominant SFTs compared to intrathoracic or other extracranial SFTs [36]. Based on these aggressive biologic features, intracranial HPCs are most prone to local recurrence and distant metastasis.

Immunohistochemically, commonly expressed markers for SFTs are CD34, CD99, vimentin, and Bcl2. SFTs are often negative for desmin, S100, actin, epithelial membrane antigen, and cytokeratins [24]. While not specific for SFT and often inconsistently expressed, the classic immunohistochemical pattern may assist with making a diagnosis of SFT. Intracranial HPCs are characterized by positivity for CD34 and negativity for epithelial membrane antigen; this is in contrast to meningiomas, which are typically negative for CD34 and positive for epithelial membrane antigen [24].

With regard to molecular diagnostics, the defining molecular characteristic of SFTs is that they are translocation-associated and arise from the NAB2/STAT6 gene fusion with shared 12q13 inversions [36]. The WHO 2016 classification of CNS tumors categorized intracranial HPCs as a subset of SFTs after determining that both were characterized by this gene fusion [4]. The gene fusion involves the replacement of a repressor domain on NAB2 with a transactivation domain on STAT6, and this yields the transcriptional activation that marks the growth response pathway causing for the uncontrolled tissue proliferation leading to SFT formation [36].

9.2.4 Risk Stratification and Staging

9.2.4.1 Intrathoracic SFTs

Multiple different risk stratification and staging schemas have been developed over the years as clinicians' understanding of SFTs has evolved with time. First developed for pleural-based SFTs in 1989 were the England criteria as described above in the histopathologic characterization of SFTs [15]. This risk stratification paradigm included assessment of mitotic figures, hypercellularity, pleomorphism, necrosis, hemorrhage, stromal/vascular invasion, size, pedunculation, and tumor site [15]. The next pleural-based staging system to be developed was by de Perrot et al. in 2002, which assessed similar criteria to England et al. but did not incorporate the presence of hemorrhage or tumor site into its classification system [19]. More recently, Tapias et al. proposed a classification system comprised of the same features initially described by England et al. with omission of pleomorphism and stromal/vascular invasion as well as the requirement for three histologic and anatomic risk factors for an SFT to be regarded as malignant [10]. In lieu of a formal staging system for intrathoracic/pleural-based SFTs, these pathologic features guide clinicians' understanding of a tumor's biological aggressiveness and risk of locoregional recurrence or distant metastasis.

9.2.4.2 Intracranial SFTs

In the risk stratification of intracranial SFTs, the most recently updated WHO 2016 classification system assigns intracranial SFTs three grades [37]:

- Grade I: hypocellular, highly collagenous tumor classically described as SFT
- Grade II: more cellular tumor with pathognomonic "staghorn" vasculature classically described as HPC
- Grade III: the previously regarded "anaplastic HPC" diagnosed with >4/10 mitoses on HPF and associated with poorer distant metastasis-free survival and overall survival

An alternative grading system proposed for intracranial HPCs of historical significance is the Marseille Grading System (MGS) developed by Bouvier et al. in 2012 at a hospital in Marseille, France [38]. At the time of development of the Marseille criteria, meningeal SFTs and HPCs were regarded as distinct entities based on the WHO classification; therefore, the MGS aimed to define prognostic factors based on tumor histology to better characterize their behavior [38]. The MGS helped determine that meningeal SFTs and intracranial HPCs shared a significant degree of histopathological and immunohistochemical properties [38], which accounts for their reclassification as one tumor entity in the most recently updated WHO classification in 2016. Bouvier and colleagues determined that prognostic factors predicting for decreased progression-free survival and overall survival on univariate analysis included a mitotic count of >5 per 10 high power fields, hypercellularity, and necrosis. A recently published analysis by Macagno et al. in 2019 aimed to further refine the MGS by reporting on the prognostic value of each individual criterion comprising it [4]. These researchers found that progression-free survival was associated with the extent of surgical resection and mitotic activity >5/10 HPF and disease-specific survival was associated with the presence of necrosis and receipt of radiotherapy [4].

9.2.4.3 Extrathoracic SFTs

Overall, with regard to staging of extrathoracic and extracranial SFTs, the AJCC eighth edition (2017) encourages providers to stage SFTs as they would any soft tissue sarcoma based on primary tumor site [39]. For extracranial SFTs, three risk calculators have been devised by the French Sarcoma Group [40–42]. Two of these include all extracranial SFT and one describes extracranial, extrathoracic SFTs only. Of note, in addition to taking into account tumor characteristics such as site, size, and cellularity, these prediction models additionally factor in receipt of radiotherapy (RT) into overall risk of recurrence and metastasis. These three risk prediction models are summarized in Tables 9.1, 9.2, and 9.3.

Table 9.1 Risk prediction model for extracranial SFTs proposed by Demicco et al. 2017 (REF: *Demicco EG, Wagner MJ, Maki RG,* et al. *Risk assessment in solitary fibrous tumors: validation and refinement of a risk stratification model. Mod Pathol 2017; 30:1433)*

Risk criteria	Points	Risk for metastasis
Mitoses (per 10 HPF)	0	0
	1	1–3
	2	≥4
Age	0	<55
	1	≥55
Size	0	0–4.9 cm
	1	5–9.9 cm
	2	10–14.9 cm
	3	≥15 cm
Necrosis	0	<10%
	1	≥10%
Risk sum stratification	**Points**	**Risk for metastasis**
	0–3	Low
	4–5	Intermediate
	6–7	High

Table 9.2 Risk prediction model for extracranial SFTs proposed by Salas et al. (2017)

Risk criteria	Points	Metastasis	Overall survival	Local recurrence
Mitoses (per 10 HPF)	0 1	≤4 >4	≤4 >4	
Age	0 1	<60 ≥60	<60 ≥60	≥60 <60
Site	0 1	Other Limb		Other Viscera
Receipt of Radiotherapy	0 1			Yes No
Risk Sum Stratification	Points	Risk for metastasis	Risk for death	Risk for local recurrence
	0	Very low	Low	Very low
	1	Low	Intermediate	Low
	2	Intermediate	High	Intermediate
	3	High		High

Table 9.3 Risk prediction model for extracranial, extrathoracic SFTs only proposed by Pasquali et al. (2016)

Risk criteria	Points	Recurrence-free survival
Mitoses (per 10 HPF)	0	≤4
	3	>4
Cellularity	0	Low
	2	Moderate-High
Nuclear pleomorphism	0	Low
	2	Moderate-High
Risk sum stratification	Points	Risk for recurrence-free survival
	0	Very low
	2	Low
	3–5	Intermediate
	>5	High

9.3 Treatment Strategies

9.3.1 Surgery

The overall treatment paradigm for all localized SFTs, regardless of primary site, is upfront complete surgical resection with wide local excision in an effort to achieve an R0 resection [43]. Following surgery with an R0 resection as single modality curative intent therapy, the reported 5-year overall survival rate for SFTs ranges from 54 to 89% [44, 45]. Existing literature has demonstrated improved local control and survival outcomes with R0 resection [4]. Furthermore, upfront surgical resection allows for quick relief of any symptoms the patient may be experiencing secondary to mass effect while allowing for pathologic confirmation of the diagnosis. The type of surgical resection performed varies greatly, depending on the site of the SFT.

For intrathoracic or pleural-based SFTs, patients may generally receive a wedge resection, especially if the tumor is pedunculated [46]. However, tumors that are large or diffuse (e.g., associated with ipsilateral metastases to the pleura) may require a lobectomy or a pneumonectomy to achieve an optimal R0 resection [47]. The decision-making process for the ideal surgical resection technique is multifactorial and should involve a discussion at a multidisciplinary tumor board with thoughtful consideration of the patient's tumor characteristics, overall performance status, suitability for the planned surgery, and potential adjuvant treatment options in the event of an R1 or R2 resection.

For patients with intracranial SFTs, extent of resection is described by the Simpson grading utilized for meningiomas as depicted in Table 9.4. Unfortunately, any neural involvement or dural sinus invasion by the HPC may make an already technically challenging surgical resection even more cumbersome. An additional important consideration for surgical resection of these tumors, especially given the exquisitely vascular nature of intracranial HPCs, is the need for preoperative embolization to address tumor vascularity prior to resection. Even with the utilization of

Table 9.4 Simpson grading criteria

Simpson grade	Degree of resection
I	Macroscopic complete removal with excision of dural attachment & abnormal bone
II	Macroscopically complete with endothermy coagulation of dural attachment
III	Macroscopically complete without resection or coagulation of dural attachment or of its extradural extensions
IV	Partial removal leaving tumor in situ
V	Simple decompression ± biopsy

embolization prior to surgery, HPCs have been shown to derive blood supply from collateral circulation. Based on these considerations, it is felt that the true gross total resection (GTR) rate for intracranial HPCs ranges from 33 to 66% [48].

For patients with extrathoracic/soft tissue SFTs, a maximal safe resection should be performed while paying attention to the adjacent normal tissue that may be involved, e.g., encasement of nerve or vasculature. For soft tissue tumors situated on extremities, limb-sparing surgery is performed as it would for a non-SFT soft tissue sarcoma.

9.3.2 Radiotherapy

Radiotherapy plays a diverse role in the management of SFTs as definitive or adjuvant therapy for curative intent treatment and as a salvage therapy option in the event of recurrence.

9.3.2.1 Indications for Adjuvant Radiation

There are no formal guidelines to inform practitioners of the benefits of adjuvant radiotherapy for patients who are status post-R0 resection of an extracranial SFT, largely owing to the lack of prospective, randomized trials performed for this rare malignancy. Existing literature has demonstrated favorable outcomes with surgery alone in the treatment of extracranial SFTs [49], especially given the less aggressive nature of hypocellular-phenotype SFTs classically identified outside of the CNS. Historically, adjuvant radiotherapy has often been omitted and reserved only for patients with tumors harboring residual disease following resection or final pathology demonstrating the more aggressive histological features described previously [4]. However, some providers have published on the use of adjuvant radiotherapy to improve local control, especially in the setting of positive margins or recurrent disease. These studies are limited to retrospective analyses with small sample sizes and short follow-up but demonstrate excellent outcomes with the addition of neoadjuvant or adjuvant radiotherapy to surgical resection. A large, retrospective multicenter study published by Bishop et al. in 2018 described outcomes for 31 patients with extracranial SFTs treated with surgical resection and neoadjuvant or adjuvant radiotherapy, including 17 patients receiving preoperative

radiotherapy (with a median dose of 50 Gy) and 14 patients receiving postoperative radiotherapy (with a median dose of 58 Gy) [50]. With a median follow-up of nearly 5 years, the authors reported a 5-year local control rate of 100%, a 5-year overall survival rate of 95%, and a 5-year distant metastasis-free survival rate of 92% [50]. The authors reported that over 70% of the tumors treated were large (>5 cm) and the 10-year complication rate was 6%.

Utilization of EBRT in the treatment of intrathoracic SFTs is not well-described, with clinical practice guided by inconclusive retrospective series and otherwise extrapolated from management of thoracic soft tissue sarcomas. In the management of thoracic soft-tissue sarcomas, retrospective series have demonstrated improved local control with the addition of postoperative radiotherapy to surgical resection [51]. For patients specifically with SFTs, some data exists demonstrating an improvement in local control with the addition of postoperative radiotherapy to surgery [52]. However, a population-based analysis of about 600 patients (of which ~35% of the study population had intrathoracic SFTs) determined that there was no significant difference in overall survival for patients who received surgery with adjuvant, postoperative radiotherapy versus surgery alone [53]. However, interpreting these results in light of the type of retrospective, population-based analysis performed, it is felt that the baseline characteristics for the two comparison groups were likely not similar; patients with higher-risk pathologic features, such as positive margins, were more likely to receive adjuvant radiotherapy than patients receiving surgery alone. Regardless, the notion that adjuvant radiotherapy improves local control without significantly prolonging overall survival is in keeping with the existing literature on outcomes for non-SFT intrathoracic and soft tissue sarcomas [46].

For intracranial HPCs, in spite of a lack of prospective data guiding clinical practice, the role of adjuvant postoperative radiotherapy is far more well-established due to the notoriously high risk for locoregional recurrence associated with this subgroup of SFTs. Adjuvant postoperative radiotherapy following GTR in the treatment of intracranial HPCs has been shown to improve local control as well as overall survival [48, 54–56]. Various studies analyzing the role of adjuvant radiotherapy have been performed in the past 10 years, and they are briefly summarized in Table 9.5 [57]. These studies have demonstrated a role for either conventional fractionation external beam radiotherapy or stereotactic radiosurgery in the postoperative setting. A detailed review of the optimal dose and fractionation regimens to utilize for both external beam radiotherapy and stereotactic radiosurgery will be provided in the following section reviewing treatment modalities in relation to SFTs of specific anatomic subsites.

9.3.2.2 Indications for Definitive Radiation

For patients with unresectable, malignant extracranial SFTs or poor surgical candidates or for patients who decline surgery, radiotherapy alone may be considered as local therapy. Poor surgical candidates include patients with comorbid conditions precluding safe performance of surgery as well as patients with unresectable tumors, e.g., SFTs with encasement of nearby vessels or nerves. One of the first retrospective series published in the Red Journal in 1987 reported on 11 patients with

Table 9.5 Summary of study analyzing outcomes for patients with intracranial HPCs receiving adjuvant radiotherapy. REF: Bernard V, Ghia AJ. "Hemangiopericytoma." In: Chang, E. L. et al. (eds) *Adult CNS Radiation Oncology* 1st edn (Springer, 2018), pp. 307–315 (Reproduced with permission)

Study year	# of patients	Median FU (mo, range)	Median tumor volume (cm^3)	Median marginal dose or mean dose (Gy, range)	New lesions (% of patients)	Extra-cranial metastasis (%)	Median OS	Summary of study findings
Rutkowski et al. (2010)	277	78	5.36	N/A	43	27	156	OS benefit demonstrated with gross total resection (GTR)
Rutkowski et al. (2012)	35	2–408	4.4	N/A	46	20	194.4	Trend towards statistical significance for improved recurrence-free survival with post-op radiation
Ghia et al. (2013)	88	N/A	N/A	N/A	N/A	N/A	111	Both GTR and post-op radiation associated with improved OS
Ghia et al. (2013)	63	N/A	N/A	60(35–66.4)	51	N/A	154	Post-op radiation associated with better local control, especially at doses >60 Gy
Sonabend et al. (2014)	227	34	5	N/A	N/A	N/A	N/A	Statistically significant improvement in OS with GTR and radiation vs GTR alone
Chen et al (2015)	38	61(15–133)	4.6	N/A	66	13	N/A	GTR with adjuvant radiation associated with improved OS and recurrence-free survival
Cohen-lnbar et al. (2016)	90	59(6–183)	4.9	14(12–16)	55	24.4	N/A	Margin dose >16 Gy associated with better local control
Kim et al. (2017)	18	71.8 (3.3–153.3)	1.2	20(13–30)	80	38.9	225.7	GK SRS may be used repeatedly for intracranial recurrence or progression

extracranial SFTs treated with definitive radiotherapy, and zero patients in their study population demonstrated a local recurrence [58]. An updated retrospective series published in the Red Journal in 2018 assessed 40 patients treated from 1990 onward (of which 16 patients were treated with definitive intent) with a median follow-up of around 5 years; the authors found an objective response rate of 67%, a 5-year local control rate of 81.3% and a 5-year overall survival rate of 87.5% [59]. Patients treated by Jha et al. received doses ranging from 31 Gy to 65 Gy with a mean curative intent dose of 57.4 Gy in 29 fractions [58], and the majority of patients in the study by Haas et al. similarly received 60 Gy. For patients treated palliatively with radiotherapy alone (most commonly to a dose around 30–40 Gy), patients demonstrated an objective response rate of 38%, a 5-year local control rate of 62.5%, and a 5-year overall survival rate of 54.2% [59]. This data by Haas et al. demonstrates a role for radiotherapy in the definitive management of SFTs, especially given that the treatment course was well-tolerated overall with patients in their cohort predominantly experiencing grade 1 acute and late-term toxicities [59]. Furthermore, Haas et al. indicated that even patients treated with palliative intent radiotherapy to lower doses derived a clinically meaningful benefit; these findings duplicate initial findings published by Mira et al. as early as 1977, who studied 11 patients treated at Memorial Sloan Kettering from 1946 to 1964 and found an objective response rate of 88% and a 2-year duration of local control with palliative-range doses ranging from 2500 to 3500 rads [60].

9.3.3 Systemic Therapy

The role of systemic therapy remains unclear for localized SFTs, but, in general, adjuvant systemic therapy is not felt to be indicated following complete resection. However, systemic therapy has been considered to be of great utility for the treatment of advanced or metastatic SFTs. A retrospective cohort study of 21 patients with advanced extracranial SFTs (defined as patients with unresectable metastatic disease or a borderline/potentially resectable primary tumor found that first-line chemotherapy yielded stable disease for about 90% of patients based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria; about 10% of patients experienced disease progression, but no patients experienced a complete or partial response [44]. While the median progression-free survival was found to be 4.6 months, the median overall survival was 10.3 years from the time of diagnosis; most patients were treated with a doxorubicin-based regimen, although some patients were treated with gemcitabine and paclitaxel [44].

For patients with intracranial SFTs, systemic therapy options that have been explored include those with established CNS permeability and efficacy in the treatment of intracranial pathology, such as temozolomide (TMZ) and bevacizumab. TMZ is an alkylating agent that triggers cell death by inducing DNA damage via methylation; TMZ has established efficacy in the treatment of high-grade gliomas, such as glioblastoma, and existing data suggests that it is well-absorbed following oral administration and its penetration of the brain and CSF is 30–40% of its plasma

concentration [61]. Bevacizumab is a recombinant monoclonal antibody that exerts its action by inhibiting vascular endothelial growth factor A (VEGF-A), which halts angiogenesis and thereby exerts anti-tumorigenic effects. A retrospective cohort study assessing TMZ and bevacizumab for patients with advanced or metastatic intracranial HPCs found that these agents improved progression-free survival for patients, demonstrating a clinical response (versus patients who were ultimately non-responders) when assessed using CT assessment of tumor size and density (the Choi criteria) [62]. Eleven out of the 14 patients studied demonstrated a partial response to therapy with a median time to response of 2.5 months [62].

Tyrosine kinase inhibitors (TKIs) are another class of drugs that has been heavily studied in the treatment of advanced/metastatic SFTs. As research investigating the use of TKIs has been rapidly evolving over the past few years, a variety of agents have been utilized. A study assessing sunitinib found that about half of the sample population studied ($n = 11$) demonstrated a partial response based on Choi criteria, and it was proposed that sunitinib's activity against SFTs may be mediated by a pathway involving an epidermal growth factor receptor called PDFGR [63]. Most recently, pazopanib has been the focus of study for systemic therapy in the management SFTs; it is the only TKI approved by the United States Food and Drug Administration (FDA) for the treatment of soft tissue sarcomas, given its ability to target multiple receptor pathways, including both VEGFR and PDGFR [64]. A prospective, single-arm, phase 2 trial studying advanced and previously progressing SFTs treated with pazopanib performed by Martin-Broto et al. in 2018 demonstrated a 51% partial response rate ($n = 36$) with a median progression-free survival of 5.6 months and a 2-year overall survival of 73% [65]. Of note, patients analyzed in this study were treated for malignant SFTs in all anatomic locations. Given the heterogeneity within SFTs as a tumor class, the optimal systemic therapy regimen remains unclear, and further study will be required to determine the best agents to utilize for each subtype.

9.4 Posttreatment and Future Direction

9.4.1 Surveillance

Of note, tumor response following delivery of radiotherapy reflects the "tumor kinetics" associated with the tumor's growth [46]; for a typically slow-growing intrathoracic SFT, the consequent response to radiotherapy has been reported to occur 3–10 months following completion of treatment [16, 66–68]. This is in comparison to a more rapidly growing intracranial HPC, which may respond more quickly; a report by Soyuer et al. indicated partial response of an intracranial HPC treated with SRS after 2 months, with complete radiographic response noted for a different lesion within 4 months [69]. However, reflecting the variability of SFTs as a tumor class, tumor response time similarly exhibits a wide range of variability, with some intracranial HPCs taking 2 years to demonstrate even a partial response [69].

Due to the natural history of SFTs with a predilection toward late local recurrence and distant metastasis, sometimes up to 20 years following initial curative intent therapy, close long-term follow-up is recommended. For patients with pleural-based SFTs, posttreatment surveillance is extrapolated from the de Perrot risk stratification schema [19]. For patients with benign pedunculated SFTs, it is recommended that patients receive yearly interval imaging. For all other types of tumors noted on final surgical pathology (benign sessile SFTs, malignant pedunculated SFTs, and malignant sessile SFTs), it is recommended that patients pursue interval imaging every 6 months for the first 2 years following treatment and then yearly thereafter. Surveillance imaging with either CT C/A/P or PET-CT is suitable, depending on the patient's initial presentation and diagnostic imaging findings [19, 70].

For patients with extrapleural SFTs, surveillance guidelines are often extrapolated from the National Comprehensive Cancer Network (NCCN) guidelines for posttreatment surveillance of soft tissue sarcomas with a general paradigm such as follows [19, 70]:

- Low-risk patients: interval imaging every 6 months for the first 3 years following treatment and then yearly up to 5 years posttreatment.
- Intermediate- and high-risk patients: interval imaging every 3–4 months for the first 2 years following treatment and then every 6 months up to 5 years posttreatment.

With regards to chest imaging:

- Low-risk patients: CT chest every 6 months for 3 years and then annually up to 10 years posttreatment.
- Intermediate- and high-risk patients: CT chest every 3–4 months for 2 years, every 6 months for 3 years, and then annually up to 20 years posttreatment.

For patients with intracranial HPCs, posttreatment surveillance may consist of serial imaging with MRI brain with contrast obtained at 3 months and 6 months following completion of radiotherapy and then every 6 months thereafter. Patients should undergo lifetime surveillance (or at least for 20 years) as intracranial HPCs are known to recur up to 20 years following initial therapy. Based on index of suspicion, clinicians may consider surveillance of common sites of metastasis including the lungs and liver with interval CT C/A/P [19, 70].

9.4.2 Management of Recurrence

For patients who experience a local recurrence following surgical resection, treatment options are limited and have primarily been studied for patients with intracranial HPCs [45], as these are the patients with aggressive SFTs that are more likely to recur. Treatment options include repeat surgical resection as well as salvage radiotherapy. Important factors to consider in the management of recurrence include neurologic functioning, extracranial disease status, timing of prior radiotherapy, and tumor volume [57].

SRS is the most studied treatment option for salvage reirradiation of recurrent intracranial HPC as it attempts to provide local control with an ablative dose. A study by Olson et al. (2010) assessed repeat SRS in the management of 13 tumors with a mean prescription dose of 17 Gy and a maximum radiosurgical dose of 43 Gy; the authors did not find receipt of prior fractionated radiotherapy or the prescription dose to be associated with tumor control in the reirradiation setting, suggesting that reirradiation with SRS is both as safe and effective as treatment in radiation-naive patients [71]. Another retrospective series by Kim et al. (2017) assessing patients with recurrent intracranial HPCs who received SRS found that durable local control was achieved with repeat Gamma Knife radiosurgery, although retreatment was frequently necessary [72]. With regard to toxicity in the reirradiation setting, reports specifically addressing this question in the assessment of recurrent intracranial HPCs are limited, given the low incidence of the tumor and lack of data specifically investigating toxicity in the setting of reirradiation, but as with reirradiation of other CNS tumors—particularly with SRS—both acute- and long-term toxicities remain an issue of concern to weigh against the benefits of therapy.

9.4.3 Future Directions

The future directions for further study of SFTs are innumerable; given how rare SFTs are, formal investigations on these tumors have been limited. There is currently no prospective randomized data to guide practice on the management of SFTs within any anatomic site. Furthermore, retrospective cohort studies assessing outcomes in these patients are often limited by sample size as well as heterogeneity of sample population, with patients included often treated over several decades with different technologies utilized. Future studies of all SFTs may seek to clarify the role of radiotherapy by prospectively collecting patients treated uniform with modern techniques (depending on tumor location and characteristics) to achieve a better understanding of local control and survival outcomes associated with adjuvant therapy. Furthermore, while a role for definitive radiotherapy in the management of intrathoracic SFTs has been suggested, there is limited data analyzing definitive radiotherapy in the primary treatment of intracranial HPCs or extrathoracic, extracranial SFTs. Lastly, future directions for the treatment of SFTs will aim to incorporate other modalities of delivering radiotherapy, including SBRT and proton therapy, and particularly at anatomic subsites in which these modalities are being increasingly utilized.

9.5 Clinical Treatment Planning Considerations

9.5.1 Patient Setup and Immobilization

Patient setup and immobilization techniques vary depending on the site of the SFT being treated. For patients with intrathoracic SFTs, patients are often simulated in the supine position with their arms placed above their head using a personalized vac

loc cradle and wingboard; this position allows for a greater possibility of potential beam angles when it comes to treatment planning. The vac loc easily conforms to the shape of the patient's upper thorax, allowing for immobilization and easy reproducibility on daily setup. Depending on the extent to which intrafraction motion is anticipated, half-body or whole-body immobilization may be considered.

For intracranial HPCs, the patient is best simulated in the supine position with their arms at their side. The patient's head and neck should remain in a neutral position parallel to the treatment table and may be immobilized with the assistance of a small thermoplastic mask in the delivery of conventional fractionation radiotherapy. If the patient is receiving frame-based SRS, the patient may additionally receive a stereotactic frame as part of their immobilization. Such a frame is typically placed by a neurosurgeon with the aid of a local anesthetic.

For patients with other types of extra-thoracic SFTs, depending on the location, patients may be simulated in either the supine or prone position. Prone positioning may be useful for treating posterior targets, both because of the ability to reduce dose anteriorly as well as displace the small bowel forward with the use of a belly board in an effort to minimize bowel toxicity. Custom casts in various shapes and sizes can be created to help with immobilization.

9.5.2 Simulation

For patients with intrathoracic SFTs, CT simulation is performed using approximately 3 mm slice thickness and use of IV contrast is encouraged when feasible to assist with differentiating tumor from other mediastinal structures. Four-dimensional (4D) CT scanning should be performed to account for respiratory motion in target volume delineation and allows for contouring of an internal target volume (ITV) that incorporates motion of the target throughout the respiratory cycle. 4D CT may be utilized for intra-abdominal tumors situated in close proximity to the diaphragm, as well, for which clinically significant tumor motion is anticipated.

For patients with certain intra-abdominal SFTs, such as hepatic HPCs, clinicians may strongly consider fiducial placement by an interventional radiologist prior to simulation. Comfort with target volume delineation in the absence of markers such as fiducials is largely clinician-dependent but is encouraged when feasible, especially for patients receiving high doses with curative intent therapy or for patients receiving treatment with a special procedure such as SBRT. A rare but potential example for which fiducial placement may be helpful for target volume delineation in the context of SFTs is hepatic metastases secondary to an intracranial HPC; such a case was described by Manatakis et al. in 2015 [73] and represents a potential opportunity in which fiducial placement may be considered prior to CT simulation for enhanced target visualization. In certain centers where MR simulation is available, it can be utilized for target delineation instead of fiducial placement as it offers greater soft tissue resolution.

For patients with intracranial HPCs, spiral CT may use 2 mm slice thickness with IV contrast and scan borders from the vertex to mid-neck with isocenter placed at the center of tumor volume. After the planning CT scan is obtained, co-registration

of the scan with a diagnostic MRI is critical for an accurate delineation of target volumes. The MRI utilized for co-registration should consist of three orthogonal planes and have thin slices (e.g., 1 mm); caution must be exerted with the image fusion process, as a displacement in co-registration of nearly 3 mm may occur [74]. Depending on the availability of MR simulation, it can be done in addition to CT simulation with the same immobilization setup. In this way, no co-registration to diagnostic MRI will be needed.

For patients with extrathoracic SFTs, especially those occurring in the lower extremity, simulation should optimize neutral positions that prioritize patient comfort. An exception to this would be a tumor situated along the dorsal aspect of a patient or on their back for which prone positioning is preferred. Rigid immobilization is utilized in the form of a custom cast to immobilize the extremity on which the SFT is being treated. With regard to patient positioning, efforts should be made to consider the following treatment planning considerations [75]:

1. Minimization of subcutaneous hot spots.
2. Allowing for a "spare strip" of limb circumference (<20 Gy).
3. Minimization of dose to adjacent soft tissue and bone.

9.5.3 Image Guidance and Motion Management for Optimized Treatment Delivery

With improved imaging capabilities, image-guidance technology was integrated into radiation oncology equipment to ensure what was seen on the outside reflected actual tumor position. Image-guided radiotherapy (IGRT) allows for greater assurance of tumor control, less normal tissue irradiation, and reduced margins. It requires volumetric 3D information to accurately assess setup and target location and quality assurance for correct delivery of planned treatment. General indications to use IGRT include tumor proximity to critical structures, tumor sensitivity to interfractional and/or intrafractional motion, tumors prone to deformation, and patient tolerance, given the required additional time for these scans. The physician determines the clinical indications for IGRT and orders it, determines the frequency of imaging, reviews imaging, gives the therapists and physicists directions for primary regions of interest (ROI), defines set up parameters, and reviews daily shifts.

Uncertainty and variability during radiation treatment can be classified into two categories: intrafraction and interfraction variability. Interfraction variability is uncertainty that occurs from fraction to fraction. This is mainly attributed to setup irreproducibility, such as anatomy changes, positioning/rotation errors, weight loss, contour deformation, skin mark shifts, etc. This is corrected by pretreatment IGRT. Intrafraction variability is uncertainty that occurs within a treatment fraction. This is mainly due to organ motion, such as respiration, peristalsis, involuntary motion, cardiac motion, bladder and/or rectal filling, bowel gas distension, etc. This is corrected by real-time IGRT and daily adaptation.

Pretreatment IGRT often consists of various modalities:

- Planar images
- MV cone-beam CT (MV-CBCT)
- MVCT fan-beam by Radixact
- kV cone-beam CT (kV-CBCT)
- kV fan-beam CT-on-rails (CTOR)
- MR Linac

Planar images are useful for alignment of bony anatomy in situations, where bony anatomy match is sufficient for precise setup without regard to internal soft tissue anatomy. As conformality of treatment plans increases with 3D volumetric information, there is a need for increasingly precise imaging. CBCT consists of 2D diverging x-ray source and flat panel detector mounted to linac gantry. As gantry rotates around the patient, planar projection images are obtained. These are reconstructed into a true 3D volumetric CT image set. CBCT permits imaging and treatment to be performed in identical patient position. MV CBCT does not require additional hardware, is less susceptible to artifacts from metallic objects compared to kV CBCT (due to the Compton effect), and allows calculation of imaging dose. However, when compared to kV CBCT, the image contrast and quality of MV CBCT is poor, and it delivers a higher imaging radiation dose. kV CBCT requires additional hardware but permits the acquisition of 3D CBCT, 4D CBCT, 2D radiography, and 2D kV fluoroscopy with same source and detector. Also, a difficulty to match kV and MV isocenters had been noted. Radixact technology combines linac with helical CT scanner with an MV fan-beam and arc-shaped detector array.

CTOR has kV fan-beam CT with gantry on sliders. The couch is isocentrically rotated to CT scanner axis after patient is setup and then rotated back for treatment. It produces diagnostic quality CT images. However, there is a delay between imaging and treatment, patient must be rotated after imaging, and there is additional cost associated with a separate CT scanner. MR Linac provides MR-guided radiation therapy (MRgRT), which allows for superior tumor and organ at risk (OAR) delineation. This results in greater avoidance of OARs, permitting precise targeting of tumor allowing for decreased margins and potential dose escalation. Improved soft tissue resolution has potential for decreased toxicity and improved local control. There is no additional imaging-associated radiation exposure with MR Linac. It allows for adaptive radiation treatment as tumor response is monitored and plan is modified to account for changes in tumor extent. Motion management is also provided by static 4D CBCT and MR Linac.

MRgRT, CTOR, CBCT, and fan-beam MVCT yield better soft tissue delineation to ensure proper alignment of internal soft tissue structures and correction of organ filling for luminal structures, compared with planar imaging. Furthermore, in certain instances, they may be utilized to perform adaptive radiotherapy, in which a treatment plan is re-optimized based on information obtained from imaging during the initial treatment fractions, thereby modifying treatment volumes to spare normal tissue and reduce toxicity. With the use of these imaging modalities, the treatment team possesses the ability to overlay delineated target volumes on the scan obtained that day prior to delivery of the patient's treatment fraction, allowing for greater setup accuracy, which gives clinicians more comfort in decreasing the size of PTV

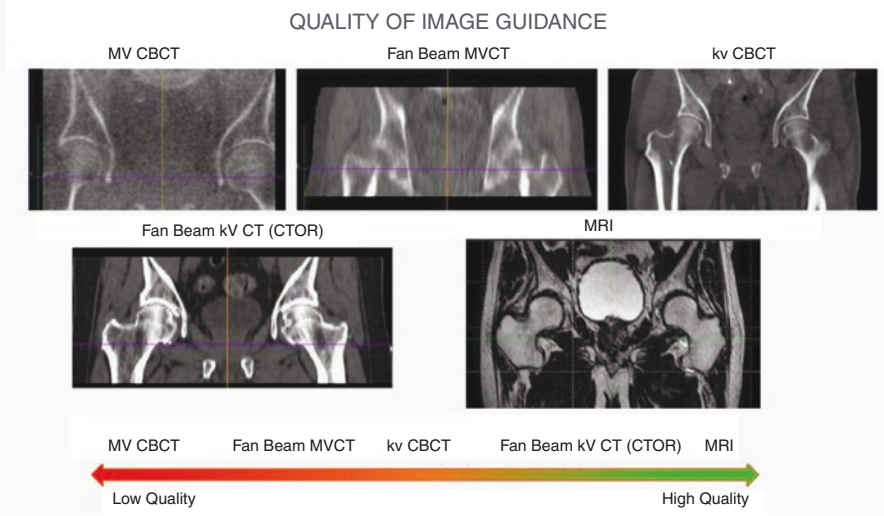

Fig. 9.2 Quality of image guidance for different studies used in image-guided radiation therapy(IGRT)

expansions that otherwise account for daily setup inaccuracies. The quality of image guidance according to modality is depicted in Fig. 9.2.

Real-time IGRT with daily adaptation for motion evaluation and management is used for patients receiving special procedures, such as SRS (or SBRT), or when intrafraction variability needs to be limited. Options for techniques to assist in the precise delivery of conformal high-dose radiation associated with SRS/SBRT include enhanced treatment room-based technology, such as ExacTrac in-room x-ray monitoring, which has the ability to detect intra-fraction tumor motion throughout treatment delivery even in the setting of non-coplanar treatments, in which there may be alterations to the couch angle or gantry position [76]. This technology involves the integration of infrared-based optical positioning with kV x-ray imaging. In the setting of SRS, ExacTrac carries the added benefit of allowing for patients to bypass use of the stereotactic frame and receive a frameless procedure, given that the treatment beam may be tracked and gating performed [76]. Furthermore, while already well-established in its use for the delivery of IMRT, CBCT has additionally being incorporated into the delivery of linac-based SRS and Gamma Knife SRS; this also allows for increased utilization of frameless technique and, for frame-based procedures, prevents clinically significant targeting errors secondary to slipping of the stereotactic frame or other frame-based errors [77].

With regard to delivery of radiotherapy to intrathoracic or intra-abdominal targets, respiratory motion management is an important consideration. Respiratory motion management may occur through a number of techniques and is often useful for minimizing imaging artifact in addition to enhancing precision of treatment delivery. Options for respiratory motion management include active deep inspiratory breath hold (DIBH) technique, respiratory gating, abdominal compression, real-time motion tracking, and MRgRT. DIBH is generally performed in two ways:

voluntary DIBH and moderate DIBH using active breathing control [78]. In voluntary DIBH, patients hold their breath at certain points during the respiratory cycle, whereas active breathing control involves the use of a special device (often incorporating a spirometer) that halts airflow at a set threshold volume and helps the patient hold their breath at this set volume [78]. DIBH requires patient cooperation and staff effort to train and coach patients. In addition to standardizing the target position and lending reproducibility to the treatment delivery process, DIBH is associated with the potential for improved dosimetry and decreased dose to adjacent normal structures.

For patients who are unable to tolerate breath hold techniques, gated treatments may be utilized; this is an especially important consideration for patients with large intrathoracic tumors, whose malignancies yield mass effect and consequent dyspnea that renders them unable to maintain normal respiratory function. Gating involves intermittent delivery of radiation occurring within a portion of the breathing cycle (gate). Gate onset is determined by respiratory monitoring, either external signal or internal fiducial markers. Respiratory gating does result in longer treatment times. In abdominal compression, a pressure device pushes on the upper abdomen, thus limiting diaphragm excursion. It allows for continuous dose delivery. However, it can be uncomfortable for patients and sometimes variably successful in reducing target motion. Real-time motion tracking refers to continuous adjustment of radiation beam or patient position to follow the changing position of the target or its surrogate. It includes coupling of target localization in real time (using methods such as fiducials, optical patient surface, correlation between external optical signal and internal fiducial imaging, etc.) with target alignment control system (using systems such as linac attached to robotic arm, treatment couch translation, etc.). MRgRT involves on-table adaptive capability and automated beam gating to allow adapting to daily changes in patient's anatomy, while its real-time tissue tracking and beam control allow greater precision to the delivery of radiation therapy.

9.5.4 Radiation Modalities/Plan Optimization

Various radiotherapy modalities have been utilized in the treatment of SFTs and include conventional external beam radiotherapy (EBRT), stereotactic radiosurgery (SRS), stereotactic body radiotherapy (SBRT), and cyclotron-based proton therapy. SRS may be performed as linac-based SRS or using Gamma Knife or CyberKnife technologies. EBRT may be performed using three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiation therapy (IMRT) using volumetric modulated arc therapy (VMAT) technique. The latter allows for improved target conformality and homogeneity owing to non-coplanar radiotherapy field arrangements; this permits "dose sculpting" with delivery of higher doses to the delineated target volumes while optimally sparing any adjacent organs at risk (OARs). Existing literature has demonstrated that this is particularly essential in the treatment of benign skull-base tumors [79].

SRS is the delivery of high-dose radiation to a very small, precise treatment volume; this may be accomplished by a linear accelerator or with Gamma Knife (Elekta, Stockholm, Sweden) and CyberKnife (Accuray, Sunnyvale, CA) technologies. SRS is often delivered in a single fraction; when multiple treatment fractions are utilized for SRS, this is referred to as hypofractionated or simply "fractionated" SRS. As compared to EBRT, SRS allows for greater precision in target localization, thereby reducing the volume of irradiated normal tissue. Furthermore, SRS yields greater patient convenience, as a treatment that may otherwise be completed in about 6 weeks with EBRT may be shortened to 1–5 treatment fractions using SRS. For these reasons, SRS is considered preferable to EBRT, when it may be feasibly performed. SRS may occur using a frameless or frame-based approach, the latter of which involves placement of a rigid stereotactic frame screwed to the patient's skull for purposes of minimizing motion during treatment delivery to improve overall accuracy when hitting the planned target. Gamma Knife acts by using intersecting beams produced from concentrically placed cobalt-60 sources that meet at a focused target point, whereas SRS performed by a linear accelerator utilizes fixed arcs comprised of beams shaped by multileaf collimators. CyberKnife is a frameless system consisting of a linear accelerator mounted on a robotic arm that makes use of non-isocentric beams to yield more conformal dose coverage. Whereas linac-based SRS involves dose prescription to the 80–90% isodose line, Gamma Knife and CyberKnife doses are typically prescribed to the 50% isodose line. This allows for a "hot spot" to be centered at the site of the tumor with rapid dose falloff.

Proton therapy has been established as an effective treatment modality with the potential further reduction in toxicity compared to other forms of radiotherapy; this is made possible by protons' mechanism of depositing most of their ionizing energy in a short distance with nearly negligible exit dose. Proton therapy is increasingly utilized for minimizing dose to OARs in patients with benign tumors and long life expectancy [74]. Proton therapy is currently performed using conventional fractionation schedules, although charged particle SRS is an investigational modality offered at select treatment centers.

Akin to SRS, SBRT is the delivery of high-dose radiation to a small treatment volume situated extracranially (hence, the inclusion of the term "body" in SBRT). SBRT involves the delivery of ablative doses in fewer treatment fractions (and hence is alternatively named "stereotactic ablative body radiotherapy" or SABR). While not frequently utilized specifically for the treatment of SFTs, SBRT has become increasingly utilized for well-circumscribed lesions within the thorax and abdomen and may be a therapeutic modality of interest in the management of intrathoracic/intra-abdominal SFTs.

The utilization of these various radiotherapy technologies will be addressed for each subgroup of SFT.

9.5.4.1 Intrathoracic SFTs

Radiotherapy for management of intrathoracic SFTs has predominantly been performed with EBRT. When administered adjuvantly in the treatment of intrathoracic

SFTs, radiotherapy is generally reserved for patients with malignant SFTs, positive or close surgical margins, large tumor size, or fast-growing tumors [46]. For the postoperative radiotherapy dose, the treatment paradigm is extrapolated from treatment of other tumor sites and is often around 50 Gy. Clinicians treating intrathoracic SFTs have historically utilized a dose ranging from 45 to 60 Gy [52, 80–82]. For patients in whom the risk of locoregional recurrence is perceived to be higher than otherwise, the optimal dose may range from 54 to 60 Gy or even higher (e.g., 60–66 Gy for patients with positive surgical margins) [46]. For patients who are not deemed surgical candidates being treated definitively with radiotherapy, a dose of 60 Gy or greater has been utilized [59].

To the authors' knowledge, there is no existing data assessing the utilization of SBRT in the management of intrathoracic SFTs. There is an ongoing phase 2 trial assessing the role of SBRT in the management of lung metastases from soft tissue sarcomas that aims to add prospective data to the existing retrospective literature on this subject (NCT02561559) [83]. A recently published retrospective review of 30 patients with sarcoma with 39 pulmonary metastases treated with SBRT found it to be safe and effective [84]. With further study, it is possible that SBRT may be utilized for the treatment of intrathoracic SFTs in addition to oligometastatic sarcoma in the lungs, as it seems to confer a decreased likelihood of grade 2 or higher acute toxicities [84].

Toxicities from radiotherapy of intrathoracic SFTs include acute toxicities of fatigue, nausea, and esophagitis, as well as the potential for radiation pneumonitis characterized by symptoms of cough, dyspnea, and low-grade fever—often accompanied by radiographic evidence of ground-glass opacities—for which patients may require treatment with a long course of glucocorticoids.

9.5.4.2 Intracranial HPCs

For intracranial HPCs, adjuvant radiotherapy is indicated in the postoperative setting following gross total resection, as both extent of resection (as defined by Simpson grade) and receipt of adjuvant radiotherapy have been found to be significantly associated with recurrence-free survival [57]. Furthermore, existing literature has suggested a role for dose escalation, given the locally aggressive nature of intracranial HPCs; for patients treated with EBRT using 3DCRT or IMRT, existing literature has demonstrated improved local control for patients receiving >60 Gy as opposed to 50 Gy [56, 57]. For patients receiving SRS, marginal dose recommendations reported in the literature range from 14 to 22 Gy, with some data demonstrating improvement in progression-free survival with margin doses greater than 16 Gy [85]. Kim et al. (2010) irradiated a mean tumor volume of 2.2 cubic centimeters with mean and median marginal doses of 18.1 Gy and 20 Gy, respectively (range: 11–22 Gy) prescribed to the 50% isodose line and observed a statistically significant improvement in local control for marginal doses of 17 Gy or higher with no noted adverse effects of radionecrosis or peritumoral edema in their cohort (n = 17) [86]. Based on these findings, a marginal dose of $\geq$16 Gy is advised.

Proton therapy is an emerging area of study in the treatment of intracranial HPCs. A feasibility phase II study sponsored by the Particle Therapy Cooperative Group (PTCOG) (NCT01117844) was developed to assess the safety and efficacy of standard dose proton radiotherapy for patients with WHO grade I–III meningiomas and hemangiopericytomas [87]. In addition to primary outcomes of safety and feasibility, the study additionally seeks to assess toxicities and quality of life outcomes. While particle therapy remains the subject of intense investigation, especially for rarer tumor types such as intracranial HPCs, it is ostensible that there could be a clinically meaningful reduction in the incidence of late-term toxicities for these patients with several year duration of disease-free survival [88].

Toxicities from delivery of radiotherapy to intracranial HPCs are often minimal in both incidence and severity (generally CTCAE grades 1 or 2). Acute toxicities include fatigue, dermatitis, alopecia, headache, and nausea with the potential for long-term toxicities of radionecrosis. If the treatment field encompasses the sella turcica, possible hormone deficiencies may result from irradiation of the pituitary gland and may occur at doses exceeding 50 Gy, with increased risk of hypopituitarism occurring with larger fraction sizes [74]. Depending on the location of the HPC being irradiated, patients may additionally be at risk for development of neurocognitive deficits or audiovisual dysfunction.

9.5.4.3 Extrathoracic SFTs

There remains an unclear role for radiotherapy in the adjuvant treatment of extrathoracic SFTs, particularly soft tissue/extremity SFTs. Several randomized trials assessing soft tissue sarcomas as a whole have demonstrated that adjuvant radiotherapy following (or prior to) surgical resection is associated with decreased local recurrence but without a statistically significant improvement in overall survival [yang]. Data specifically addressing SFTs has demonstrated largely a RECIST response of stable disease following neoadjuvant radiotherapy [89]. However, given that nearly 50% of patients with extremity sarcomas undergo unplanned excisions leaving gross residual disease or close margins [90], there is likely an important role for adjuvant radiotherapy in the management of SFTs in these locations. Clinical guidelines for soft tissue/extremity SFTs have largely been extrapolated from those for non-SFT sarcomas. Preoperative radiotherapy commonly occurs using 50 Gy, whereas the postoperative radiotherapy dose is typically higher and around 60–66 Gy. IMRT is often preferred to 3DCRT based on its more favorable toxicity profile [75].

Toxicities from management of extrathoracic SFTs greatly depend on the location. For patients with soft tissue/extremity SFTs, acute toxicity is often related to delayed wound healing and acute wound complications for patients being treated in the preoperative setting. For those receiving postoperative radiotherapy, potential late toxicities include fibrosis, decreased range of motion potentially limiting use of the affected extremity, and edema secondary to surgical disruption of lymphatics. It is critical to anticipate the potential for development of these toxicities for patients receiving postoperative radiotherapy, as the irradiated volume in the postoperative

setting is often higher than that of the preoperative or definitive setting. For patients with SFTs affecting specific disease sites (e.g., head-and-neck, retroperitoneum), the expected toxicity profile mimics those of tumors commonly treated in those respective anatomic regions.

9.5.5 Dosimetric Treatment Planning Considerations

9.5.5.1 Target Volumes

Intrathoracic SFTs

Gross Tumor Volume (GTV)
For patients who have received surgical resection, the GTV includes the resection cavity with any residual tumor noted on postoperative, contrast-enhanced CT or MRI. For patients receiving definitive radiotherapy, the GTV includes all visible tumor on imaging.

Clinical Target Volume (CTV)
The CTV includes gross disease plus a margin for microscopic areas at risk (for patients receiving definitive radiotherapy) or microscopic areas at risk within the postoperative tumor bed (for patients having received resection). This margin for potential microscopic disease is defined by the clinician after considering specific risk stratification for SFTs, all available imaging, and the anatomic barriers to spread.

Internal Target Volume (ITV)
The ITV consists of the CTV and additionally accounts for respiratory motion of the target noted on 4D CT scanning. ITV can be avoided with gating or minimized by abdominal compression.

Planning Target Volume (PTV)
A routine expansion of 3–5 mm is applied to the ITV and depends on the institution's image guidance capabilities.

Intracranial HPCs

Gross Tumor Volume (GTV)
For patients who are status post gross total resection, the GTV is defined as the tumor bed with any residual nodular enhancement noted on postoperative axial T1 post-contrast MRI. For patients with intact lesions receiving definitive radiotherapy, the GTV is simply defined as the enhancing mass noted on T1 post-contrast MRI imaging.

Clinical Target Volume (CTV)
Delineation of the CTV allows for the clinician to engage in careful consideration of any contiguous sites of microscopic spread. The CTV often incorporates a 1–2 cm margin – based on the idea that this area encompasses the region in which the patient is most likely to recur – while respecting intracranial anatomic boundaries. The CTV additionally should encompass the dural tail if one is noted on imaging.

Planning Target Volume (PTV)
The PTV incorporates inter-fraction variability in daily setup/patient positioning and, based on the modality of radiotherapy being administered, may range from 0 to 5 mm.

In the case of stereotactic radiosurgery (SRS), especially frame-based SRS in which setup errors are of lesser concern, the prescription dose may be delivered to the GTV. For patients treated with SRS, Balagamwala et al. published three important calculations to perform for treatment planning in the treatment of meningiomas that may be extrapolated to the treatment of intracranial HPCs [91]:

1. Conformality index: ratio of prescription isodose volume to tumor volume ≤ 2
2. Heterogeneity index: ratio of tumor volume maximum dose to prescribed dose ≤ 2
3. Gradient index: ratio of volume receiving half the prescription isodose to the volume receiving the full prescription isodose ≥ 3

Extrathoracic SFTs

Gross Tumor Volume (GTV)
For patients with SFTs receiving neoadjuvant radiotherapy in the preoperative setting or definitive radiotherapy, the GTV is defined using MRI T1 post-contrast images along with any gross disease noted on physical examination. For patients receiving postoperative radiotherapy, the GTV is comprised of any clinically or radiographically evident residual tumor as well as the surgical bed.

Clinical Target Volume (CTV)
For patients receiving preoperative or definitive radiotherapy, the CTV often consists of a standard expansion derived from soft tissue sarcoma guidelines and clinician experience, additionally encompassing any peritumoral edema noted on T2 MRI when possible. Historically, this may have consisted of a 1.5–2 cm radial expansion with a 4–5 cm longitudinal expansion proximally and distally along the extremity [92]; however, based on the updated results of RTOG 0630, reduced target volumes may be considered and have demonstrated equivalent local control outcomes with reduced late toxicity [93]. In RTOG 0630 with daily IGRT, patients with grade 2–3 tumors measuring less than 8 cm were treated with a CTV expansion of 1 cm radially and 2 cm superiorly and inferiorly; patients with grade 2–3 tumors

larger than 8 cm were treated with a 1.5 cm radial expansion and 3 cm superior/inferior expansion. Expansion of the CTV off the GTV additionally involves omission of anatomic barriers that are presumed to inhibit microscopic disease spread, such as adjacent bone, fascial planes, or skin.

For patients receiving postoperative radiotherapy, the CTV initially involves tumor bed, scar, drain site, and preoperative tumor (per presurgical imaging) plus a 4 cm longitudinal and 1.5 cm radial expansion, cropped at anatomic boundaries off of the GTV, and this is "coned down" later in treatment to a 2 cm longitudinal expansion while still maintaining a 1.5 cm radial expansion. Consider placing bolus on scar based on clinical suspicion and if not using intensity modulated radiation therapy (IMRT). The initial CTV is then coned down to deliver the boost portion. This includes tumor bed and preoperative GTV plus a 2 cm longitudinal and 1.5 cm radial expansion. Usually, the cone down occurs after 50 Gy in 25 fractions.

Planning Target Volume (PTV)

PTV expansions vary based on institution and may range from 0.5 to 1 cm.

A treatment plan for a patient with an extrathoracic, extracranial SFT of the left upper back receiving postoperative radiotherapy is shown in Fig. 9.3.

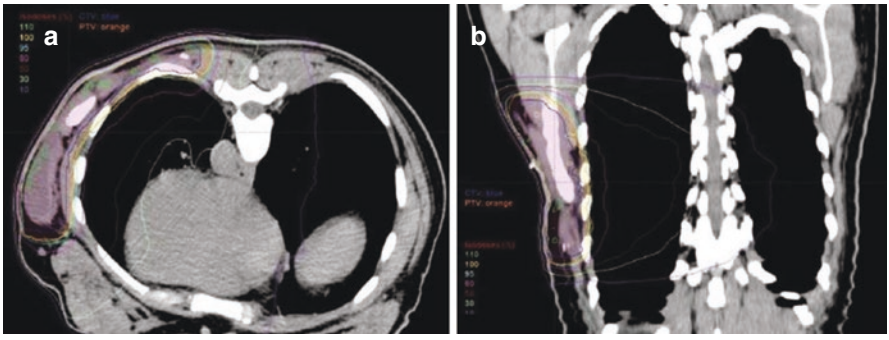

Fig. 9.3 A malignant solitary fibrous tumor of the left upper back in a 45-year-old woman who underwent marginal excision of a 3.5 cm tumor with multiple positive margins. Radical re-excision showed residual microscopic tumor and negative margins. Postoperative radiation therapy was delivered using intensity-modulated radiation therapy (50.4 Gy) for the first course and opposed oblique fields for the second course (12.6 Gy) to a total dose of 63 Gy

(**a**) Axial slice of a planning image shows the clinical target volume (CTV), which includes the operative bed with a margin (blue), planning target volume (PTV) (orange), and covering isodose lines

(**b**) Coronal planning image shows CTV (blue), PTV (orange), and isodose lines (Reference: Perez & Brady's Principles and Practice of Radiation Oncology (Perez and Bradys Principles and Practice of Radiation Oncology), 6 Ed. Chapter 83. Soft Tissue Sarcoma (excluding Retroperitoneum), Elizabeth H. Baldini (Reproduced with permission)

9.5.5.2 Dose Prescription

General Dose Guidelines

(Doses should be discussed on a case-by-case basis in a multidisciplinary setting.)

Intrathoracic SFTs:
Adjuvant >50 Gy (60–66 Gy if positive margins)
Definitive >60 Gy
Intracranial HPCs:
Adjuvant RT >60 Gy
SRS ≥16 Gy
Extrathoracic SFTs:
Preoperative dose ~50 Gy
Postoperative 60–66 Gy

When feasible, ideally 95% of the PTV should receive the prescription dose, and at least 98% of the GTV should receive the prescription dose [94].

9.5.5.3 Organs-at-Risk (OAR) Tolerances

OARs of interest when delivering EBRT to intrathoracic SFTs include the lung, spinal cord, heart, esophagus, and brachial plexus. Based on dose constraints from lung data reported in NCCN Guidelines Version 7. 2019 (recommendations based on concurrent chemoradiation), RTOG 1308 [95] and RTOG 1106 [96], we recommend the following:

- Lung – GTV: V20 ≤ 35%, V5 ≤ 60–65%, mean lung dose ≤20 Gy
- Spinal cord: max point dose ≤50 Gy
- Heart: V30 ≤ 50%, V45 ≤ 35% (RTOG 1308), V40 ≤ 35% (RTOG 1106), V50 ≤ 25%, and mean ≤ 20 Gy
- Esophagus: mean dose ≤34 Gy and max dose (0.03 cc) ≤ 74 Gy (RTOG 1106), V60 ≤ 17% and max ≤105% prescription dose
- Brachial plexus: median dose ≤69 Gy (NCCN), V70 ≤ 3 cc, V74 ≤ 1.0 cc,and V75 ≤ 5 cc (RTOG 1308)

If SBRT were to be utilized in the management of an intrathoracic SFT, specific dose constraints utilized for lung SBRT would be employed per NCCN Guidelines Version 7. 2019. Additional intrathoracic normal structures to be considered include the tracheobronchial tree, ribs, skin, and great vessels.

The maximum allowed dose constraints for OARS of interest when treating intracranial HPCs with IMRT are [57]:

- Spinal cord <50 Gy
- Brainstem <60 Gy
- Optic nerves <55 Gy
- Optic chiasm <56 Gy
- Lens <5 Gy
- Retinae <50 Gy
- Cochlea <45 Gy

The maximum allowed dose constraints for OARS of interest when treating intracranial HPCs with SRS are [57]:

- Brainstem <12.5 Gy
- Optic chiasm <10 Gy (recommended: < 8 Gy)
- Cochlea <12–14 Gy (recommended: < 4 Gy)

OARs of interest when delivering EBRT to extrathoracic, extracranial SFTs depend on the location and are generally extrapolated from soft tissue sarcoma data. Based on dose constraints reported in RTOG 0630 [93], we recommend the following:

- Anus/vulva: V30 ≤ 50%.
- Testis: V3 ≤ 50%.
- Lungs: V20 < 20%.
- Kidneys: V14 < 50%.
- Longitudinal skin/subQ strip: V20 ≤ 50%.
- Fem heads: V60 < 5%.
- Bone: V50 ≤ 50%.
- Joints: V50 < 50%.
- Avoid full Rx dose to skin over areas commonly traumatized (e.g., the elbow, knee, shin).
- Bone V50 < 50% except when tumor invades bone or if circumferential involvement more than ¼ of bone or when the bone will be subsequently resected.
- For other OAR, RT dose should be <TD5/5 limit.
- Avoid skin in CTV or PTV unless involved.
- Avoid skin bolus if IMRT otherwise bolus the scar.
- Avoid biopsy scar if small and will be resected.

9.5.6 Physics and Quality Assurance

Quality assurance (QA) is an integral aspect in the safe and effective delivery of radiotherapy, and medical physicists are team members often tasked with this important role. The American Association of Physicists in Medicine (AAPM) has described its quality assurance processes in several task group reports outlining quality assurance of various aspects of treatment delivery, from IGRT to medical accelerators to special procedures. QA overall is a multistep process that

encompasses the following components: (1) equipment-specific QA, (2) patient-specific QA, and (3) procedure-specific QA [97]. Each will be briefly addressed here:

9.5.6.1 Equipment-Specific QA

During the initial commission of a treatment machine and calibration, equipment-specific QA performance metrics are determined, and it is decided which of these will be achieved on a daily, monthly, or annual basis [97]. Daily assessments for imaging technology include IGRT positioning/repositioning and collision interlocks, among other metrics, for both planar imaging and CBCT [98]. Quality assurance with regard to IGRT aims to assess image quality, spatial accuracy, precision of registration and couch movements, and congruence of imaging and treatment isocenters [99]. Another crucial daily assessment is linear accelerator output constancy, which is also assessed monthly and annually [97]. Output constancy at certain dose rates is assessed monthly, and monitor unit linearity is assessed annually [97].

9.5.6.2 Patient-Specific QA

Patient-specific QA performed by medical physics includes:

- Verification of patient setup and immobilization
- Independent review of the approved treatment plan
- Confirmation of treatment delivery parameters
- Dose delivery measurements
- Participation in chart rounds/departmental peer review
- Running the treatment plan in advance to check treatment integrity

9.5.6.3 Procedure-Specific QA

Procedure-specific QA involves monitoring of systems-level processes including workflow and staffing [97]. Team members should be appropriately trained in the type of radiotherapy delivery in which they are participating; this is especially critical for the performance of special procedures such as SRS/SBRT. Procedure-specific QA additionally entails taking appropriate action if any treatment incidents occur, both actual events and near misses [97].

9.6 Summary of Radiotherapy Treatment Algorithm

Figure 9.4 depicts a summary algorithm with the general treatment paradigm for the three subclasses of SFTs discussed in this chapter.

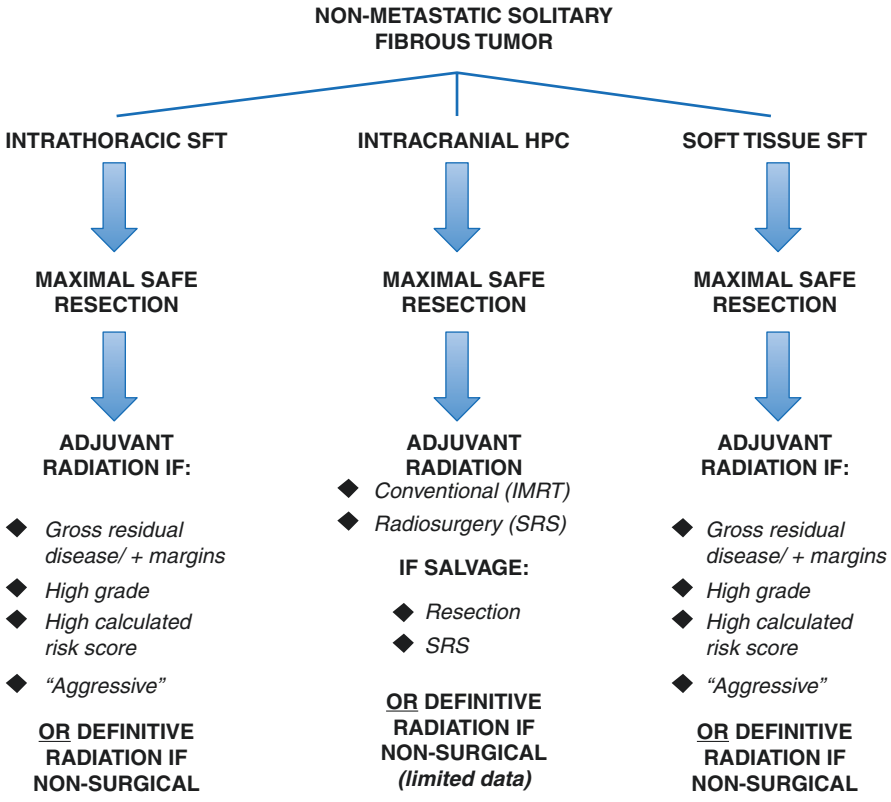

Fig. 9.4 General treatment paradigm for management of nonmetastatic SFTs

9.7 Conclusion

Solitary fibrous tumors (SFTs) comprise a histologic spectrum of rare soft tissue neoplasms demonstrating fibroblastic differentiation. A subgroup of SFTs is hemangiopericytomas based on the shared molecular feature of a NAB2-STAT gene fusion. These tumors range in behavior from clinically benign to malignant and aggressive, and the latter class has a propensity toward late recurrence and metastasis, sometimes up to 20 years following delivery of curative intent therapy. The utilization of adjuvant radiotherapy in the postoperative setting is a well-established recommendation for treatment of intracranial HPCs, whereas the role of radiotherapy in the management of intrathoracic and soft tissue/extremity SFTs remains less clear. IMRT or SRS may be utilized in treating intracranial HPCs, and salvage reirradiation often involves use of SRS. Published reports on definitive radiotherapy in the management of intrathoracic SFTs have demonstrated excellent outcomes. Future research in the study of SFTs to expand clinical practice guidelines include prospective trial activities, utilization of SBRT, and exploration of particle therapy for intracranial HPCs.

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Radiation Therapy for Angiosarcomas

10

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10.1 Introduction

Angiosarcomas (AS) are an aggressive subtype of soft tissue sarcoma derived from malignant endothelial cells of vascular or lymphatic origin [1]. They are an insidious tumor and, thus, typically present with advanced disease, making treatment difficult and potentially morbid. Given their rarity, prospective data is limited, and current treatment guidelines are derived from small retrospective series. In general, multidisciplinary management of this disease is required, including input from surgical, medical, and radiation oncology. This chapter provides an overview of AS including current management of the various clinical subtypes, including advances in treatment techniques in surgery, radiation therapy, and systemic therapy.

10.2 Epidemiology

AS represent, approximately 2% of all soft tissue sarcomas [2]. Based on data from the Surveillance, Epidemiology, and End Results (SEER) Program, AS represented 1.6% of all cutaneous soft tissue sarcoma cases diagnosed from 1992 to 2004 [3]. They arise throughout the body, most often as cutaneous lesions, but can arise from any soft tissue structure [4]. AS can occur at any age but are more common in the elderly with the cutaneous subtype observed most often in elderly white males [3, 5]. The incidence of AS has been increasing over the last 30 years with the distribution pattern also changing [1, 6]. There has been a rise in cutaneous AS, now accounting for approximately 50% of all AS, likely secondary to an increase in cutaneous sarcomas following radiation therapy [6]. Of the remaining 50%, about 14% is localized to breast parenchyma, 11% is soft tissue, and the remaining is divided between heart, bone, spleen, liver, and other sites [5].

10.3 Etiology

While most cases are sporadic, there are several well-described specific risk factors, including previous radiation exposure, chronic lymphedema, exogenous toxin exposure, and familial syndromes [1, 5]. Radiotherapy-associated sarcomas are rare but may account for up to 5% of all soft tissue sarcomas [7–10]. While radiotherapy-associated AS may occur at any site, it is most completely described for breast cancer [11–13]. In a retrospective study from the Netherland Cancer Registry consisting of nearly 300,000 patients, no patients who underwent mastectomy for breast cancer developed an AS [12]. In patients who received radiation as part of breast cancer therapy, 0.1% developed a radiotherapy-associated AS in either the breast or chest wall with older patients at increased risk [12]. Radiation therapy is an independent risk factor for AS, separate from chronic lymphedema [1, 6]. By definition, these tumors must (1) be biopsy proven, (2) arise within or adjacent to a prior radiation therapy field, (3) occur several years after completing radiation therapy, and (4) originate in an area that is without lymphedema [6, 10]. Radiotherapy-associated

sarcomas have a worse prognosis than sporadic soft tissue sarcomas [9, 14]. In a retrospective study assessing the clinical and functional outcomes of patients with radiotherapy-associated soft tissue sarcoma, Riad et al. reported that patients with radiotherapy-associated sarcoma have a greater risk of local and systemic recurrence with similar functional outcomes compared to patients with sporadic soft tissue sarcoma [14]. In a separate retrospective study from Memorial Sloan-Kettering, patients with radiotherapy-associated sarcomas had inferior disease-specific survival compared to patients with sporadic soft tissue sarcoma [9].

While chronic lymphedema of any origin is associated with AS, the most common observed scenario is in women with breast cancer treated with mastectomy who suffer from years of chronic severe lymphedema, first described by Stewart and Treves [1, 6, 15]. The incidence of developing AS in patients surviving at least 5 years after radical mastectomy is up to 0.45% [16]. While the mechanism is uncertain, one theory suggests that blockage of lymphatic drainage results in impaired antigen presentation, which subsequently results in an immunologically privileged site due to avoidance of immune surveillance [17]. Lymphedema secondary to other conditions such as congenital hereditary lymphedema (Milroy's disease) and chronic infections like filariasis have been associated with development of AS but in a limited capacity described primarily in case reports [1, 18, 19].

Toxic chemical exposure is associated with the development of AS primarily in the liver [20]. Exposure to vinyl chloride monomer used in the production of polyvinyl chloride was found to be highly associated with hepatic AS, based on a study from Great Britain [21]. Other chemicals associated with hepatic AS include the radiocontrast agent Thorotrast (colloidal thorium dioxide) [22, 23], androgenic steroid use [24], and arsenic [25]. AS have also been reported following either iatrogenic or accidental introduction of a foreign material into the body [6, 26]. A case of a colon AS forming at the site of a retained surgical sponge has been reported [27] as well as arising at the site of Dacron vascular grafts [28, 29], orthopedic implants [30, 31], and even a chronic gouty tophus [32].

Finally, certain familial syndromes are associated with AS, including neurofibromatosis [33, 34], Klippel-Trenaunay syndrome [35], Maffucci syndrome [36], xeroderma pigmentosum [37], bilateral retinoblastoma [38], and Aicardi syndrome [39]. Patients with *BRCA1* and *BRCA2* mutations have also been suggested to have an increased risk of AS following treatment for breast cancer [40].

10.4 Imaging

Given the infiltrative nature of AS, it is typically challenging to determine the extent of these lesions clinically, particularly on the scalp. Imaging, primarily MRI, is a useful tool in identifying extent of disease for patients with AS of the head and neck region. AS are typically contrast-enhancing lesions often with non-enhancing areas indicative of tumor necrosis [41]. One diagnostic imaging finding on MRI is high-flow serpentine vessels with low signal intensity on T1- and T2-weighted images in

a nonspecific soft tissue mass [41]. As the lungs are one of the most common sites of metastasis, a chest CT should be included as part of standard workup.

10.5 Pathology

Histologically, AS are difficult to distinguish from benign or inflammatory lesions and rarely have distinct borders separating them from adjacent normal tissue [1]. Tumors that are well differentiated appear as irregular dilated vascular channels, which dissect the underlying dermis to form a network [42]. Higher-grade AS are characterized by more chaotic architecture with ill-defined vascular structures and sheets of endothelial cells making differentiation from carcinoma and melanoma difficult (Fig. 10.1) [1, 42]. The most frequent immunohistochemical markers for diagnosing AS are CD31 and CD34 [43, 44]. Additional nuclear immunohistochemical markers include Avian v-ets erythroblastosis virus E26 oncogene homologue (ERG) and FLI1 [42, 44–46]. Additional markers, which are less

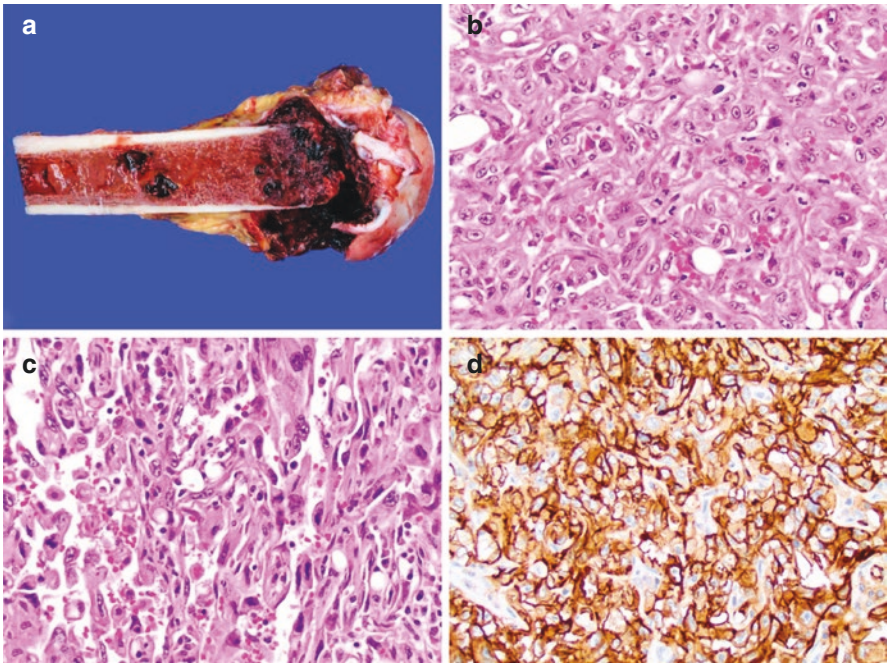

Fig. 10.1 *Epithelioid angiosarcoma of the left femur.* (**a**) Gross image of the primary angiosarcoma showing a large expansile hemorrhagic tumor with cortical bone destruction, involving the left distal femur. There are two smaller foci of tumor cephalad to the main tumor representing multifocal discontinuous involvement. (**b**) Hematoxylin and Eosin-stained section showing malignant epithelioid vascular neoplasm with limited vasoformation (Mag., ×400). (**c**) Hematoxylin and eosin-stained section showing prominent vasoformation, pleomorphism, and easily discernible mitosis, morphologically consistent with epithelioid angiosarcoma (Mag., ×400). (**d**) CD31 immunohistochemical stain, strongly and diffusely decorating the tumor cells (Mag., ×400)

frequently used, include von Willebrand factor, BNH9, factor VIII-related antigen, PROX-1, and *Ulex europaeus* [42].

10.6 Clinical Subtypes

10.6.1 Primary Cutaneous Angiosarcoma

10.6.1.1 Diagnosis

Primary cutaneous AS is the most common clinical subtype accounting for approximately half of all cases [6]. More than half of all cases occur in the head and neck region with the scalp being the most common site [47]. It most commonly affects the elderly, typically after the seventh decade and is slightly more common in men than women [6, 47]. Initially, cutaneous AS may resemble a bruise, hemangioma, or infection and may be mistaken for a benign lesion leading to delays in diagnosis and more advanced disease when definitive treatment is finally initiated. Larger lesions may result in tumor fungation, ulceration, and hemorrhage [1]. MRI is helpful to determine extent of disease. In addition to imaging, the use of grid pattern punch biopsies or Mohs mapping to delineate tumor margins has been reported [48].

10.6.1.2 Management

Since head and neck is the most common site of primary cutaneous AS, the management discussion will focus on lesions in this region. Given the rarity of this malignancy, there are no randomized trials and few prospective studies with most of the data and subsequent treatment guidelines formulated from retrospective series. As with all rare malignancies, patients with AS should be managed at specialist centers by a multidisciplinary care team.

Surgery

For localized disease, radical surgery with the goal of achieving negative margins (R0 resection) is the treatment of choice [1]. Incomplete resection has been associated with worse outcomes [5, 49, 50]. While wide resection margins are recommended, this can be challenging because of tumor location and the infiltrative nature of these tumors [1]. One centimeter gross margin is recommended at resection. Intraoperative frozen section has been shown to have negative predictive value of only 33%, with the suggestion that reconstruction only be completed following review of permanent pathologic specimens [51]. Frequently, the surgical site is not closed until negative margins are confirmed at which time definitive closure and reconstruction can be performed. Flap-based reconstruction or local tissue rearrangement is usually required over a skin graft due to the scalp location and need for post-resection radiation.

Radiation Therapy

Due to the high risk of local recurrence, adjuvant radiation therapy is typically recommended with multiple retrospective studies supporting its utility. Pawlik et al. reported a retrospective series of 29 patients with scalp AS treated at the University

of Michigan between 1975 and 2002 [51]. The majority of patients underwent surgical excision with only 21.4% of patients achieving final negative surgical margins. Twenty-three patients received postoperative radiation therapy, which included the whole scalp to a dose of 60 Gy in 1.8–2 Gy fractions with a boost to sites of macroscopic disease for a total dose of 60–72 Gy. While radiation therapy was not seen to impact the time to overall (local or distant) recurrence, it was found to significantly prolong the time to local recurrence ($P = 0.03$). Guadagnolo et al. reported on the MD Anderson experience of cutaneous AS of the face and scalp treated between 1962 and 2009 [52]. Of 70 patients total included in the study, 39% received both surgery and radiation therapy with a radiation dose of 60–70 Gy. Combined modality therapy consisting of surgery and radiation therapy compared to either modality alone was associated with improved local control, disease-specific survival, and overall survival. Patel et al. reported on 55 patients with scalp and face AS treated at Mayo clinic between 1973 and 2012 [53]. Patients receiving radiation therapy as part of their treatment were observed to have improved locoregional control on univariate analysis.

Due to the infiltrative nature of scalp AS with a high risk of local recurrence, large radiation fields are typically used including the entire scalp. Traditionally, total scalp irradiation involved the use of numerous electron fields with surface matching until the introduction of the lateral electron-photon technique in the early 1990s [54]. The electron-photon field matching technique employed two lateral 6 MV photon fields treating the scalp with margin both internally and externally. Custom lead blocking was used to limit the dose to brain tissue on lateral photon fields (Fig. 10.2a). Lateral 6 MeV electron fields were then added as supplemental dose to treat the blocked portion of the photon fields with 4 mm of overlap between photon and electron field borders (Fig. 10.2a). Using 6 mm of bolus, scalp dose was

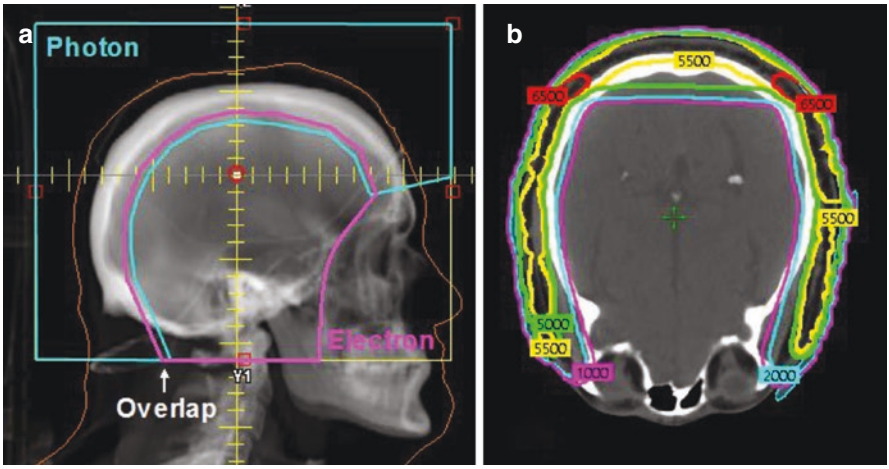

Fig. 10.2 (**a**) Lateral view of the blocked photon and electron field match similar to the technique used by Tung et al. [54] (**b**) The isodose distribution in the axial plane with a prescription dose of 55 Gy and 6 mm of bolus

commonly prescribed to 55 Gy to be delivered in 1.8–2 Gy increments with sequential electron field boosting to macroscopic disease. Similar techniques were employed at MD Anderson between 1962 and 2009 and the University of Michigan between 1975 and 2002 with scalp prescription doses of 60 Gy at 2 Gy per fraction [51, 52]. In addition to the base 60 Gy, macroscopic disease could similarly be boosted to a total dose of 60–72 Gy [51, 52].

While a viable treatment method, potential complications with this traditional technique would arise based on the convex curvature of the skull and the simple lateral beam arrangement. It was not unusual to see unwanted high dose to the patient's scalp in the areas of field overlap, commonly as high as 115%–125% of prescription dose (Fig. 10.1b). In conjunction, prescription dose could infiltrate the superior aspect of brain based on gantry limitations and field borders, along with the increased difficulty involving setup matching during treatment. Likewise, electron-photon field matching could lead to reduced dose in scalp at depth along with the areas of dose overlap superficially.

In addition to dosimetric concerns, the lateral field geometry limited treatment to scalp-only treatment. If an AS patient presented with face involvement, more supplemental electron matching would be required. In this process, setup time, shifting between treatment fields, and match inconsistencies were common factors to monitor throughout the course. Likewise, custom lead blocks could be both heavy and labor intensive during fabrication. Based on the extensive scalp involvement associated with the treatment of AS, the ability to deliver dose to treatment targets while limiting dose to critical organs, such as the brain, remains a challenging objective. This objective can present difficulties for both 2D- and 3D-conformal treatment planning techniques based on scalp anatomy and treatment delivery.

As an alternative to these traditional techniques, the expanded use of intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and other modulated-based planning methods can be explored for radiotherapy of AS. A single isocenter IMRT technique can eliminate many of the shifting and field matching requirements during a patient's treatment, reducing many of the concerns associated with traditional 2D and 3D match-based techniques. Additionally, inverse planned optimization can allow for simultaneous integrated boosting (SIB) to high-risk areas in a single plan, eliminating the need to sequentially boost with electron fields. In the following case, VMAT planning was utilized to generate the treatment plan for a patient with AS of the right scalp. The potential dosimetric benefits accompanying this modulated-based method are detailed throughout the process.

For the following case presentation, the patient had AS of the right scalp after resection with close surgical margins and multiply recurrent disease at the surgical incision site. In addition, the patient had new lesions involving the right temporal region and right face. The patient was discussed at multidisciplinary sarcoma tumor board, and the consensus was treatment with radiation therapy with concurrent chemotherapy.

Simulation

With involvement of the entire scalp and right face, collaboration with multiple radiation oncology department groups, including physics and dosimetry, was

helpful to set simulation goals prior to commencing patient setup. Similarly, establishing the treatment method of choice prior to the simulation process allowed for optimal selection of setup devices prior to fabrication. Given the extensive treatment area, right face inclusion, and curvature of the scalp, a VMAT photon technique was favored over electron treatment methods.

With a photon-based method, the area required bolusing to effectively eliminate skin-sparing. With the convex curvature of the scalp, traditional bolusing methods, such as sheet-bolusing or water-dampened cloth, were determined to introduce unacceptable air gaps and inconsistencies in density. As a result, a customized wax (density = 0.9313 g/cm^3) bolus structure employing a 3D-printed/milled method was used for this patient. In order to generate such a device, a preliminary computed tomography (CT) dataset was required for bolus delineation. At the time of this preliminary scan, the treatment field contents were outlined using radiopaque wire to ensure proper bolus margins (Fig. 10.3). This process entailed accurate delineation of the patient's external body habitus as well as rendering a bolus structure of appropriate uniform thickness (1 cm) in the treatment planning software (Fig. 10.4). Additionally, acceptable margin was added to the wired treatment area for daily setup discrepancies. Fabrication resulted in two-pieces divided longitudinally along the hemispheres with index points to aid in reproducibility (Fig. 10.4).

Once bolus fabrication was complete, the patient was simulated in a stable supine position, head first, with arms at sides. The bolus was placed snuggly on the patient's scalp with a customized headrest to index around posterior contents of the bolus. A thermoplastic mask was used to immobilize the patient's skull, maxilla, mandible, and shoulders (Fig. 10.5). For comfort and tolerance, the patient was given an indexed knee sponge to elevate the legs.

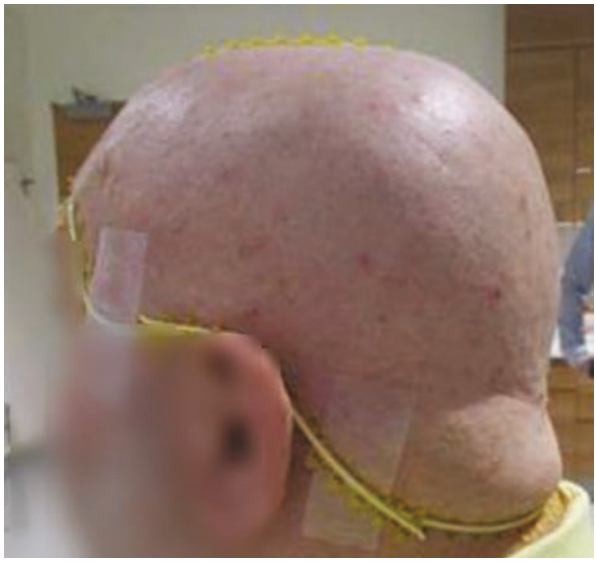

Fig. 10.3 The treatment area was outlined using radiopaque wire to aid in target delineation and bolus fabrication

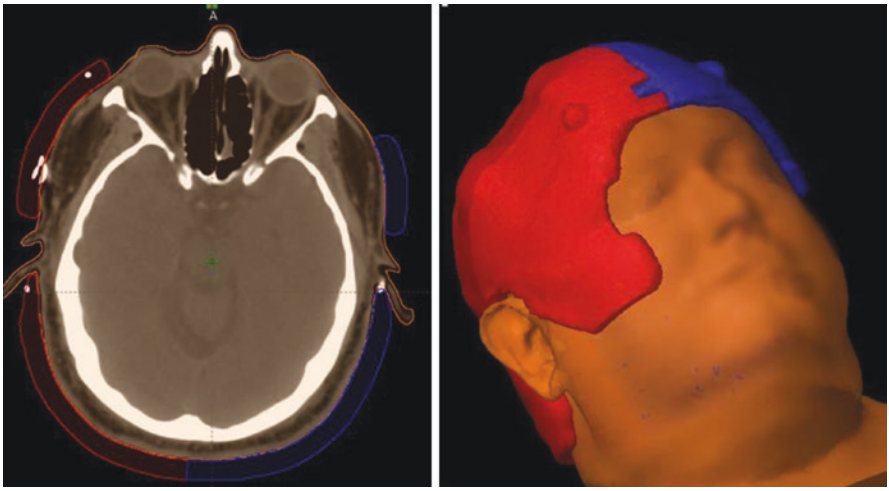

Fig. 10.4 The bolus was rendered from the external contour using uniform 1 cm thickness, extending with margin beyond the contents of the treatment area. The bolus was fabricated in two pieces with index points anteriorly for use with the thermoplastic mask

Fig. 10.5 The patient was simulated with a thermoplastic head and shoulders mask over the bolus with a customized head rest posteriorly

Target Delineation Including Organs at Risk (OAR)

The high-risk clinical target volume (CTV) was delineated to include the tumor bed on the right face and right anterior scalp, along with residual disease present at the time of consult and simulation (Fig. 10.6). This area was prescribed 66 Gy in 30 fractions. The low-risk CTV included the entire contents of the patient's scalp, along with the tumor bed and residual disease (Fig. 10.6). This area was prescribed 60 Gy in 30 fractions to be delivered concomitantly with treatment of the high-risk area. Planning target volumes (PTV) were created by expanding respective CTV structures 3 mm uniformly. Resultant PTV and CTV structures were extracted to the

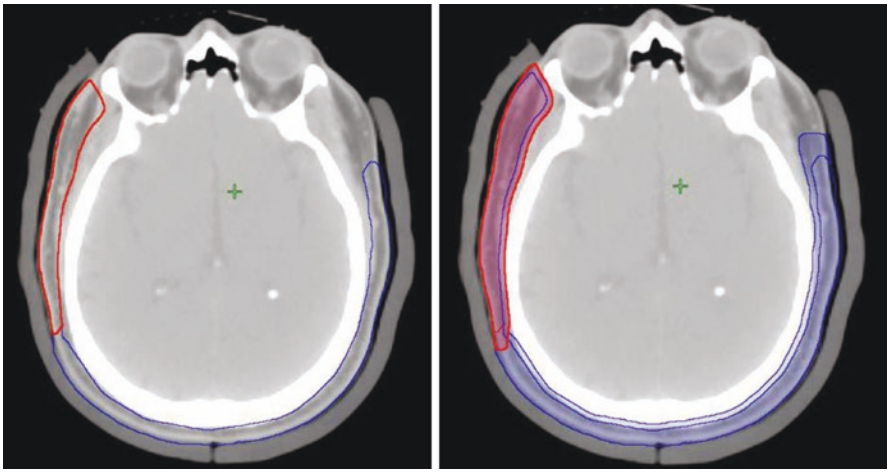

Fig. 10.6 The high-risk CTV (red, left) and low-risk CTV (blue, left) were expanded 3 mm uniformly to create the high-dose PTV (red, right) and low-dose PTV (blue, right). All target contours were cropped to the external surface of the skin for evaluation

superficial periphery of the skin contour (Fig. 10.6). Local anatomic OAR delineated in the plan for dosimetric evaluation included the following: brain, brainstem, brainstem planning risk volume (PRV) with 3 mm uniform expansion, spinal cord, spinal cord PRV with 3 mm uniform expansion, bilateral cochlea, bilateral lacrimal glands, bilateral globes of the eye, bilateral lens, bilateral optic nerves, optic chiasm, and optic PRV with a 3 mm uniform expansion from the optic pathway.

Treatment Planning

For this patient's treatment plan, the delivery technique consisted of four full coplanar VMAT arcs with tracking jaws. Collimator jaws were staggered and offset in four planes to promote the dose-sparing of medial brain with both jaws and multileaf collimators (MLC) while allowing peripheral treatment to the scalp and face (Fig. 10.7). With the superficial treatment contents and required bolusing, a 6 MV energy setting was utilized for treatment delivery. Per the treatment prescription, the high-dose PTV was planned to receive a uniform 66 Gy to be delivered in 30 fractions to at least 95% of the target volume. In the same plan, the low-dose PTV was designed to receive 60 Gy to at least 95% of the treatment volume concomitantly. During optimization, external margin was added to PTV targets to promote flash within the treatment plan, increasing dose to the skin surface while adding plan robustness. Likewise, limiting dose to the optic structures, brainstem, lacrimal glands, globes, and brain was prioritized during treatment planning through the use of optimization tools. Emphasis was also placed on general dosimetric falloff medially through the use of iterative optimization tools created by the planning team. Dosimetric tolerances were evaluated for brain, optical structures, brainstem, midbrain structures, and lacrimal glands during treatment review. Likewise, global dose

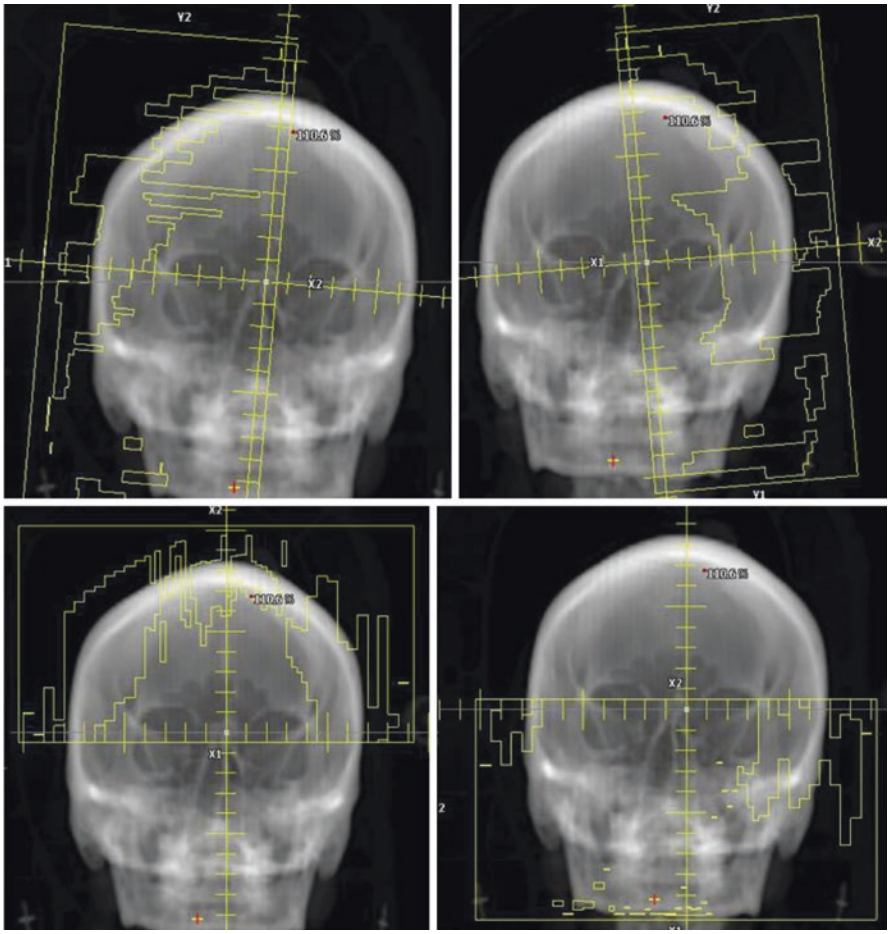

Fig. 10.7 Independent collimator jaws were staggered superiorly, inferiorly, left, and right for each 360-degree VMAT arc to limit dose to midline structures while delivering peripheral dose to treatment targets

maximums and target minimums were reviewed. An axial cross-section of the completed treatment plan with isodose lines is shown in Fig. 10.8.

Treatment Delivery

This patient's treatment was delivered over the course of 6 weeks utilizing onboard imaging (OBI) and daily cone-beam computed tomography (CBCT) to minimize setup variation. In conjunction with image guidance (IGRT), treatment margins on image sets were assessed during weekly checks and imaging review. To assist with daily setup, this patient was treated on a Varian TrueBeam® linear accelerator with 6-degree table correction capabilities. This allowed for adjustments to pitch, yaw,

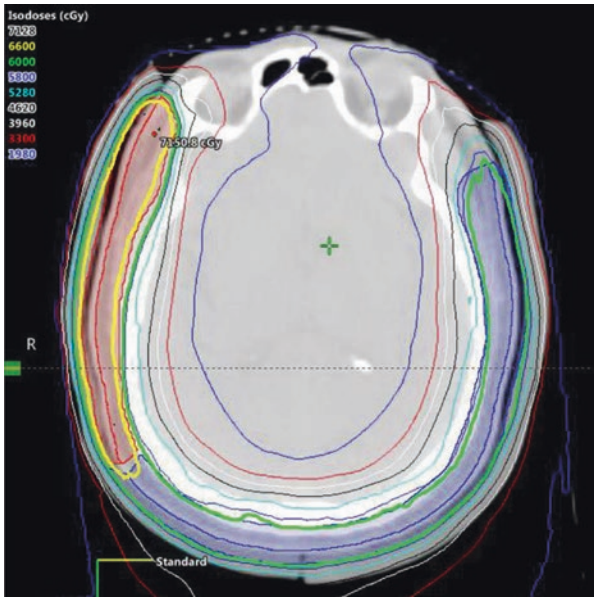

Fig. 10.8 66 Gy was delivered to the high-dose PTV (red) while delivering 60 Gy concomitantly in 30 fractions to the low-dose PTV (blue). Emphasis was placed on limiting low-dose to midbrain and OAR as seen by the 19.8 Gy isodose line (blue)

and roll along with translational corrections in the *X*, *Y*, and *Z* planes. All corrections were reviewed and approved if within tolerance prior to treatment.

Safety/Quality Assurance (QA)

IMRT QA was delivered on the VMAT treatment plan prior to delivery utilizing portal dosimetry. Results were compared to the approved treatment plan and confirmed using department adherence guidelines. In conjunction with IMRT QA, an assortment of requisite secondary checks of the plan were performed during routine departmental physics checks. Of note, particular emphasis was placed during checks on appropriate usage of external flash. With full scalp treatment, the rendering of an external margin during radiation treatment planning in addition to the standard internal margin is often necessary based on setup.

For scalp and skin lesions treated with photons, it is recommended that in vivo measurements be administered on the first fraction. In this example, in vivo dosimetry was applied using optically stimulated luminescent dosimeters (OSLD) to evaluate superficial dose to the patient's scalp. Multiple OSLDs were placed at various locations on the targeted area prior to treatment. The locations were then recorded and imaged for reference. Following the completion of the treatment fraction, measurements were read, documented, and confirmed with the care team. At this point, any adjustments to the plan based on measurement may be performed.

Systemic Therapy

For patients with localized disease, the role of perioperative chemotherapy remains unclear due to the scarcity of data. Neoadjuvant chemotherapy alone has not shown a clear statistical benefit in survival or recurrence-free rate; however, it may

represent a valid treatment option, especially for AS of the face with periorbital involvement [55]. Moreover, the combination of neoadjuvant chemotherapy with radiation therapy may render excellent local control and lead to a less extensive surgery [5, 55]. For patients with locally advanced/unresectable tumors or patients not undergoing surgery, either definitive radiation therapy or chemoradiation is a reasonable treatment option. The role of adjuvant chemotherapy, either alone or concurrent with radiation, is controversial [1, 56, 57]. In a retrospective study of nonmetastatic cutaneous AS of the scalp and face, outcomes were not significantly better in patients who received any chemotherapy in addition to local therapy (5-year overall survival 45 vs 39 percent, $P = 0.54$) [52].

Systemic treatment for metastatic/locally advanced AS generally follows similar principles as other soft tissue sarcomas. However, AS is particularly sensitive to taxanes with a clinical response rate to doxorubicin plus ifosfamide reported to be up to 30% [58, 59], while a review by the European Organisation for Research and Treatment of Cancer showed a response rate of 62% to paclitaxel [60]. In the ANGIO-TAX-PLUS-0906 phase II trial, paclitaxel given weekly resulted in a progression-free survival (PFS) of 45% at 4 months and a median overall survival of 8 months [61]. Additional studies have reported on the effectiveness of single-agent taxane or concurrently with radiation therapy [62, 63]. A summary of studies evaluating systemic therapy for AS is included in Table 10.1.

Primary and secondary AS have increased expression of angiogenic receptor tyrosine kinase transcripts, including VEGFR1/2/3 [75–77], as well as mutations in several angiogenesis-related genes [78]. Given these findings, antiangiogenic tyrosine kinase inhibitors (TKIs) for AS have been assessed [63, 73]. The response rate to bevacizumab alone was 8% with a median PFS of 3 months, and adding

Table 10.1 Systemic therapies for angiosarcoma (Reprinted with permission from Khan, J. et al.: J Clin Oncol 36 (2)., 2018:196–201. © (2018) American Society of Clinical Oncology. All rights reserved)

Therapy	Response rate (%)	Median PFS (months)
Chemotherapy		
Doxorubicin (including liposomal formulations) [49, 59, 64]	29–50	3.7–4.2
Doxorubicin + ifosfamide + mesna [49]		5.4
Paclitaxel [49, 59, 61, 64–66]	7.14–89	
Ifosfamide [49]		1.6
Gemcitabine [49, 67]	64	
Vinorelbine [49]		3
Growth factor-targeted therapy		
Sunitinib [68]	50	
Sorafenib [68–70]	13–21	
Pazopanib [71, 72]	17–20	
Bevacizumab [73]	9	3
Imatinib [74]	0	2.76

bevacizumab to weekly paclitaxel did not improve the response rate (28% with the combination compared to 46% with paclitaxel alone) or PFS (6.6 months in both groups) [63, 73]. The response rates of AS to sorafenib and pazopanib, both multi-targeted TKIs, have been shown to be approximately 20% [69, 71]. Current trials are focused on assessing the use of immunotherapy and additional combinations of angiogenic targeted agents [4].

10.6.2 Angiosarcoma Associated with Lymphedema

10.6.2.1 Diagnosis

Lymphedema-associated AS typically arises following surgery for breast cancer. Patients present with purplish-red, macular, or polypoid lesions in the lymphedematous extremity (Fig. 10.9) [15]. The lesions can coalesce, spread further down the extremity onto the wrist and hands as well as the thorax, and will frequently ulcerate and weep.

10.6.2.2 Management

Given its rarity, consensus guidelines for management of lymphedema-associated AS do not exist. Primary surgical therapy is typically used upfront including wide local excision or even amputation with adjuvant therapy, such as systemic therapy and radiation used in select cases. Patients with this type of AS are more prone to local and distant recurrence and death [79].

10.6.3 Breast Angiosarcoma

10.6.3.1 Diagnosis

Primary AS of the breast arises from the mammary parenchyma rather than the overlying skin. In many published series, parenchymal breast AS and AS arising

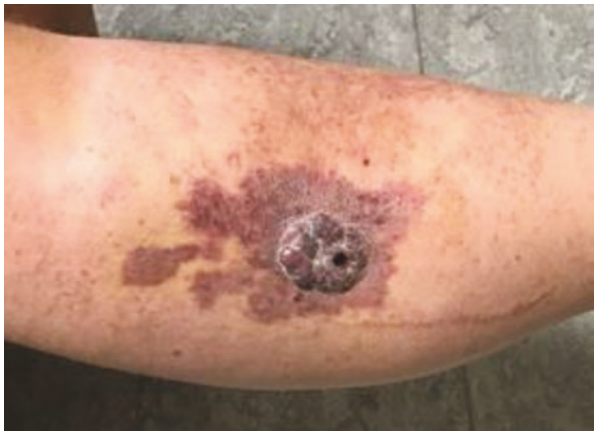

Fig. 10.9 Patient presenting with an angiosarcoma of the right lower leg in the setting of chronic lower extremity lymphedema

from the skin of the breast are combined, making it difficult to fully characterize the clinical features of parenchymal breast AS. Breast sarcomas, in general, are rare and consist of less than 1% of all breast malignancies with AS one of the main primary histologic subtypes [80, 81]. Patients are young with median ages of approximately 40 and typically present with a large painless mass or nodule [82, 83]. Median tumor sizes range from 5 to 7 cm, and regional lymph nodes are seldom involved [82, 83]. Breast AS are graded, although the significance of grade on patient outcome has been called into question [82]. Locoregional recurrence rates are moderate with high rates of distant metastasis. In the series published by Nascimento et al., the rate of local recurrence at a median follow-up of 29 months was 24.4% with nearly 60% developing metastasis at a median of 34 months after diagnosis [82]. In the published series from MD Anderson, the 5-year recurrence free survival rate was 44% with a 5-year overall survival of 61% [83].

10.6.3.2 Management

The optimal management of breast AS has not yet been determined. If feasible, the primary management is surgical, typically mastectomy due to the size and infiltrative nature of these lesions. Axillary lymph node dissection is indicated, if lymph node metastasis is identified on preoperative imaging or exam. The role of systemic therapy either in the neoadjuvant or adjuvant setting is unclear, although some centers favor neoadjuvant therapy. In the series from MD Anderson, chemotherapy was not associated with improved recurrence-free survival or overall survival in either univariate or multivariate analysis [83]. Similarly, the role of adjuvant radiation therapy is unclear. In the same study by Sher et al., there was no benefit of adjuvant radiation therapy on local-regional recurrence-free survival [83]. In patients who developed metastatic disease, however, a 48% response rate was observed in patients treated with a first-line anthracycline-ifosfamide or gemcitabine-taxane chemotherapy combination [83].

10.6.4 Soft Tissue Angiosarcoma

AS arising from the extremities occurs in about 15% of cases, while those arising from the trunk occur in less than 10% of cases [1]. Management of soft tissue AS of the extremity and retroperitoneum follows algorithms of other soft tissue sarcomas and is included in Chaps. 1 and 2, respectively. The majority present as high-grade lesions. Surgical resection with negative margins remains the mainstay with the addition of radiation and chemotherapy for high-grade lesions.

10.6.5 Radiation-Induced Angiosarcoma

10.6.5.1 Diagnosis

Secondary malignancy is a rare but late sequela of radiation therapy. In adults exposed to therapeutic radiation therapy, the incidence of radiation-associated

sarcoma is estimated to be much less than 1%, while children have a higher incidence of radiation-induced sarcoma with a reported incidence closer to 1% [84, 85]. Of radiation-induced sarcomas in adults, AS represents approximately 20% of histologic subtypes [9]. In the large series from Memorial Sloan-Kettering Cancer Center, which included 130 patients with radiation-associated soft tissue sarcomas, the median interval between radiation and the development of sarcoma was 10 years [9]. Radiation-induced AS is best described for breast cancer following breast conservation surgery and adjuvant radiation therapy. In a recent study based on the Finnish Cancer Registry, of 132,512 patients diagnosed with an invasive breast carcinoma between 1953 and 2014, radiation-associated sarcomas were identified in 96 patients with AS the most common histologic subtype accounting for 52% of the reported cases [86]. The median latency was 11 years for all radiation-associated sarcomas and 7.7 years for AS. Patients present with violaceous plaques of the skin that may be raised or flat, and a high index of suspicion is required for any changes of the skin in a patient with prior radiation therapy. Various criteria for diagnosing a radiation-associated sarcoma have existed over the years. In general, the various criteria agree that the tumor must arise within or adjacent to a previously treated field, a latency of some period of time has elapsed, and the sarcoma be confirmed histologically and be distinct from the patient's initial malignancy [10, 87, 88]. Radiation-induced AS of the breast is well described and arises from the skin but may involve the breast parenchyma, as opposed to primary AS of the breast which arises from the parenchyma [82]. Patients with radiation-associated sarcomas have a worse prognosis than patients with sporadic soft tissue sarcoma [9]. Gladdy et al. compared the outcomes of patients with radiation-associated vs sporadic soft tissue sarcomas treated at Memorial Sloan-Kettering Cancer Center [9]. After adjusting for the five most common histologic types, age, tumor size, site, depth, and margin status, radiation-associated soft tissue sarcomas had a 1.7-fold worse disease-specific survival than patients with sporadic soft tissue sarcoma.

10.6.5.2 Management

Radiation-induced angiosarcomas are primarily managed with surgical resection with wide local resection preferred. In one retrospective review of patients with radiation-associated sarcomas, the 5-year survival rate was 39% in those treated with surgery vs 0% in patients receiving chemotherapy alone [89]. If a wide resection is not possible, other options include amputation if it is an extremity tumor or adjuvant re-irradiation if a marginal resection is performed. In the large series from Memorial Sloan-Kettering Cancer Center, patients with positive microscope or grossly positive margins had inferior disease-specific survival [9]. For breast, mastectomy is the treatment of choice for most patients with satellite lesions, making it difficult to obtain negative margins. Re-irradiation can be considered, in general, with radiation-induced angiosarcoma but must be weighed against potential toxicity. There are limited reports which describe the benefits of re-irradiation [14, 90, 91]. One retrospective study from Princess Margaret Hospital demonstrated a local control benefit with adjuvant re-irradiation following surgical resection; however, 50% of patients ultimately developed distant metastases [14]. One additional option

for patients with unresectable disease is combining re-irradiation and hyperthermia with limited data showing reasonable local control [92]. The role of systemic therapy in this setting is unclear. A series of radiation-associated AS of the breast from MD Anderson revealed a reduced risk of local recurrence in patients who received systemic therapy following surgical resection; however, no benefit in distant recurrence-free survival was observed [93].

10.7 Summary

- Angiosarcomas are a rare, aggressive subtype of soft tissue sarcoma with insidious growth patterns, which make advanced presentations common.
- Angiosarcomas can occur anywhere in the body but most commonly are seen involving the cutaneous scalp in elderly white men.
- Additional clinical subtypes include lymphedema-associated angiosarcoma, primary breast angiosarcoma, soft tissue angiosarcoma, and radiation-induced angiosarcoma.
- Given the complexity of this tumor, multidisciplinary management at experienced institutions is key and should involve surgical, medical, and radiation oncology.
- Given the rarity of angiosarcoma, there are few prospective studies with most of the available data derived from single-institution retrospective series, making it difficult to formulate treatment guidelines.
- For localized scalp angiosarcoma, a negative margin resection with adjuvant radiation therapy is typically recommended to maximize local control.
  - Modern radiation treatment planning and delivery can overcome many of the shortcomings of more traditional 2D and 3D approaches.
  - For patients with locally advanced or disease not amenable to surgery, concurrent chemoradiation can be considered.
- Additional research is needed to develop more effective local and systemic therapies for management of this aggressive soft tissue sarcoma.

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Radiation for Dermatofibrosarcoma Protuberans

11

Kathryn E. Hitchcock and William M. Mendenhall

Contents

11.1 Introduction

Dermatofibrosarcoma protuberans (DFSP) is a rare, low-grade sarcoma that originates in the deep layers of the skin. It metastasizes rarely but is known to aggressively invade the subcutaneous tissues, underlying muscle, superficial organs, like the parotid gland, and occasionally the bone [1]. It may grow by direct extension or may develop satellite nodules [2]. It has been known to occur in the gingiva and orbit [3]. Neglected tumors form collagenous exophytic nodules, and early reports

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describe the tumor as a "sarcomatous tumor resembling keloid" [4]. DFSP is thought of as being highly prone to recurrence, but this may be a result of its indolent course leading to inappropriately conservative management at initial diagnosis [5, 6].

The disease manifests most commonly in the fourth decade of life, with a mean age at diagnosis of 41 years, but DFSP can occur at any age [1, 7]. It is equally common in women and men and affects those of Black heritage more commonly than those of European descent (7 per million versus 4 per million annual incidence) or Asians and Pacific Islanders (2.7 per million) in the United States [1, 8]. The reported incidence of DFSP is increasing, but it is unknown whether this trend is biologically driven or caused by improvements in access to expert pathologic analysis of uncommon diseases.

Figure 11.1 shows the distribution of lesions in 82 DFSP patients diagnosed by McPeak et al. at the Memorial Hospital of New York City from 1949 to 1967 [6].

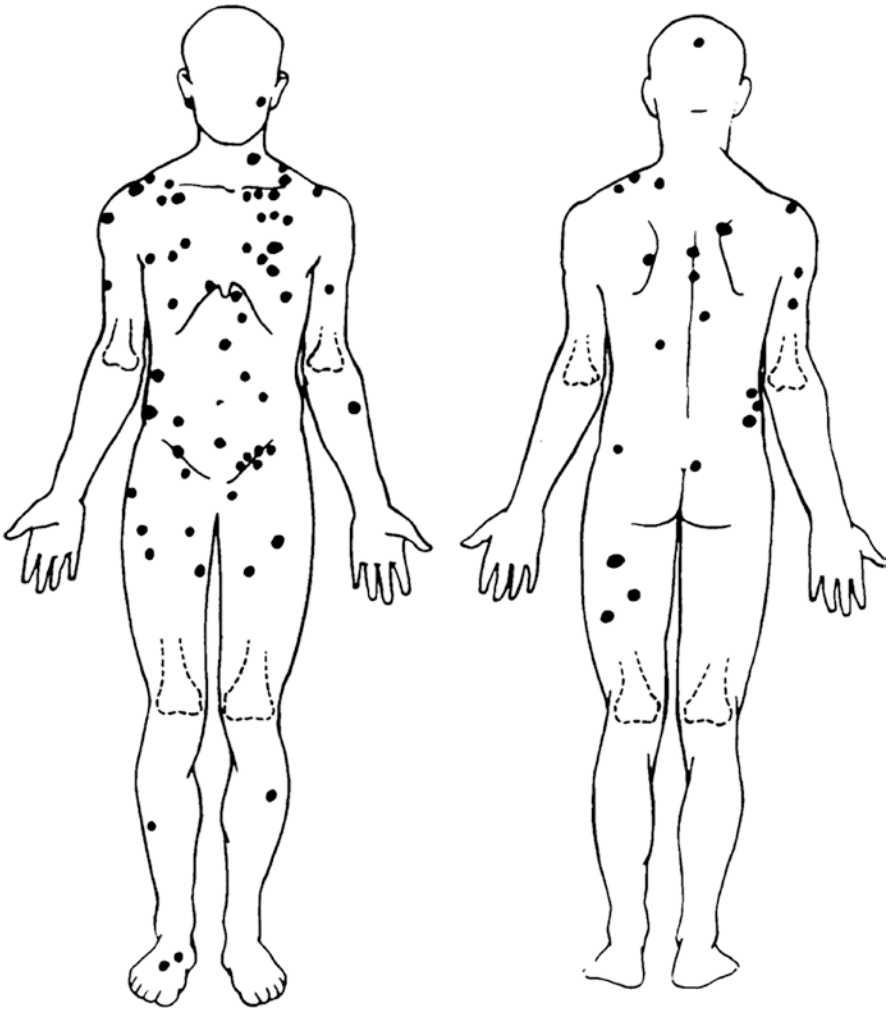

Fig. 11.1 Scattergram showing the distribution of dermatofibrosarcoma protuberans (DFSP) in 82 patients seen at the Memorial Hospital of New York City between 1948 and 1967. Used with permission from McPeak et al. *Annals of Surgery* 166(5):803–16, 1967

Other authors describe a distribution that is half on trunk, slightly fewer on the extremities, and about 10% on the head and neck [9, 10].

11.1.1 Staging

In the seventh edition of its staging system, the American Joint Committee on Cancer (AJCC) added DFSP alongside soft tissue sarcomas, but they removed it in the eighth edition, marking it as "No AJCC staging system" [11, 12]. The disease has long been described using the American Musculoskeletal Tumor Society (MSTS) system, which designates all low-grade soft-tissue sarcomas as stage I regardless of extent or size. All DFSP are therefore staged as follows according to the MSTS staging system: IA, confined to subcutaneous compartment; or IB, extends beyond subcutaneous compartment.

11.2 Management Principles

11.2.1 Workup

Due to its indolent course, DFSP is frequently temporarily disregarded or neglected, then worked up conservatively, leading to delayed treatment. It often appears as a slow-growing, violaceous, blanching, indurated plaque on which firm nodules arise and may coalesce forming a fibrotic mass with expansile borders. It can more rarely present as an atrophic or depressed lesion [13]. Neglected tumors may develop ulceration and bleeding when the overlying skin stretches and becomes atrophic [6]. The clinical differential diagnosis can include basal cell carcinoma, dermatofibroma, neurofibrosarcoma, liposarcoma, desmoid, melanoma, schwannoma, and atypical scar. The last can be distracting as DFSP has been known to arise in previously normal scars [14–16].

Diagnosis is established with a punch, core, or incisional biopsy. Sampling that is too shallow misses the important deep subcutaneous compartment and frequently results in a missed diagnosis in this disease [17]. DFSP lesions consist of hyperpigmented, acanthotic epidermis overlying a locally invasive, highly cellular nodule in the dermis consisting of collagen, fibroblasts, and histiocytes. The nodule is usually well perfused with many capillaries present [13]. Benign-appearing spindle cells form the bulk of the lesion in a cartwheel pattern that is nearly pathognomonic but may appear in other rare soft-tissue tumors [6]. Figure 11.2 shows the characteristic gross and microscopic appearances of the disease. DFSP is CD34-positive, which distinguishes it from dermatofibroma and keloid [18, 19]. In 90% of cases, it can be further distinguished by the presence of t(17;22)(q22;q13) (COL1A1;PDGFB) [20, 21]. Several variants have been identified, including granular cell, myoid, pigmented, myxoid, sclerotic, and giant cell [5], but all are managed identically.

Some DFSP have fibrosarcomatous areas consisting of high-grade tumor (called DFSP-FS), but these have much higher metastatic potential and should

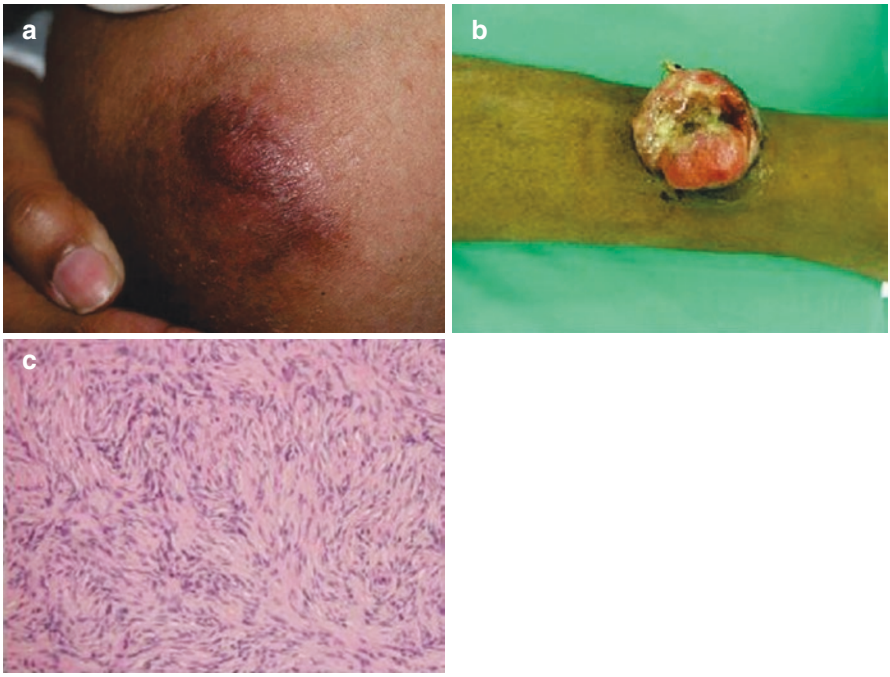

Fig. 11.2 (**a**) Early dermatofibrosarcoma protuberans (DFSP) is most often a violaceous, blanching, thickened plaque. (**b**) If untreated, DFSP forms surface nodules that can coalesce and cause ulceration and bleeding of the overlying skin, resulting in a malodorous, necrotic mass. (**c**) The characteristic H&E stained microscopic appearance of DFSP, characterized by a highly cellular mass of spindle cells in a characteristic cartwheel pattern with low mitotic count. Used with permission from Andersen and Hall, *Scandinavian journal of plastic and reconstructive surgery*, 16(2):211–4, 1982

be treated as high-grade malignancies [22]. The distinction may be made by mitotic figure count with a cutoff often drawn between 0 and 4 mitoses per high-power field in DFSP, and 5+ in sarcoma, as supported by available studies [23]. These fibrosarcomatous regions are CD34-negative [24]. The primary tumor may grow more quickly in these cases, and the probability of metastasis is significantly higher [25]. Taken together, the group of case descriptions available in the published literature suggests that metastasis from DFSP only occurs in the presence of fibrosarcoma [26, 27].

The choice of imaging should depend on what will be most useful in treatment planning. Magnetic resonance imaging (MRI) may be useful in predicting the extent of the needed resection and anticipating the breadth of margins that may be obtained without excessive morbidity [17, 28]. It is important to recall, however, that the pathologic extent of the disease is nearly always significantly greater than the clinical [29]. Metastasis is present in approximately 3% of cases [6, 21], and metastatic workup should be guided by the clinical picture.

11.2.2 Treatment Options

11.2.2.1 Surgery

In the modern era, the primary treatment for DFSP has always been wide local excision with recommended margins of anywhere from 1 to 5 cm, with 3 cm being most common [30–33]. Many sources recommend the removal of the underlying fascia. DFSP is known to invade with fingerlike projections that make the acquisition of negative margins extremely challenging [29]. For this reason the width of margin considered acceptable without adjuvant therapy is a complex issue. Ratner et al., who used Mohs micrographic surgery to precisely determine the extent of DFSP, found that even 10-cm margins would have been insufficient to clear the tumor in 2 of 58 patients; they calculated that 1-cm margins would have been inadequate in 71% of patients, 2 cm in 40%, 3 cm in 16%, and 5 cm in 5% [29]. This is critical information since excision that achieves clear margins can result in a local control rate of over 90%, which can drop below 50% in the case of positive margins [3, 10, 33–35].

Since the 1980s, Mohs micrographic surgery has been advanced as the least disfiguring option for the resection of DFSP that results in acceptably low rates of recurrence [13, 36–38]. The advantage of Mohs lies in its greatly improved chances of delivering a clear margin. The drawback is it may require many resections over multiple days to accomplish, as many as 165 in one series [29], and is performed under local anesthesia. The Mohs resection of large lesions may therefore be extremely taxing for the patient. As an alternative to this investment, in appropriate cases, one large series proved that meticulous pathology performed on resections with only 2-cm margins resulted in outcomes comparable to Mohs [39–41].

The radiation oncologist who is referred a case with an incomplete pathology report should request re-assessment. For wide local excisions, a complete margin assessment is mandatory, and insufficient width should prompt discussion with the surgeon to determine whether re-excision is feasible. In the head/neck and groin, especially, a wide margin may not be possible without unacceptable loss of function, resulting in high rates of recurrence in these regions [3, 27, 42]. Mohs surgeons, often terse in their assessments, should be pressed to report the presence or absence of a fibrosarcomatous component. If these cases are discussed in a tumor board, the National Comprehensive Cancer Network (NCCN) recommends requesting delayed reconstruction to avoid tumor seeding if margins are later revealed to be positive.

11.2.2.2 Radiotherapy

Because DFSP is a rare disease, outcomes from the addition of radiotherapy have not been tested in any definitive, prospective trials. Expert consensus, as summarized in the NCCN guidelines, is that radiotherapy is appropriate for DFSP that cannot be resected with a negative margin and that it may also be appropriate to use in the case of recurrence. Following a pooled meta-analysis of 12 studies of DFSP treated with surgical resection and postoperative radiotherapy, Chen et al. concluded that it would not be unreasonable to consider adjuvant radiotherapy in any DFSP patient [43].

In DFSP resected with a positive margin, the addition of radiotherapy improves local control [27, 34, 44]. Recommended doses range from 45 to 70 Gy, depending on the institution [27, 34, 43, 45–48]. Some groups have tried preoperative radiotherapy with doses at the lower end of the range, as in the treatment of soft-tissue sarcomas. Definitive radiotherapy for unresectable disease, although not well tested in the span of published cases, can be used with some success [27, 44, 48].

11.2.2.3 Systemic Therapy

Imatinib mesylate, a tyrosine kinase inhibitor, has been investigated for use in DFSP as it counters the driver of tumor cell growth, the continuous activation of the PDGF receptor beta protein-tyrosine kinase by deregulated expression of PDGFB caused by DFSP's characteristic translocation. Phase II trials of imatinib with metastatic or locally advanced DFSP were performed by the European Organisation for Research and Treatment of Cancer and the Southwest Oncology Group. Both showed that imatinib is modestly active in DFSP with the t(17;22) [49]. It appears that it is ineffective in the absence of that specific mutation [20].

Imatinib may be useful for unresectable tumors, particularly if they have already been irradiated. Some investigators have noted utility in using imatinib to downsize unresectable tumors with the goal of making them surgically approachable [50, 51]. Due to the development of drug resistance, patients who initially respond well to imatinib therapy may later experience rapid progression of their disease [52].

11.2.2.4 Follow-Up

Due to the potentially high rate of recurrence, close follow-up of these patients may be necessary. The NCCN recommends history and physical with consideration of local imaging every 6–12 months [17]. Late recurrences after 5 years are uncommon but present in many studies, so patients should be educated carefully on self-monitoring and are best followed for longer periods of time [3, 9, 40].

11.3 Radiation Therapy Techniques and Planning

11.3.1 Choice of Modality

The modality chosen for the radiation of DFSP should be as with other skin cancers. Superficial lesions in which the surgical closure leaves a relatively flat surface are ideal for treatment with electrons. For tumors that invade the bone, cartilage, or the skull base, photon or proton therapy is needed. The rare shop that retains orthovoltage capabilities will find them very useful in the treatment of this disease.

Brachytherapy has been used in the treatment of DFSP for decades. In the literature, brachytherapy is primarily described in case reports, as a few patients are included in a larger DFSP treatment series or as a small proportion of patients are included in older studies on brachytherapy for soft-tissue sarcoma. Marks et al. report good results with brachytherapy combined with external-beam radiotherapy, even in three patients who received no surgery [53].

11.3.2 Simulation

When treating with photons, standard immobilization for the body site of the tumor should be used. When treating a site on the limbs, careful attention should be given to immobilizing the hand or foot to prevent rotational malposition that cannot be corrected with shifts. In shallow tumors, a slightly turned limb can result in grossly poor alignment. Barium or wire should be used to mark the boundaries of the tumor bed during simulation as they may not be obvious on computed tomography (CT).

11.3.3 Target Definition

When using electron therapy, the goal is to cover the tumor bed and selected margin with the 90% isodose line, both in depth and at the lateral edges. A customized lead cutout may be required to collimate the beam on the skin surface. Careful attention must be given to drawing target boundaries on the skin, especially when near a critical structure like the eye, remembering that local recurrence in the region may be considerably more morbid than radiation. The use of a bolus should be carefully considered; some portion of the tumor bed will likely be too shallow to be within the 90% line without it. While 1 cm of bolus is ideal, the topography of the resection site may make 0.5 cm more practical. Laterally, a minimum of 1.5–2 cm of margin should be used around the resection if using lead collimation on the skin, or 2–3 cm if treating without. Consideration should be given to expanding the margin in any region where a close or positive margin is suspected, given the tendency of this tumor to emit finger-like projections. Margins up to 5 cm have been routinely used with good result.

When using orthovoltage, a bolus is unnecessary. Lateral borders can be decreased by 0.5 cm compared to electrons since there is no constriction at depth. Unless exit dose is a concern, such as with lesions involving the scalp, orthovoltage is preferred.

For complex, deeply invading tumors, treatment with photon or proton radiotherapy will almost certainly be required. Our rule of thumb for electron versus photon/proton therapy is a tumor bed that extends beyond 1.5 cm below the surface of the skin. This is because the primary utility of electron radiotherapy is in its ability to spare deep tissues like the eye, the brain, and the mucosa. Beyond 1.5 cm, this advantage is lost, and achieving adequate coverage is challenging. Even for advanced tumors, the regional lymph nodes are not treated electively in DFSP. The clinical target volume (CTV) should consist of the tumor bed with a reasonable expansion; we use 1 cm isometrically, edited for boundaries to tumor spread. The planning target volume (PTV) expansion should be per the usual practice at the institution for the body site treated.

When forced into treating DFSP with primary radiotherapy, as when a patient is medically inoperable, we recommend a much larger CTV expansion of 3–5 cm to account for the impressive extent of DFSP beyond what is revealed by imaging and examination as observed on subsequent microscopic examination of surgical specimens.

11.3.4 Dose

At the University of Florida, we treat DFSP with the same dose and fractionation used for other cancers of the skin.

At 2 Gy per fraction, we recommend the following doses:

70 Gy for gross disease;
66 Gy for positive margins; and
60 Gy for negative margins.

Doses are reduced by 10% when using orthovoltage because of its greater relative biologic effect.

11.4 Physics/QA

When treating with electrons, the most important physics quality assurance concern should be to ensure that an appropriate beam energy has been chosen that will completely cover the entire depth of the surgical defect plus a margin to the 90% isodose line. In addition, an adequate lateral skin margin must be ensured to compensate for the constriction of the electron isodose lines at depth, particularly when a bolus is used.

11.5 Treatment Algorithm

1. Primary treatment is surgical resection with either meticulous examination of the margins of a wide local excision or Mohs micrographic surgery used to ensure negative margins. Imatinib may help render unresectable tumors resectable.
2. Radiotherapy is used for close/positive margins where the margin cannot be cleared with re-resection or unresectable disease. Consider adjuvant radiotherapy in regions where a recurrence and attempted second resection would be unacceptably morbid (this may often be true for head/neck or groin tumors).
3. For unresectable disease that fails to respond to radiotherapy, deliver imatinib.

11.6 Summary

– DFSP is a rare, slow-growing malignancy originating in the deep layers of the skin. It can be locally aggressive but metastasizes very rarely.
– DFSP is low grade. If a higher-grade fibrosarcomatous component is present, it should be treated as a soft-tissue sarcoma.
– Initial misdiagnosis is common, and inexperienced physicians often treat too conservatively, leading to a prolonged clinical course.

– Once the diagnosis is confirmed with a deep biopsy, the correct initial management is surgical excision, using a method that ensures that the margin of the specimen is completely assessed.
– Adjuvant radiotherapy is indicated for close/positive margins that cannot be re-resected, for unresectable disease, or for use as adjuvant therapy in a location where recurrence and second surgery would be unacceptably morbid.
– Imatinib has proven useful for unresectable disease unresponsive to radiation and may help render unresectable disease resectable.

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Radiation Therapy in the Management of Cutaneous Squamous Cell Carcinomas

12

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Contents

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12.1 Early Stage Disease

Surgery is the mainstay of management for the majority of cSCCs. Radiation therapy may be used in lieu of primary surgical management when there are concerns for poor cosmesis, patient's refusal, or inability to undergo surgery due to medical issues or technical factors. Radiation therapy is employed in the postoperative setting to reduce the risk of recurrence when high-risk features are noted in the pathology specimen. Alternative options for the management of early stage SCCs, in select patients, include cryotherapy and topical therapies. These topics, however, are beyond the scope of this chapter.

12.1.1 Surgical Management of Early Stage cSCCs

Surgical approaches for early stage cSCCs include wide local excision (WLE) and Mohs micrographic surgery (MMS). MMS is an advanced surgico-pathologic technique characterized by intraoperative margin assessment. Though there is no randomized data comparing WLE and MMS in cSCCs, data in BCCs has suggested fewer long-term recurrences in the management of primary and recurrent facial BCCs [1]. The use of MMS in cSCCs is primarily supported by retrospective series. MMS is considered appropriate for all aggressive cSCCs, for any recurrent cSCCs, and for most nonaggressive SCCs excluding small tumors (<2 cm) of low-risk areas of the trunk and extremities, according to consensus recommendations by the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery [2]. As such, we recommend that if surgery is to be considered in the primary management of early stage cSCC, Mohs surgery should be considered.

12.1.2 Indications for Adjuvant Radiation After Surgery for Early Stage cSCCs

Adjuvant radiation has been shown to reduce locoregional recurrence in a wide variety of cancers. Data supporting adjuvant radiation for early stage cSCCs is supported primarily by retrospective series. In order to select patients for adjuvant radiation, the risk of recurrence without radiation should be sufficiently high to justify the potential risks. Multiple series have suggested that the clinical and pathologic features which predict for a higher rate of locoregional recurrence than would be expected with surgery alone include high-risk primary site, increasing tumor thickness, desmoplastic growth pattern, perineural invasion (PNI), recurrent tumor after prior surgery, positive surgical margins, and immunosuppression.

Primary cSCCs of the ear and lip have been associated with increased risk for locoregional recurrence [3]. However, in a prospective observational study, ear

primary site was only associated with a higher risk of metastases, but not local recurrence, and tumors of the lip were not associated with either an increased for local recurrence or metastases [4]. As such, consideration for adjuvant radiation in patients with early stage ear and lip tumors may be indicated but should be placed in the context of other risk features.

Tumor thickness and desmoplastic growth pattern have been associated with increased risk of locoregional recurrence and metastasis. In particular, tumors under 2.0 mm thick did not metastasize in a prospective observational study [4]. In the same study, tumors greater than 2.1 mm had propensity to metastasize, and tumors thicker than 6.0 mm were associated with increased risk of local recurrence. This has been integrated into the American Joint Commission on Cancer eighth edition staging system, and tumors 6 mm or more in thickness are now classified as T3 tumors and should be considered for nodal assessment using clinical imaging, sentinel lymph node sampling, or elective nodal dissection. Thus, even in the setting of negative lymph nodes, adjuvant radiation should be considered for tumors ≥6 mm thick due to the high risk of locoregional recurrence. Finally, in this same study, desmoplasia was independently associated with increased risk of local recurrence, and these patients should be considered for adjuvant radiation as well.

PNI has also been associated with an increased risk of locoregional recurrence in skin cancers [5–7]. Optimal cutoffs for adjuvant radiation therapy are controversial. Patients with named nerve involvement or clinical symptoms from perineural involvement should be treated as advanced disease (see section on advanced disease). Patients with lesser nerve involvement should be considered for adjuvant radiation, particularly if nerves involved have a diameter of ≥0.1 mm [6] or with microscopic extensive perineural involvement [7], given a series suggesting poorer outcomes in these scenarios.

Positive surgical margins or recurrent cSCC in the setting of a prior margin-negative resection should be considered as indications for adjuvant radiation based upon both empiric principles and supporting data [8–10]. In the setting of a positive margin, further surgery to clear the margin should be considered first. In patients for whom further surgery to clear a positive margin is not feasible due to cosmetic or technical factors, adjuvant radiation should be recommended [10]. A similar rationale for adjuvant radiation may be considered for patients with negative margins for whom surgery at recurrence would not be feasible. In the setting of a recurrence after a prior margin-negative resection, adjuvant radiation is indicated as the need for escalation of local therapy is clear [8, 9].

Finally, patients with immunosuppression are at an increased risk of developing aggressive cSCCs as a competent immune system plays a critical role in surveillance and regulation of tumorigenesis. Multiple series have shown an increased risk of locoregional recurrence in immunosuppressed patients and also the benefit of adjuvant RT in this setting [11–14]. As such, all immunosuppressed patients with early stage cSCCs should be considered for adjuvant RT with the strength of the recommendation being conditional on the presence of other risk features.

12.1.3 Radiation as Primary Management of Early Stage cSCCs

Radiation is associated with excellent local control outcomes for cSCCs. Series vary widely in reported long-term local control, with some reporting control rates as high as 95% with primary radiation [15], while others report 80% or lower [16]. This wide range in outcomes represents a heterogeneous population of tumors including early stage lesions, lesions recurrent after primary surgery, and advanced lesions which may be surgically or medically inoperable.

Radiation may be used in primary treatment of early stage cSCCs for multiple reasons including patient operability, cosmetic appearance, and functional outcomes. The first reason is obvious: If there are concerns about a patient's ability to tolerate a surgery from an anesthesia standpoint or due to concern regarding healing, radiation serves as an effective curative alternative. Radiation should be strongly considered as the definitive treatment modality for early stage lesions when surgery may be cosmetically disfiguring. Clear examples of this are in early stage lesions of the helix of the ear or the nasal bridge for which WLE would compromise the underlying structure and for which good reconstructive options are not available or would lead to an unnatural appearance. Finally, radiation therapy can be used as primary treatment for cSCCs to help preserve function. This is best illustrated in cSCCs of the eyelid/canthal regions and oral commissure. Surgery in these regions may leave patients with facial asymmetry or poor ocular or oral function. Primary radiation in these settings may serve an organ-sparing modality.

12.1.4 Radiation Dose and Fractionation Schemes for the Management of Early Stage cSCCs

The literature is full of a wide variety of dose and fractionation schemes for cSCCs. No prospective randomized data exist comparing the efficacy or safety of any of these schemes; however, regimens that use higher doses per fraction should be used with caution. In fact, most series reporting high dose per fraction regimens (3 Gy per fraction or higher) use the so-called electronically generated low-energy sources (ELS) (i.e., orthovoltage therapy, superficial therapy, electronic brachytherapy, among others) [17] or conventional brachytherapy. Thus, these regimens are only well established for minimally invasive, small tumors which may be adequately treated with these modalities.

Regardless, conventionally fractionated (1.8–2.0 Gy per fraction to 60–70 Gy in 30–35 fractions) and moderately hypofractionated regimens (2.5–2.75 Gy per fraction to 50–55 Gy in 20 fractions) have been well established across many series and are likely safe regardless of modality. For the common radiation oncologist, who does not have access to an ELS unit or is not proficient with conventional brachytherapy and likely relies on megavoltage photon and electron therapy, both conventionally fractionated and moderately hypofractionated schemes can be employed in almost any case.

12.1.5 Radiation Techniques for the Management of Early Stage cSCCs

ELS techniques including orthovoltage X-rays and electronic brachytherapy are ideal for definitive radiation therapy of small, superficially situated cSCCs in difficult locations. Due to the low depth of penetration, ELS should be reserved for tumors up to 5 mm depth of invasion. Further, due to the large penumbra of such sources and to account for potential microscopic spread beyond the clinical extent of a tumor, margins of up to 1–2 cm should be considered on gross disease or the operative bed. This may be reduced in the presence of nearby critical structures.

Figure 12.1 shows the setup of a patient with a cSCC in situ of the right lower eyelid treated using orthovoltage technique. Due to the superficial nature of the tumor and the ability to block any penetrating radiation through the eyelid using a lead shield, orthovoltage technique is ideal in this circumstance. An approximately 1 cm margin was used to create a Cerrobend block around the lesion. A 2.5 cm cone was used, and prescription was to a total dose of 35 Gy in 5 fractions with an X-ray energy of 100 kVp. Approximately 1 week after treatment, the patient developed some erythema and crusting around the eye which resolved by a month after treatment.

Brachytherapy (both low-dose and high-dose rate) is an excellent treatment option for early stage cSCCs but should only be performed at high-volume centers. Multiple techniques may be used including advanced surface applicators and, in some cases, interstitial needles. Similar to ELS, a margin of about 5 mm beyond the visible tumor should be considered, though again treatment margin may be narrowed around critical structures. If the tumor is superficial and situated on a relatively flat surface, a simple depth calculation may be all that is necessary, though advanced planning may be needed to properly cover deeper tumors, complex shapes, and tumors that are situated on an irregular surface or to help spare critical structures.

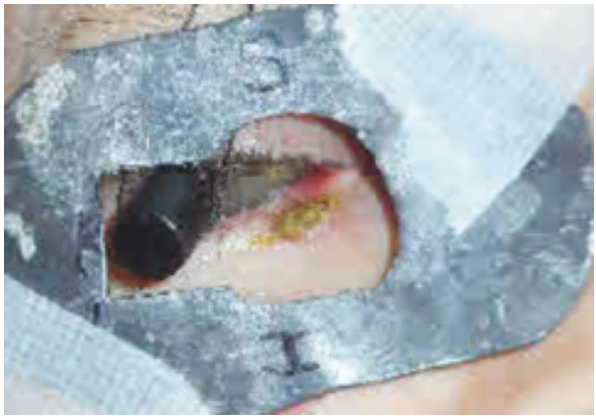

Fig. 12.1 *Clinical setup for patient with cutaneous SCC in situ of the right lower eyelid using orthovoltage technique.* A lead eye shield is place, and a Cerrobend cut out with a 1 cm margin was used to block the surrounding skin. A 2.5 cm cone was used with a photon energy of 100 kV. The prescribed dose was 35 Gy in 5 fractions

Megavoltage (MeV) electron therapy may also be used for early stage cSCCs as an alternative to ELS for superficial tumors or tumors more deeply invasive than 5 mm. Similar considerations need to be made for MeV electron therapy as for ELS, including ensuring an adequate margin to encompass microscopic tumor spread as well as to account for the penumbra of the electrons themselves. Special considerations for MeV electrons compared to ELS include the need for bolus and larger margins for penumbra are described below.

Bolus or a tissue equivalent should always be considered when using MeV electron therapy for multiple reasons. With lower-energy electrons, the maximum depth dose (d_{max}) is deep to the skin surface; thus, bolus is used to compensate for the buildup region allowing maximum dose to be deposited at the skin surface. With higher-energy electrons, d_{max} approaches the surface and may remain close to prescription for several centimeters. Thus, bolus can also be used to reduce the dose deposited in deeper tissues. Keeping these considerations in mind, a prescription isodose line and bolus thickness should be optimally chosen by the physician to adequately cover the tumor and keep hot spots within reason while sparing deeper structures. To do this, physicians should rely on electron depth-dose curves or CT-based planning. Finally, given the high variability and heterogeneity of the dose deposition of electrons with non-flat surfaces and air gaps, the bolus may compensate for an irregular surface, and any potential space between the bolus and skin surface should always be minimized using a filler such as petroleum jelly or water to ensure homogeneous dose distribution.

Additionally, when using MeV electrons, larger field size margins may be needed to account for penumbra. In particular, one needs to account for the fact that higher isodose lines constrict at increasing depth. Physicians should consult with their medical physicists to ensure adequate margins for penumbra given the selected electron beam energy and field size. Further, in vivo dosimetry should be performed routinely at the start of any treatment to ensure adequate dose deposition at the skin surface.

Due to their deep penetration, MV photons are typically only used for more advanced cSCCs. If, however, there is a reason to consider their usage in early stage cSCCs, such as a lesion wrapping around the nasal bridge, bolus should always be used. Figure 12.2 shows an example of such use in a patient with a BCC of the nasal bridge treated with opposed lateral technique using MV photons. A custom 3D-printed bolus (2a) was used to create a uniform surface and ensure uniform dose deposition (2b). Using this technique, radiation exit through the patient was spared, which would have been unavoidable using an electron beam with an en-face setup. Also this uneven surface would have made electron therapy not ideal. This patient could alternatively have been treated using ELS techniques, but due to advanced age, he did not want to commute to our main campus for treatment using our orthovoltage unit.

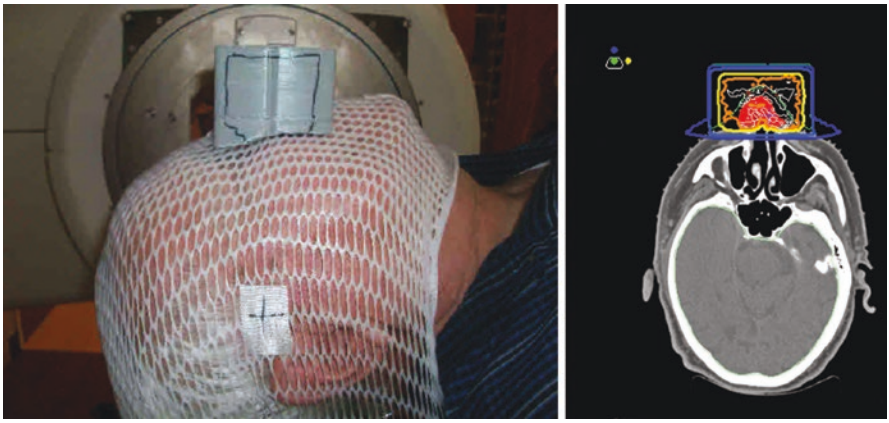

Fig. 12.2 *Utilization of MV photons and customized 3D bolus for early stage BCC of the nasal bridge.* Given the unique wraparound nature of the nasal bridge malignancy, MV photons with customized 3D-printed bolus (depicted on the patient in the left panel) were used as opposed to ELS or MeV electron technique to spare dose exit through the patient. The isodose distribution is depicted on the right, showing the prescription dose in orange and the field edge in dark blue

12.2 Advanced Disease

Advanced cSCCs include those with lymph node involvement, a substantial risk of lymph node involvement, or clinical or significant pathologic evidence of perineural spread. All advanced cSCCs should be managed with primary surgery if feasible to thoroughly stage the patient and for therapeutic benefit. Adjuvant radiation may be given based upon high-risk clinical and pathologic features. Primary radiation therapy has been associated with poorer outcomes for advanced cSCCs when compared to primary surgery followed by adjuvant radiation [18–20]. Primary radiation may still be curative and is used for unresectable disease, medically inoperable patients, and situations when surgery may be cosmetically disfiguring.

12.2.1 Surgical Management of Advanced Stage cSCCs

The goal of surgery in advanced cSCCs is to at least clear all macroscopic disease and to pathologically define the extent of the primary tumor and the involvement of regional lymph nodes and to assess the degree of perineural spread.

According to a large prospective series, the risk of lymph node recurrence in clinically node-negative cSCCs is greater than 20% in patients with tumor thickness of greater than 6 mm compared to under 5% in tumors with less tumor thickness [4]. This series also suggests higher regional recurrence rates in ear primary tumors and in immunosuppressed patients. Given this information, patients with clinically

node-negative cSCCs with one of these risk features (tumor thickness of at least 6 mm, ear primary, immunosuppressed) should be considered for imaging and/or sentinel lymph node staging of lymph nodes. If lymph nodes are clinically or pathologically positive, a completion nodal dissection should be performed.

Surgery should also be used to pathologically assess and clear any perineural spread in patients with advanced cSCCs. Prior to surgery, all patients with advanced cSCC should undergo a thorough history and physical examination including a cranial nerve examination to assess for clinical perineural involvement. In particular, findings of facial numbness or weakness should trigger concern for cranial nerve (CN) V or VII involvement, respectively, and further imaging with an MRI of the skull base should be ordered (CT with contrast may be considered if the patient cannot undergo MRI though is suboptimal for assessing perineural spread). If there is gross involvement of cranial nerves on imaging, surgery should be planned to clear all gross perineural involvement, if feasible. This may require referral to a tertiary care center with expertise in skull base surgery. If there are no clinical features of perineural spread, but pathologically there is concern for significant perineural involvement (>0.1 mm or named nerve involvement), an MRI of the skull base should be similarly ordered to assess for gross perineural spread with consideration for additional surgery to clear any gross perineural involvement on imaging.

12.2.2 Indications for Adjuvant Radiation After Surgery for Advanced Stage cSCCs

Adjuvant radiation is generally indicated in all advanced cSCCs. In addition to the reasons mentioned previously for early stage cSCCs, adjuvant RT should be considered for any advanced primary tumor, pathologic lymph node involvement, or significant perineural spread.

As mentioned in the setting of early stage cSCCs, tumors with at least 6 mm of depth of invasion are associated with increased risk of locoregional recurrence [4] and decreased disease-specific survival [21]. Similarly, invasion beyond subcutaneous tissues such as bone erosion is associated with worse oncologic outcomes [22]. As such, adjuvant radiation should be strongly considered for patients with these features. Given the higher risk of lymph node involvement with such tumors, consideration should be made to include the first echelon lymph nodes if pathologic lymph node assessment is not feasible or if these nodes will be incidentally irradiated in treating the primary site. Regional recurrence rates in the setting of elective nodal radiation are very low (<5%) [23].

Adjuvant radiation is generally indicated after surgical resection in all patients with lymph node involvement. Most retrospective series suggest a significant benefit for adjuvant radiation compared to surgery alone in patients with pathologic lymph node involvement in cSCCs [19, 24–26]. However, in patients with a single intraparotid or cervical nodal metastasis measuring ≤3 cm without extracapsular spread, observation may be considered as one series suggests a low (<10%) risk of recurrence after nodal dissection [27].

Resected PNI of named nerves or clinical PNI is an absolute indication for adjuvant radiation. In a series of patients with resected extensive microscopic PNI (defined as more than two nerves involved), both neural recurrence-free survival rates (94% vs 25%) and disease-free survival (73% vs 40%) are superior with adjuvant radiation including the nerve tracts compared to observation [5]. In another series of patients with completely resected gross PNI who underwent adjuvant RT, 5-year locoregional control was 62% with a 5-year disease-specific survival of 75% [28].

Finally, it bears mentioning that unlike the known benefit in mucosal SCCs [29, 30], there is no clear benefit for use of concurrent chemotherapy with adjuvant radiation for cSCCs with high-risk features including extracapsular spread. The only randomized trial, TROG 05.01 did not show any benefit for concurrent carboplatin over adjuvant radiation alone in patients with gross totally resected cSCC with high-risk features including T3 or T4 primary, in transit metastasis, in parotid nodal metastasis, or in high-risk cervical nodal involvement (2+ nodes and/or extracapsular spread) [31]. That said, some practitioners consider the use of concurrent systemic therapy to intensify therapy in groups of patients at very high risk of local, regional, and distant spread due to a multitude of high-risk features. These decisions are always complex and in the ideal circumstance agreed upon in a specialty-specific tumor board setting.

12.2.3 Radiation as the Primary Management of Advanced Stage cSCCs

Radiation remains a curative modality for advanced stage cSCCs and should be offered to all patients who refuse or cannot undergo surgical resection for their cSCCs due to medical or surgical inoperability.

In the setting of a large primary tumor, definitive radiation may be used with curative intent. In a large series of patients with exclusively T4 disease (defined as cartilage, bone, skeletal muscle, or nerve involvement), radiation alone successfully controlled disease in 53% of patients at 5 years. Among patients that failed, 79% were able to undergo successful salvage, with an ultimate 5-year local control rate of 90% [32]. In another series of patients with T3 or T4 cSCCs, 3-year DSS was only 38% with definitive RT; however, the median RT dose was only 60 Gy [18]. Similar outcomes have been seen in patients with gross lymph node involvement treated with definitive radiation therapy alone [20, 33, 34].

Radiation alone has similarly been shown to control gross perineural spread in about 50% of cases [35–38]. This remains critically important, as resection of tumors with gross perineural spread may cause significant morbidity and mortality.

To improve outcomes in patients with unresected disease, concurrent systemic therapy has often been used off study with a proposed radiation sensitizing benefit as seen in the setting of mucosal SCCs [39, 40]. This has not been prospectively validated so this should be used with caution. A single prospective phase II trial using platinum-based concurrent chemotherapy in patients with locally advanced

cSCCs did show a modest CR rate of 63% [41]. Other studies have used inhibitors of the EGFR pathway such as erlotinib [42] and gefitinib [43]. Cetuximab has been used concurrently in the adjuvant setting [44].

12.2.4 Radiation Dose and Fractionation Schemes for the Management of Advanced Stage cSCCs

As mentioned earlier, there are no prospective randomized data to compare the efficacy and safety of any radiation regimen over another for advanced stage cSCCs. However, due to the fact that the most common location for an advanced cSCC to present is the head and neck region, radiation doses are taken from the mucosal SCC literature. As such, it is strongly recommended to use doses of 2.0–2.2 Gy per fraction to 60–66 Gy in 30–33 fractions to the operative bed in the adjuvant setting and doses of 2.0–2.2 Gy per fraction to 66–70 Gy in 30–35 fractions to gross disease in the definitive setting. Elective regions may be covered using doses of 50 Gy in 2 Gy fractions if a sequential boost technique is used or 54 Gy in 1.8 Gy fractions if a simultaneous integrated boost technique is used. One series recommends the use of 60 Gy to cover nerve tracts electively in the setting of gross perineural spread, and this may be considered if OAR constraints can be respected [5].

The use of hypofractionated regimens for large volumes should be cautionary due to limited experience, though prospective data has established the safety of 55 Gy in 20 fractions (2.75 Gy per fraction) to gross disease with 44–48 Gy in 20 fractions (2.0–2.4 Gy per fraction) to elective disease for head and neck mucosal SCCs and may be considered for patients who are elderly and may have difficulty receiving 6–7 weeks of definitive treatment [45].

12.2.5 Radiation Techniques for the Management of Advanced Stage cSCCs

Given the larger target volumes required to treat advanced stage cSCCs, it is usually only feasible to treat these lesions with MV photons; however, MeV electrons may also be considered in select situations when the treatment field is of limited size and depth. Given the need to define a larger target volume, CT- and/or MR-based treatment planning is necessary. Further, intensity-modulated radiation therapy (IMRT) is strongly recommended to spare nearby organs at risk (OARs), particularly for cSCCs of the head and neck.

We recommend at least a two CTV approach (CTV_{high} and CTV_{low}) for defining treatment volumes for cSCCs, similar to that usually used for mucosal SCCs of the head and neck. The CTV_{high} represents the area of high-risk or known tumor volume, and the CTV_{low} represents an area treated electively as it is at risk for subclinical and/or microscopic tumor spread. We will address the treatment volumes defining the CTV_{high} for the definitive and adjuvant setting separately and then address the CTV_{low} as it pertains to nodal regions and coverage of nerve tracts.

In the definitive setting, the GTV is defined as all gross tumor on imaging and clinical examination. At least a 1.0–1.5 cm anatomically confined (by fascial planes and uninvolved OARs) expansion on the visualized GTV should define CTV_{high}. This is based on data from Khan et al., which looking at pathologic specimens determined the optimal margin on gross tumor needed to encompass 95% of gross disease [46]. In this series, a minimum 11 mm margin was necessary to cover microscopic spread on gross disease for cSCCs under 2 cm in greatest dimension, while a 14 mm margin was necessary for cSCCs greater than 2 cm in greatest dimension.

In the adjuvant setting, the CTV_{high} is defined as the entire operative bed (including the primary site, dissected lymph node regions and resected nerve tracts) with consideration of a 0.5–1.5 cm anatomically confined margin. A separate additional boost CTV (CTV_{boost}) can be considered to address microscopic positive margins, areas of nodal extracapsular extension, or gross disease with higher dose, at the discretion of the treating physician.

Defining the CTV_{low} will depend on the clinical scenario, though generally the CTV_{low} will include at-risk undissected lymph node regions without clinical or imaging involvement and elective coverage of peripheral nerve tracts.

The role of elective lymph node coverage for cSCCs is controversial due to high salvage rates of nodal failure with surgery and adjuvant radiation, and we do not routinely recommend it. However, three scenarios may merit inclusion of elective lymph node regions in the CTV_{low}. The first scenario is in a nonoperative patient with substantial risk of lymph node involvement (tumor thickness of at least 6 mm) or, in a similar vein, a patient with such a tumor who would not tolerate a lymph node dissection in the future. For such patients, the benefit of elective nodal coverage is obvious. The second scenario is that in which treatment of the primary site will result in significant incidental irradiation of the elective nodal region. For example, in a patient with a cSCC of the cheek overlying the parotid, it is reasonable to include the parotid lymph nodes and even cervical lymph node levels IB and II into the CTV_{low}. This is because there will be minimal added morbidity with elective coverage. The third scenario for inclusion of elective lymph nodes is that in which a limited lymph node dissection has been completed with pathologic evidence of involved lymph nodes. For example, in a patient who underwent a level IB-III cervical neck dissection which showed pathologic involvement of lymph nodes, inclusion of cervical lymph node levels IV and V in the CTV_{low} is preferred.

Defining elective lymph node volumes will vary based upon the anatomic site. Most commonly though, cSCCs arise in the head and neck, and Gregoire et al. have provided an excellent atlas detailing the lymph node levels of the head and neck [47]. This reference provides a thorough detail on which head and neck sites drain to which nodal levels and how to define these volumes. Outside the head and neck, treatment of elective lymph nodes may be more difficult. Truncal tumors may drain to a variety of lymph node regions including the axillary nodal regions, inguinal regions, and cervical regions. Extremity tumors may drain very far away from the primary site. Elective nodal radiation in these settings should be used in only the most unique of circumstances.

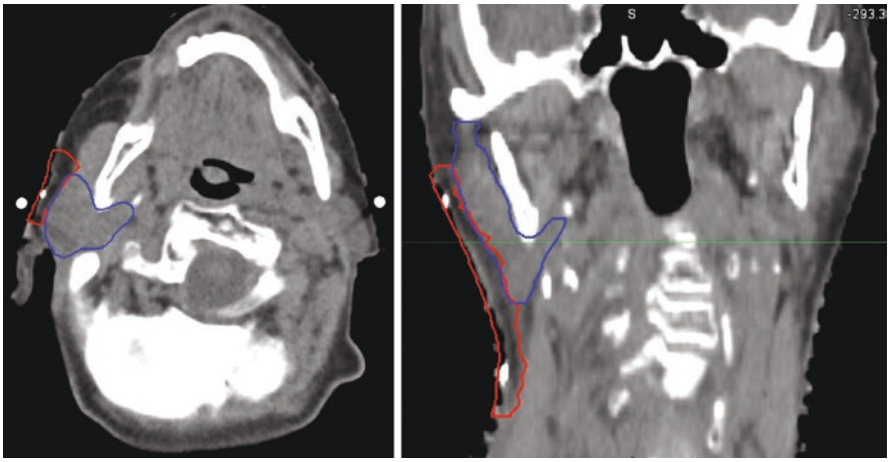

Fig. 12.3 *CTV volumes for patient with cutaneous SCC of the right jawline with 7 mm depth of invasion and small nerve perineural invasion.* The images depict axial (left) and coronal (right) views of CTV volumes for a patient with a deeply invasive SCC of the right jawline. The red volume represents the CTV_{high} and includes the postoperative bed with margin, and the blue volume represents the CTV_{low} and includes the elective lymph node region which was the underlying parotid gland. Elective lymph nodes were treated because the parotid would receive substantial incidental radiation from treating the primary site

Figure 12.3 demonstrates the case of an elderly female with a high-risk cutaneous SCC of the right jaw line. She underwent Mohs surgery with pathology demonstrating a 1.4 × 1.2 cm cSCC with 7 mm depth of invasion and small nerve PNI (0.05 mm). Given the significant depth of invasion and the location of the tumor near the immediately draining intraparotid lymph nodes, this region was electively included in the CTV_{low} (blue) which received 44 Gy in 20 fractions. The CTV_{high} is highlighted in red which received 50 Gy in 20 fractions.

The extent of nerve tract coverage in the CTV_{low} for cSCCs is also not well defined. All patients with clinical signs of perineural invasion or gross perineural invasion on imaging should include the entire uninvolved nerve track and intersecting nerve tracts included in the CTV_{low}. For example, in a patient with gross involvement of the infraorbital nerve, the CTV_{low} should include the path of the maxillary branch of the trigeminal nerve tracing back to the pterygopalatine fossa, foramen rotundum, Meckel's cave, and possibly up to the trigeminal nerve root touching the brainstem.

Nerve tract coverage should also be considered in patients with significant pathologic PNI without clinical symptoms or imaging evidence of nerve involvement. There is no defined measurement threshold for significant pathologic PNI; however, consensus generally falls on elective nerve tract coverage for the so-called named nerves (i.e., pathologic perineural invasion of the facial nerve or supraorbital nerve). For nerves less than 0.1 mm in dimension, elective nerve tract coverage is generally not indicated. In between these two extremes, a careful consideration of the risks

and benefits of the extent of elective nerve tract coverage should be made for each individual patient and clinical scenario.

Defining the CTV_{low} for elective nerve tract coverage for cSCCs involves a thorough understanding of the innervation pathways of involved nerves. Given that this clinical scenario primarily arises in the head and neck, the pathways of most important significance are of the two cranial nerves: the trigeminal nerve (CN V) and the facial nerve (CN VII). CN V is at risk due to the sensory innervation of the face by the three branches of the nerve: the ophthalmic branch (V1), the maxillary branch (V2), and the mandibular branch (V3). CN VII is typically at risk either due to lymph node involvement of the parotid gland, the lobes of which are divided by the main trunk of the facial nerve, or by the involvement of the branches of CN VII distal to the parotid gland. These CN pathways may intersect, and thus, including portions of both pathways in the CTV_{low} should be considered depending on the clinical scenario [48]. Detailed descriptions of contouring relevant volumes for CN V and VII have previously been detailed in the literature [48–50].

Figure 12.4 demonstrates a patient with a cSCC of the left eyelid who underwent Mohs surgery. After multiple stages of Mohs surgery, a tumor was found tracking back to the supraorbital foramen. Given the inability to clear this nerve surgically, Mohs surgery was aborted and MRI imaging was obtained. This imaging demonstrated enhancement of the distal supraorbital nerve in the orbit without enhancement more proximally. Radiation was recommended for definitive management of residual disease after flap reconstruction of the Mohs defect was performed. Gross enhancing nerve on MR imaging plus a 5 mm microscopic margin was included in the CTV_{boost} (solid red) and was treated to 66 Gy in 30 fractions (red isodose line), the Mohs surgical bed and surgical flap plus margin were included in the CTV_{high} (solid green) and was treated to 60 Gy in 30 fractions (yellow isodose line), and the pathway of the supraorbital nerve to the trigeminal nerve was included in the CTV_{low} (solid blue) and was treated to 54 Gy in 30 fractions (light gray isodose line). This pathway included the frontal nerve, the ophthalmic nerve passing through the superior orbital fissure, the trigeminal ganglion in the Meckel's cave, and the trigeminal nerve root. Bolus was used to ensure adequate coverage of the eyelid and flap, and a plastic eye shield used for Mohs surgery was used daily to create separation and effectively spare the cornea while treating the eyelid to a prescribed dose.

After defining CTVs, a PTV margin should be determined. This should be based upon the anatomic site and image guidance. For cSCCs of the head and neck, a 3 mm margin should be sufficient with a thermoplastic mask if daily image guidance with CT or MR is used. Outside of the head and neck, margins of 5–10 mm should be considered due to more daily setup uncertainty.

Finally, the use of bolus in advanced stage cSCCs is critically important and may serve multiple purposes. Unlike in mucosal SCCs, the skin surrounding the tumor is always at risk, and undercoverage of the skin may increase the risk of failure. Bolus at least 5 mm in thickness should always be added to a generous area (typically at least 1 cm) surrounding gross tumor in the definitive setting and the surgical scar in the adjuvant setting. This will ensure adequate coverage to the skin and is often best placed at the time of simulation. Alternatively, bolus can be modeled in the

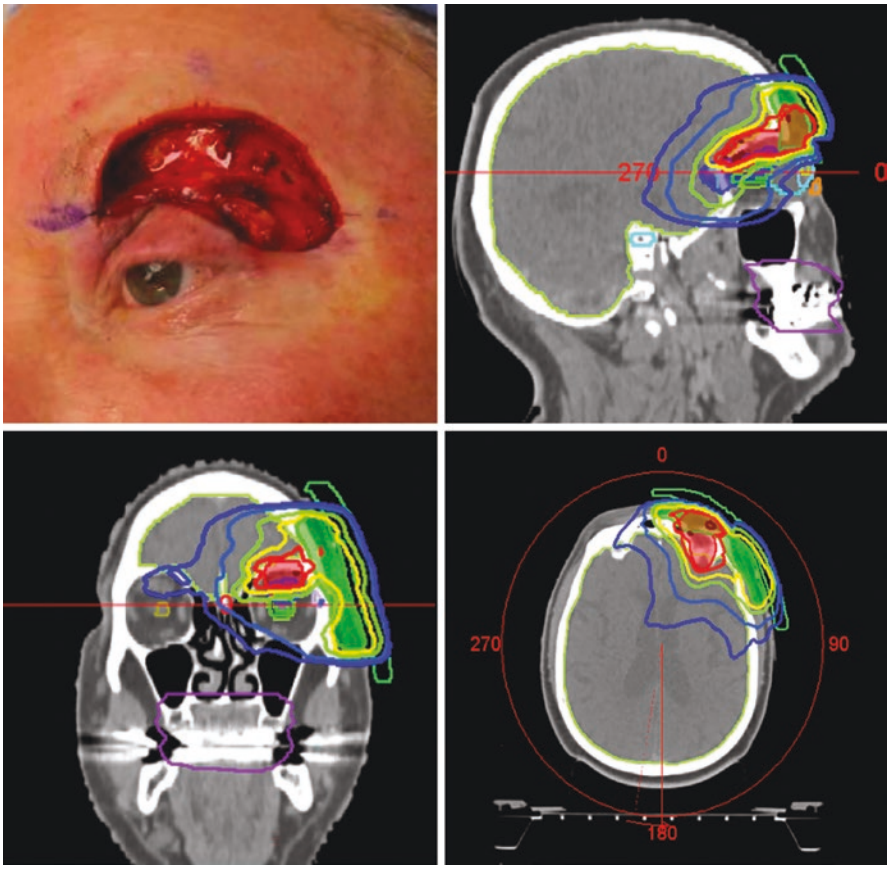

Fig. 12.4 *Treatment plan for patient with cutaneous SCC of the left eyelid with perineural invasion to the supraorbital foramen.* The image on the top left shows the Mohs surgical defect for a patient with an early stage cSCC of the left upper eyelid which after resection showed gross perineural invasion to the supraorbital foramen. Coronal (bottom left), sagittal (top right), and axial (bottom right) views of the radiation treatment plan are depicted. The red volume (CTV_{boost}) received 66 Gy in 30 fractions (red isodose line) and included gross residual disease and enhancement of the frontal and supraorbital nerves with margin, the green volume (CTV_{high}) received 60 Gy in 30 fractions (yellow isodose line) and included the operative bed and flap reconstruction of the Mohs defect, and the blue volume (CTV_{low}) received 54 Gy in 30 fractions (green isodose line) and included the frontal nerve, the ophthalmic nerve passing through the superior orbital fissure, the trigeminal ganglion in Meckel's cave and the trigeminal nerve root

treatment planning system to ensure coverage of the PTV at the skin surface and then added to the patient at the time of treatment delivery. Regardless, in vivo dosimetry should be used to verify adequate dosage to the skin surface.

Bolus may also be used to help spare OARs in patients with advanced stage cSCCs by allowing dose buildup through the bolus resulting in better deep tissue sparing. A unique application of this is for patients with whole scalp treatments. By

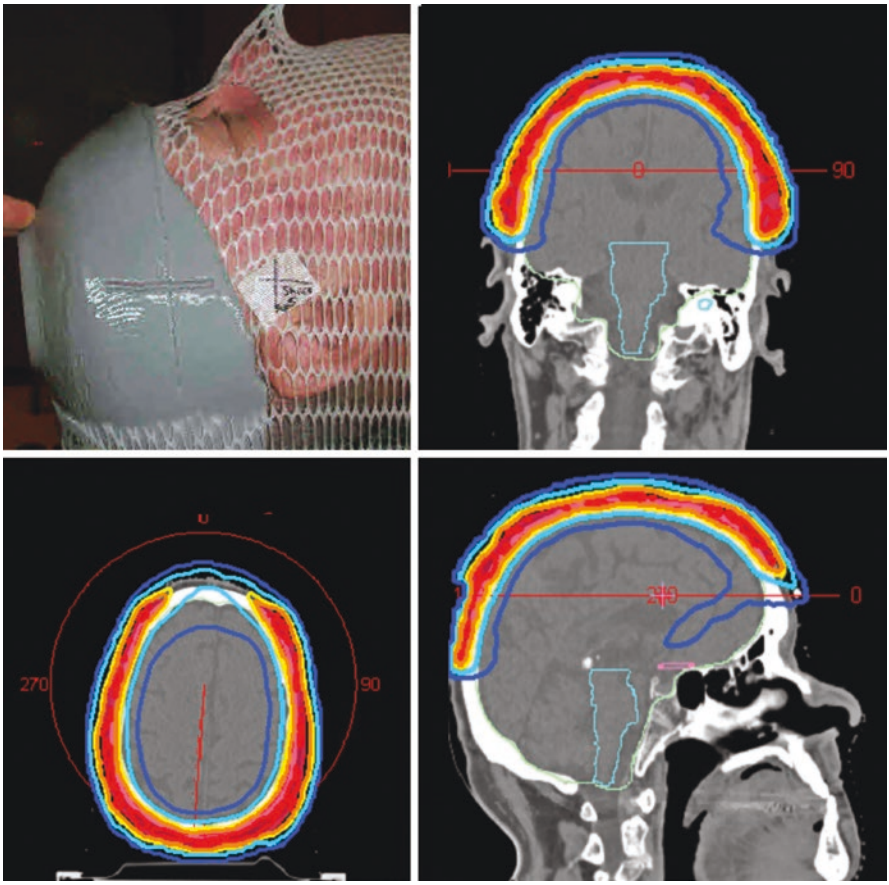

Fig. 12.5 *The use of 3D bolus for patient with cutaneous SCC of the scalp with single cell spread.* Given the uncertain margin necessary to cover for a patient with single cell spread from cutaneous SCC, the decision was made to treat the whole scalp using a custom 3D-printed 1-cm thick bolus (top left). Coronal (top right), axial (bottom left), and sagittal views of the radiation treatment plan are depicted. The red volume is the PTV and received prescription dose of 55 Gy in 20 fractions (orange isodose line). The brain is well spared due to the optimization of dose deposition in the bolus with the 20 Gy (dark blue) isodose line limited to a small peripheral margin of the brain

using a thick scalp bolus (1 cm) and using IMRT treatment planning, the brain may be spared while treating the scalp to prescription dose. This scalp bolus effectively allows radiation dose to be built up in the bolus rather than in the deeper tissues and steep fall off can be achieved. This is illustrated in Fig. 12.5, using the case of a chronically immunosuppressed patient with a highly aggressive cSCC of the scalp with single cell spread at the time of Mohs surgery suggestive of in transit metastases. Due to the uncertainty of the margin necessary to treat all diseases, a whole-scalp treatment was recommended. A 1-cm-thick 3D-printed bolus (gray) was developed for the patient using his treatment planning CT to ensure reproducibility.

The PTV is highlighted in solid red. Using IMRT planning and the brain as an avoidance structure, 55 Gy in 20 fractions (orange isodose line) was delivered to the entire scalp, while effectively sparing the majority of the brain to less than 20 Gy in 20 fractions (dark blue isodose line).

12.3 Conclusion

Radiation treatment is critically important in both the definitive and adjuvant management of cSCCs. Patients with cSCCs should be discussed in a multidisciplinary setting including a radiation oncologist to determine the optimal role of both surgery and radiation in management. Treatment planning decisions should be customized to each clinical scenario and may involve a wide variety of radiation techniques.

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Basal Cell Carcinoma

13

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Contents

13.1 Epidemiology

Non-melanoma skin cancers (NMSC) are the most commonly diagnosed malignant neoplasms in the Caucasian population of the United States. Eighty percent of cases are basal cell carcinomas (BCC), but a reliable estimate of incidence is imprecise

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due to lack of registration in cancer registries [1]. The National Cancer Institute estimates that approximately 5.4 million NMSC cases were diagnosed in 2012, and the majority were BCC [2]. Fair-skinned individuals are more commonly affected, and the incidence of BCC in white patients has risen more than 10% per year with resultant increase in associated treatment procedures and healthcare expense [3, 4].

13.2 Natural History

BCC arises from the basal layer of epidermis and its appendages. It commonly develops from hair follicles. Approximately 70% arise on the sun-exposed head and neck and 15% present on the trunk. While it is considered an indolent process, BCC can be locally invasive resulting in disfigurement and may result in destruction of surrounding structures. The particular biological behavior may vary by histologic subtype (see below).

Tumors have a low propensity for nodal or distant metastases with an overall incidence of 0.01% [5]. When spread does occur, it does so in a stepwise fashion, progressing first in regional nodes and then distantly. Spread is usually associated with locally advanced disease. Perineural/neurotropic involvement is rare, occurring in only 2% of cases and is associated with aggressive histology [5].

While BCC is associated with low mortality, it can result in decreased quality of life and significant healthcare costs.

13.3 Subtypes

BCC lesions may present in a variety of manifestations, depending on the lesion histopathology. Each has its distinctive clinical and histologic features and may have a varying natural history [6–9].

Subtype	Incidence	Location	Appearance	Presentation
Nodular (Fig. 13.1)	80%	H&N	Color: pink/flesh-colored. Pearly/translucent. May have varying degree of pigment Shape: papule Other features: – Telangiectasia. – "Rolled" border"– Periphery is more raised than the middle – Ulceration frequent	Slow growth. May result in peripheral and deep invasion and perineural spread

Subtype	Incidence	Location	Appearance	Presentation
Superficial (Fig. 13.2)	15%	Trunk	Color: light red to pink. May have spotty brown/ black pigment Shape: macules, patches or thin plaques Other: – Slightly scaly – Non-firm – Center may be atrophic – Periphery may be indistinct and rimmed with fine translucent papules	Slow, superficial progression. May become nodular or ulcerative over years
Morpheaform/ sclerosing (Fig. 13.3)	5%	H&N	Color: pink/flesh-colored Shape: papules or plaques Other – Flat, firm, or indurated – Frequently atrophic – Ill-defined borders	Aggressive growth. May result in peripheral or deep invasion. Perineural invasion more common.
Infiltrative (Fig. 13.4)	<5%	H&N	Color: Opaque or yellow Other – Blends subtly with the surrounding skin	Aggressive growth. May result in peripheral or deep invasion

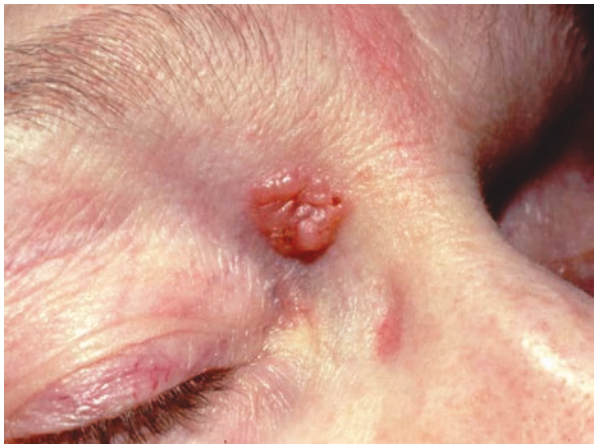

Fig. 13.1 Nodular basal cell carcinoma. Image reproduced with permission from Michael L Ramsey, MD, Geisinger Medical Center, published by Medscape Drugs & Diseases (https://emedicine.medscape.com/), Basal Cell Carcinoma, 2019, available at: https://emedicine.medscape.com/article/276624-overview

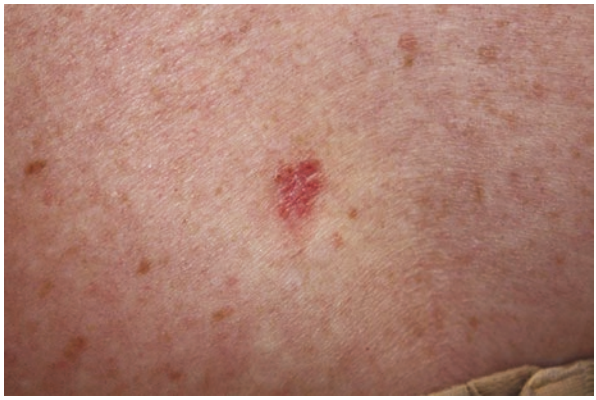

Fig. 13.2 Superficial basal cell carcinoma. Image reproduced with permission from Robert S Bader, MD, Broward Health, published by Medscape Drugs & Diseases (https://emedicine.medscape.com/), Basal Cell Carcinoma, 2019, available at: https://emedicine.medscape.com/article/276624-overview

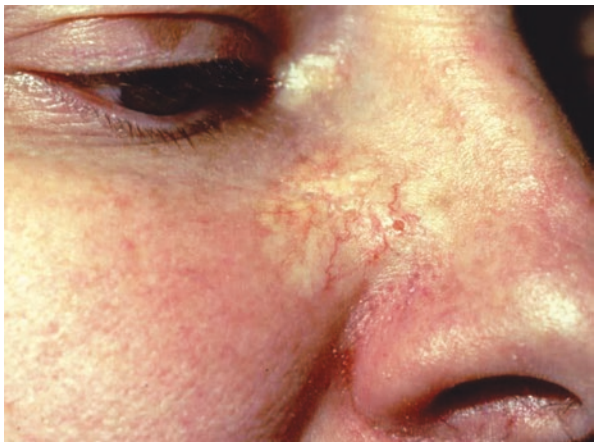

Fig. 13.3 Morpheaform basal cell carcinoma: image reproduced with permission from Michael L Ramsey, MD, Geisinger Medical Center, published by Medscape Drugs & Diseases (https://emedicine.medscape.com/), Basal Cell Carcinoma, 2019, available at: https://emedicine.medscape.com/article/276624-overview

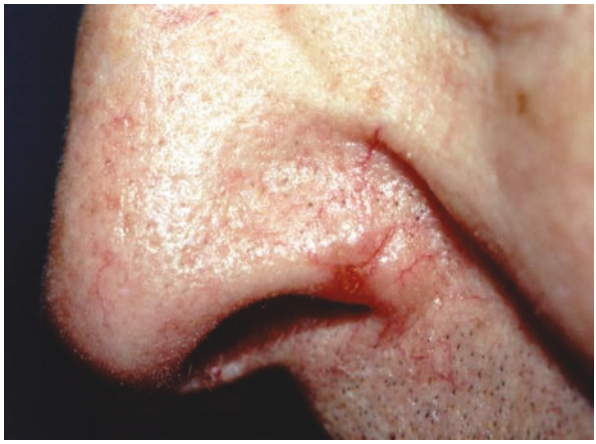

Fig. 13.4 Infiltrative basal cell carcinoma: image reproduced with permission from Michael L Ramsey, MD, Geisinger Medical Center, published by Medscape Drugs & Diseases (https://emedicine.medscape.com/), Basal Cell Carcinoma, 2019, available at: https://emedicine.medscape.com/article/276624-overview

Other, rare BCC subtypes have been described including basosquamous cell carcinoma that may behave aggressively.

13.3.1 Risk Stratification

Cutaneous carcinomas of the H&N, including BCCs of the region, are staged according to the eighth edition of the AJCC Cancer Staging Manual (Table 13.1) [10]. Exceptions include carcinomas of the eyelid and Merkel cell carcinomas. There is no staging system for cutaneous carcinomas outside of the H&N region.

The majority of BCC lesions present early and treatment is based rather on risk factors for recurrence rather than stage. NCCN guidelines has defined criteria for "low risk" and "high risk" of recurrence (Table 13.2) [11]. Note that the presence of any high-risk factor places the patient in the high-risk category.

Table 13.1 Staging BCC of the H&N

Primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor smaller than or equal to 2 cm in greatest dimension
T2	Tumor larger than 2 cm but smaller than or equal to 4 cm in greatest dimension
T3	Tumor larger than 4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion[a]
T4	Tumor with gross cortical bone/marrow, skull-base invasion and/or skull-base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull-base invasion and/or skull-base foramen involvement
Regional lymph nodes (N)	
Clinical N (cN)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−) Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−) In bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)

(continued)

Table 13.1 (continued)

Primary tumor (T)	
T category	T criteria
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−) Metastasis in any node(s) and clinically overt ENE [ENE(+)]
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and ENE(+)
Note*:* A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+)	
Pathological N (pN)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+) Larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−) Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−) In bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, ENE(−)
N2a	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+) A single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+) Multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+) A single contralateral node of any size and ENE(+)
Note*:* A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+)	

Table 13.1 (continued)

Primary tumor (T)			
T category	T criteria		
Distant metastasis (M)			
M category	**M criteria**		
M0	No distant metastasis		
M1	Distant metastasis		
Prognostic stage groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1	N1	M0	III
T2	N1	M0	III
T3	N1	M0	III
T1	N2	M0	IV
T2	N2	M0	IV
T3	N2	M0	IV
Any T	N3	M0	IV
T4	Any N	M0	IV
Any T	Any N	M1	IV

[a]Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber or presenting with clinical or radiographic involvement of named nerves without skull-base invasion or transgression

Table 13.2 Risk factors for recurrence

	Low risk	High risk
Location/size	Area $L < 20$ mm Area $M < 10$ mm	Area $L \geq 20$ mm Area $M \geq 10$ mm Area H
Borders	Well defined	Poorly defined
Primary vs recurrent	Primary	Recurrent
Immunosuppression	No	Yes
Site of prior RT	No	Yes
Pathologic subtype	Nodular Superficial	Aggressive growth pattern
Perineural involvement	Negative	Positive

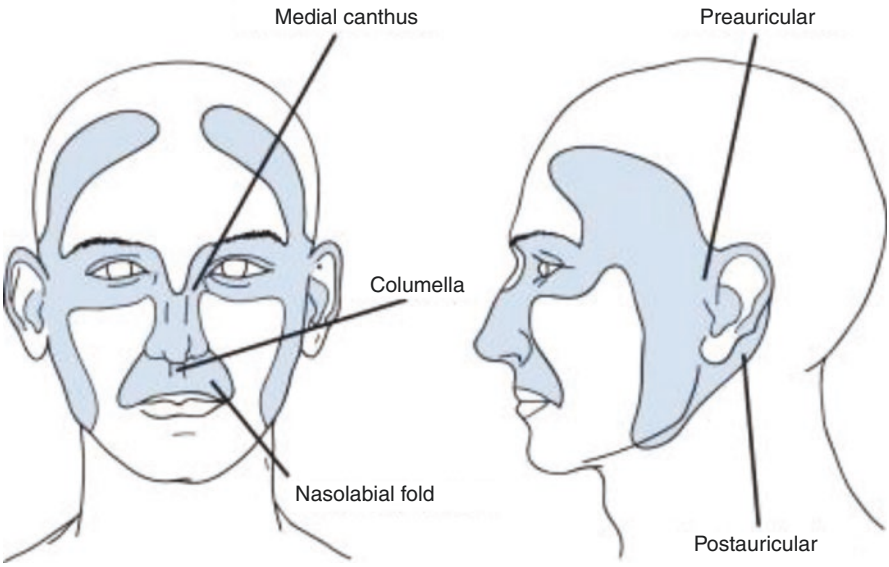

Fig. 13.5 *H* zone of the face. Reprinted from Clinical Radiation Oncology fourth Edition, M. Veness and J. Howle, Cutaneous Carcinoma, 2016, with permission from Elsevier

Figure 13.5 depicts the *M* and *H* zones of the face. Area *L* includes the trunk and extremities but excludes with hands, nail units, pretibial skin, ankles, and feet. The *H* zone is located at the midface and includes the periauricular region, glabella, medial canthus, nose, nasolabial region, and columella [11]. The region contains embryonal fusion planes, and histopathology often reveals extensive infiltration of deeper structures. Due to its location, there is understandable high concern for optimal cosmetic and functional outcome, which drives the employment of narrow surgical and radiation margins. Thus, lesions involving the *H* zone are at high risk for recurrence regardless of size. Tissue-sparing techniques, such as MOHS and staged excision, are recommended in order to have complete complex margin assessment.

13.3.2 Management Options

13.3.2.1 Excision

Standard excision with postoperative margin assessment has been employed for decades and results in a 5-year local control of approximately 98% [12]. For low-risk lesions, a 4 mm margin will result in complete removal in over 95% of cases [13]. A wider margin is recommended for high-risk lesions. If tissue rearrangement or a skin graft is required to close the surgical defect, intraoperative margin assessment is recommended before closure.

13.3.2.2 MOHS Micrographic Surgery (MMS)

MMS is the preferred surgical technique for high-risk lesions as it allows for intraoperative margin assessment. When compared to standard excision, MMS is associated with improved local control in both the primary and locally recurrent setting, 1% vs 10.1% and 5.6% vs 17.4%, respectively [14].

13.3.2.3 Curettage and Electrodesiccation (C&E)

C&E involves scraping away of a tumor with a curette and denaturing the area with electrodesiccation. It does not allow for margin assessment. While some reports demonstrate a 5-year local control ranging from 91 to 97%, others note 20–30% recurrence rates [12].

13.3.2.4 Superficial Therapies

Topical therapies, cryosurgery, and photodynamic therapy result in inferior local control and should be reserved for patients who cannot undergo surgery or radiation therapy. The five-year local control is in the 80% range [15].

13.3.3 Radiation Therapy

13.3.3.1 Patient Selection

Patient referred for radiotherapy are typically older and may have contraindications to surgery due to competing comorbidities or advanced age. The five-year local control ranges from 92 to 96% for external beam and 95 to 99% for brachytherapy [16, 17]. It is important to note that these figures are laden with bias, as patients who are referred may have tumors in less optimal areas, where expansion margins are compromised.

13.3.3.2 Modality Comparison

To date, there is only one report of level one evidence comparing surgery or radiotherapy. This trial compared 347 patients treated from 1982 to 1987 at Goustave-Roussy and reported a 4-year local control rate of 0.7% for surgery and 7.5% for radiation as well as patient reported "good" cosmesis of 87 vs 69%. It is important to note that radiation in this trial was not standard and is quite outdated. Fifty-five percent of patients received LDR interstitial therapy and 33% received superficial contact therapy [18]. The relevance of this data to modern radiation therapy is limited.

More recently, a systematic review identified key observational studies that assessed tumor recurrence after a variety of treatment modalities (Table 13.3) [17].

Brachytherapy was recently compared to MMS in a matched pair analysis [19]. At a median follow-up of 3.5 years, local control was 99.5% for brachytherapy and 100% for MMS ($p = 1.00$) in 208 lesions each, respectively. There was no difference in patient reported or clinician reported cosmesis.

Table 13.3 Modality comparison

Modality	LR	CI	# Prospective reports
Excision	5.4%	2.5–9.1	12
MOHS	3.0%	2.2%–3.9%	10
EBRT	6.4%	3.0%–11.0%	7
Brachy	5.2%	1.6–10.5%	4

13.3.3.3 Treatment Recommendations

Low-risk lesions include C&E in areas without hair growth, standard excision with postoperative margin assessment, or radiation therapy. High-risk lesions may be treated with MMS, standard excision with postoperative margin assessment, or radiation therapy [11]. Postoperative radiation is recommended for high-risk patients with close/positive margins, extensive PNI, or named nerve involvement.

13.3.4 Radiation Techniques

A variety of techniques may be utilized to treat BCC. This depends on the tumor location, size, and depth. Prescription dose and fractionation may vary based on these factors, as well as desired cosmesis and functional consideration.

13.3.5 External Beam Radiation

13.3.5.1 Orthovoltage/Supervoltage

Superficial x-ray (usually 75–300 kVp) units such as these deposit a maximum dose (*D*max) at the skin surface with exponential decrease in dose with depth. These units are no longer widely available.

13.3.5.2 Electron Beam

Modern linear accelerators produce electron energies from 6 to 20 MeV, offering varying degrees of dose fall off depending on the depth of treatment desired. Low-dose, 6–9 MeV energies are most commonly utilized. Electrons offer a region of uniform dose followed by rapid dose falloff.

Depth-dose profiles for commonly used energies can be obtained from beam data detailing depth-dose profiles specific to their linear accelerator. Differences between linear accelerators can be clinically significant.

The electron beam energy chosen reflects the depth of tissue requiring treatment. Electrons are moderately "skin sparing," particularly at low energies due to scatter, with *D*max below skin surface. As a result, placement of a tissue equivalent material (bolus) on the skin is commonly used to draw the beam isodose lines to the skin surface (Fig. 13.6). A flexible bolus is preferred to better conform to the skin surface.

The thickness of bolus considered depends on the energy chosen with a goal of placing Dmax at the skin surface and the 90% isodose line including bolus a few

Fig. 13.6 Superflab bolus. Courtesy of Civco Radiotherapy

millimeters deeper than the base of the lesion [20]. A commonly used estimate for the depth in cm at which the 90% isodose line will be is the electron energy divided by 4. For example, a 12 MeV electron energy likely will be effective to a 3 cm depth. The depth-dose curve falls sharply thereafter. When in doubt, it is recommended to use a higher energy to ensure coverage of the target [21].

Electron beam therapy is prescribed "en face," a French term for facing forward. The gantry of the linac must be rotated so that the beam axis is perpendicular to the surface to be treated. Electrons are best employed on flat skin surfaces. The depth-dose profiles, above, are measured in a water bath. Beam perturbation increased with obliquity and greatly affects dose profile. Obliquity results in increased side scatter, a shift in Dmax to the surface, and decreased depth of penetration. Uneven air gaps and sharp surface irregularities produce localized hot and cold spots [21]. For lesions with sharp angles and irregularity, such as the nose, ear, periorbital region, and extremities, brachytherapy may be preferable (see below).

Patient-specific, custom bolus may be utilized and may be preferred in regions with large irregularities and obliquities. These devices may be uniform or, more commonly, variable thickness. A number of "in-house" or industry solutions may be utilized. Bolus may be handmade using thermoplastic sheets, thermoplastic pellets, or dental putty. These methods may be error prone due to inconsistent thickness during the molding process, may result in undesired air gaps, and may have limited durability. Air gaps may result in scattering of electrons and reduction in dose.

A modern solution that has been introduced in many institutions utilizes 3D printers. Institution-specific or commercially available software is available that can create a bolus from DICOM data transmitted from the patient's CT data set. Tissue-equivalent filament material is utilized. Commercially available custom bolus includes BolusECT from dotdecimal and Modulated Electron Bolus from both Civco and Adaptiiv. Figure 13.7 illustrates the advantage of using a 3D bolus, while Fig. 13.8 depicts an example of 3D-printed bolus.

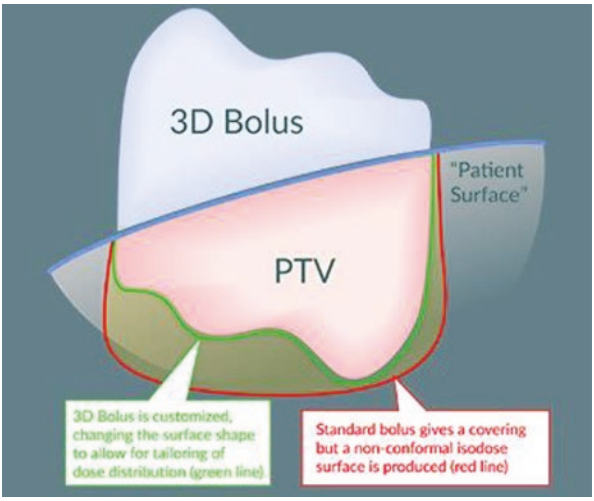

Fig. 13.7 3D bolus cartoon. Courtesy of Adaptiiv

Fig. 13.8 Example of 3D-printed bolus. Courtesy of Adaptiiv

13.3.5.3 Patient Setup

For small, early-stage lesions, simulation may be largely clinical, and CT simulation may not be required. Larger, irregular, bulky lesions or lesions in regions with minimal subcutaneous tissue, such as a periorbital lesion, may benefit from CT simulation to better delineate tumor thickness.

On the treatment table, the patient should be immobilized in a reproducible position. It is preferable that the plane of the skin to be treated is horizontal and perpendicular to the linac gantry. Horizontal positioning may facilitate the placement of bolus and lead shield for skin collimation, if utilized.

The lesion is visualized and a margin drawn on the patient with a marker with assistance of a ruler. Once finalized, if the patient is to undergo CT, this margin is then "wired" using radiopaque linear markers that can be visualized by CT. Surgical literature suggests a 4 mm GTV to CTV expansion for low-risk lesions and 6 mm for high-risk lesions [13]. Note that infiltrative lesions may have greater subclinical

disease extension and would require a more generous margin. The additional margin from CTV to PTV depends on the field size and energy to be utilized, as well as whether beam collimation will take place at the cone or on the patient's skin.

Skin to surface distance (SSD) is typically 100 cm, while the measured distance will be less, depending on the thickness of bolus utilized. An electron cone is fitted to the linac treatment head. This applicator is available in several sizes and serves to collimation the electrons to attenuate lateral scatter. The cone is positioned a few cm from the desired treatment surface. The distal part of the cone is fitted with an aperture, which can facilitate the placement of an electron cutout for collimation.

The most widely used method is collimation at the cone. The lead cutout is most commonly constructed using Lipowitz metal (trade name Cerrobend). This metal is an alloy that can be shaped at relatively low temperatures. Most institutions construct the cutout in a designated, on-site, mold room. There are commercial solutions available that can obviate the mold room, such as dotdecimal electron cutout [22]. The minimum thickness of lead required for blocking a given electron energy to <5% transmission is energy divided by 2. An additional mm may be added for safety. The thickness required for Cerrobend is 20% greater than that of lead [21].

When collimating at the cone, the treatment field typically encompasses tumor plus a 1.5–2 cm margin. Margins may be reduced when treating tumors close to a critical structure such as the eye. It should be noted that reduced margins have been associated with reduced local control from electron beam therapy. One may consider skin collimation in this case, or use an alternative modality, such as excision or brachytherapy.

Caution should be exercised when treating with a small field size. Central axis depth dose is field size dependent, with dose decreasing with decreasing field size due to decreased scatter. Depth dose may be reduced for small field sizes or extensive blocking with Dmax shifting to the surface, compared to broad beams. It is recommended that the overall size of the cutout should be large enough so that the cone/collimator setting is at least 4 × 4 cm [21].

Skin collimation may also be employed when using low energy electrons (Fig. 13.9). Skin collimation is not employed for higher energy electrons, as thicker lead is required which is not as easily molded and may result in patient discomfort. This technique places a 3–4 mm thick lead cutout directly on the skin surface. Due to its thin nature, the lead sheets may be molded to conform to the surface contour. It is used for field shaping and conforms to the geometry of the desired volume. As collimation is taking place on the skin rather than scattering in air, expansion margins may be reduced [21, 23].

Special shielding devices are recommended when treating lesions near the eye, nose, mouth, and ear. For the eye, after topical anesthetic placement, a tungsten shield is placed directly under the eyelids to protect the lens and superficial eye structures. This eye shield reduces the dose to <5% for energies up to 9 MeV (Fig. 13.10).

"Exit dose" blocking is employed for lesions of the other aforementioned sites using internal shielding (Fig. 13.11). The nasal septum, nasal canal, and underlip/gingival/buccal regions of the oral cavity are shielded with lead strips coated with

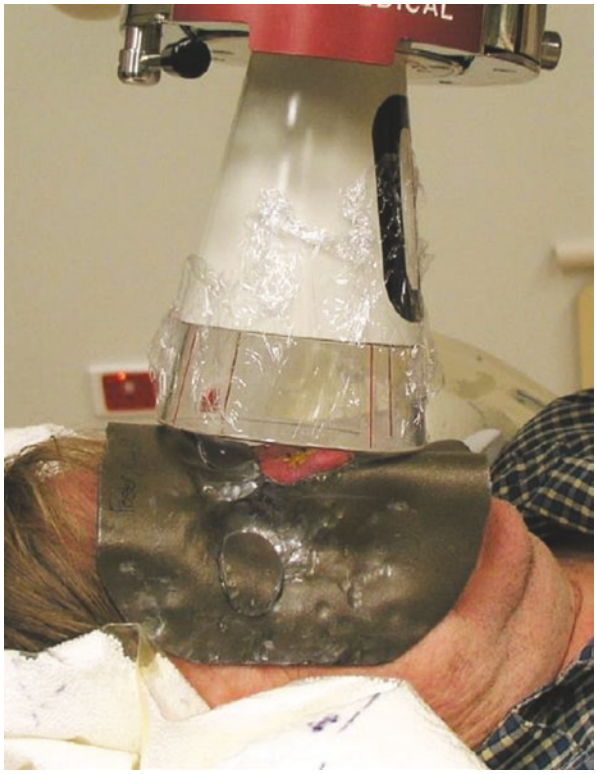

Fig. 13.9 Example of skin collimation. Patient undergoing electron beam therapy to the left nose. Note additional layer of lead over eyes to further reduce scattered dose. Reprinted from Clinical Radiation Oncology fourth Edition, M. Veness and J. Howle, Cutaneous Carcinoma, 2016, with permission from Elsevier

Fig. 13.10 Tungsten eye shields. Courtesy of Civco Radiotherapy

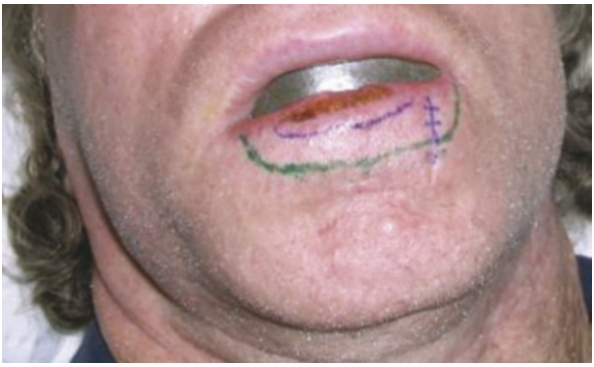

Fig. 13.11 Example of an oral cavity lead shield. This patient is receiving definitive radiotherapy for a lower lip carcinoma. Reprinted from Clinical Radiation Oncology 4th Edition, M. Veness and J. Howle, Cutaneous Carcinoma, 2016, with permission from Elsevier

wax or acrylic. The coating serves to absorb electron backscatter from the lead, which can be quite substantial [24].

Given the numerous variables noted above, as well as a degree of discrepancy between dose computed on a treatment planning system compared to actual dose measured on a patient, it is recommended that in vivo dosimetry be performed. There are a number of methods for remote determination of absorbed dose using in vivo dosimetry. These methods include thermoluminescent dosimeters (TLD) and optically stimulated luminescent dosimeter (OSLD). The readout process for OSLDs is more time efficient and thus more commonly employed.

If there is a clinically relevant discrepancy between calculated dose and measured dose, one may use the measurement to calculate dose scaling.

13.3.5.4 Prescription

Several fractionation schedules may be utilized in the treatment of BCC with EBRT. The dose for irradiation with electrons is prescribed at 90%. In general, more protracted schedules using lower dose (2–2.5 Gy) per fraction achieves the most optimal cosmetic results. Other factors that are considered include age, lesion size, and site. For most patients, 50–55 Gy in 20 fractions is effective with acceptable cosmesis and low toxicity. A more hypofractionated approach of 40 Gy in 10 fractions of 30 Gy in 5 fractions may be employed for a patient with poor performance status or limited transportation ability. A dose shorter than 4 weeks is not recommended in the adjuvant setting [11]. When treating lesions near a critical organ, such as the eye, it is important to consider organ tolerance. Dose constraints are provided in 2 Gy/fx, and if an alternative prescription is used, EQD2 calculations may be necessary.

13.3.5.5 Electron Arc Therapy

Arc therapy is commonly employed with photons to deliver IMRT treatments. It may also be employed in electron beam delivery to treat superficial tumors along curved surfaces. Instances in which this technique would be useful include large limb lesions as well as chest wall lesions that extend across the midaxillary line and anterior/posteriorly. Electron arcs may prove to be superior to abutting electron

fields to prevent field junction problems and superior to photons to avoid unnecessary irradiation of underlying tissue. Many linacs are either not equipped or not commissioned for electron arc therapy, and its clinical use is limited [21].

13.3.5.6 Photon Beam Therapy

Photons are rarely employed in the treatment of BCC. Extensive, deeply infiltrating tumors, especially those with bone or cartilage involvement, may require mixed electron-photon therapy, or photon therapy alone.

13.3.5.7 Brachytherapy

Skin brachytherapy (BT) may be delivered via superficial applicators or interstitial techniques. Superficial BT, as the name implies, is delivered to skin surface lesions. Interstitial BT utilizes rigid needles or plastic tubes and is applied to deeper, bulkier lesions. Surface BT may be delivered using low-dose rate (LDR), pulsed dose rate (PDR), high-dose rate (HDR), or electronic. Interstitial BT may be similarly delivered with the exception of electronic. In clinical practice, HDR and electronic BT are most commonly utilized.

There are several potential advantages of BT over EBRT. Prescriptions are hypofractionated, typically 6–10 in total, offering patient convenience. Dose is delivered in a short time, typically in the order of minutes. Most notably, dose from a brachytherapy source follows the inverse square law, allowing for optimal dose distribution to a tumor with rapid dose fall off. This may translate to less dose to surrounding normal tissue [25, 26].

13.3.6 Applicators

13.3.6.1 Contact BT

Small lesions on regular surfaces may be treated by shielded superficial radionuclide applicators. Two commercially applicators are available, namely, the Leipzig (Elekta and Varian) and Valencia (Elekta) applicators. The Leipzig applicator is cup shaped, composed of tungsten, and available in a range of diameters. The HDR source emerges as its vertex and results in non-flat dose distribution, resulting in an inhomogeneous dose to the target. The Valencia applicator adds a flattening filter to homogenize dose distribution. This added attenuation results increased treatment time. With a typically treatment depth of 3 mm, the skin surface dose is approximately 135%. A 1 mm plastic cover cap remains on the Valencia applicator and serves to maintain this low surface dose. Removal may increase surface dose by a factor of 2.8.

A transparent acrylic template, La Fe-ITIC, may be utilized to assist with delineating appropriate expansions and applicator selection [27].

13.3.6.2 Surface Flaps

Commercially available flaps may be utilized for larger surfaces without significant irregularity. Examples include the chest wall, cheek, and dorsum of the hand and foot. These consist of a single layer of silicone rubber material 10 mm in diameter with

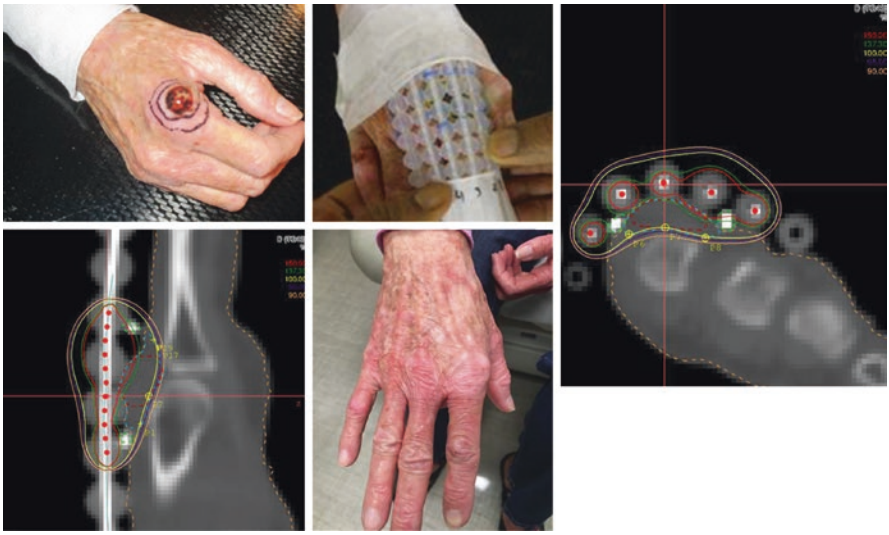

Fig. 13.12 Case example of a 41-year-old woman on immunosuppression for autoimmune hepatitis who developed lesion over the right second metacarpophalangeal joint treated with surface brachytherapy using a Frieberg flap

catheters embedded through the center. This ensures a 5 mm source to skin distance. Available flaps include the Freiburg™ flap (Elekta Instrument AB, Stockholm, Sweden), the H.A.M.™ (Mick Radio-Nuclear Instruments and Eckert & Ziegler BEBIG, Berlin, Germany), and the Catheter Flap set™ (Varian Medical Systems, Palo Alto, CA, USA). Figure 13.12 demonstrates a case example of a Freiburg flap.

13.3.6.3 Custom Applicators

Custom surface mounds may be created for irregular surfaces, such as the nose, fingers, and pinna. Similar to the custom bolus described above, these may be constructed using polymers, acrylic resin, dental wax, or a thermoplastic material. Molds are adapted to the patient surface, and catheters are embedded/weaved through. A common application includes the use of a thermoplastic mask with catheters adherent to wax or resin.

3D-printed custom applicators may be fabricated with customized catheter positions that follow the patient's anatomy (Fig. 13.13). Similar to 3D-printed electron bolus, the patient's DICOM data from their CT simulation is digitized.

13.3.6.4 Treatment Planning and Prescription

Surface brachytherapy is typically prescribed to a depth of 3–5 mm. Tumors greater than 5 mm cannot be adequately treated to depth without substantial skin dose. In these cases, interstitial BT or EBRT should be considered.

Brachytherapy is typically delivered every other day. Commonly used prescriptions include 42 Gy in 6 fractions, 40 Gy in 8 fractions, or 40 Gy in 10 fractions. A more protracted fractionated may be employed for larger targets as well as for the pretibial location [27, 28].

Fig. 13.13 3D-printed custom applicator for a nose case. Courtesy of Adaptiiv

13.3.6.5 Treatment Toxicity and Patient Management

Treatment of a skin cancer with radiation will result in moist desquamation toward the end of treatment or shortly thereafter depending on the fractionation employed. Typical precautions include avoidance of heat, cold, sunlight, friction, and harsh skin products. During treatment, daily moisturization with a bland emollient is recommended. Moist desquamation is managed with the application of silver sulfadiazine cream. Following recovery, patients are instructed to exercise lifetime sun precautions over the irradiated area. Late effects may include hypopigmentation, hyperpigmentation, telangiectasis, fibrosis, and skin atrophy. It is recommended that patients follow routinely with dermatology as they are at high risk for developing an additional primary cutaneous malignancy over their sun-damaged skin.

13.3.6.6 Palliation

Patients with neglected BCC may present with locally advanced disease involving bone, cartilage, muscle, or nerves. They may not be amenable to definitive intent therapy and may be effectively palliated with radiation. Radiation may reduce local morbidity, such as pain and bleeding. Optimal dose fractionation depends on tumor bulk, location, and the patient's life expectancy.

13.4 Systemic Therapy

Systemic therapy for BCC is not often employed and reserved for patients with locally advanced disease not amenable to definitive or palliative local therapy and patients with numerous lesions (often associated with immunosuppression or genetic predisposition) or the rare instance of distant metastases.

13.4.1 Targeted Therapy: Hedgehog Pathway

Aberrant signaling of the hedgehog (Hh) pathway is a pivotal defect in the pathogenesis of BCC [29]. Signaling is initiated by the cell surface receptor smoothened homolog (SMO). SMO is normally is inhibited by another cell surface receptor, the patched homolog 1 (PTCH1). Hedgehog ligand binding to PTCH1 prevents this

inhibition and facilitates cell proliferation. Mutations of PTCH1 or SMO may result in constitutive pathway activation [30].

Vismodegib and sonidegib are SMO inhibitors that have phase II data supporting its use [31, 32]. A meta-analysis of studies evaluating the two agents noted a similar overall objective response rate 62 and 55%, respectively, for locally advanced disease. In patients with metastatic disease, the response rates were 39 and 15%, respectively. In the setting of limited data, either agent is appropriate [33].

13.4.2 Non-Targeted Agents

Itraconazole is an antifungal agent that inhibits the hedgehog signaling pathway, but data supporting its use is limited data [34].

Chemotherapy. Small case series suggest response with platinum-containing regimens [35].

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Melanoma

14

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Contents

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14.1 Pathology

14.1.1 Epidemiology

The incidence of cutaneous melanoma varies considerably between nations according to skin tone of the local population and degree of UV exposure, with Australia/New Zealand having the highest age standardized incidences of 49 new cases per 100,000 per year, compared with an incidence of 21.2 per 100,000 per year in the USA and a global incidence of 3.1 per 100,000 per year [1–3]. Within national populations, cutaneous melanoma disease burden varies significantly by ethnicity, occurring at a higher incidence in whites than in non-whites [4], and by geography, increasing in incidence with proximity to the equator. It affects adults predominantly, with the highest number of incident cases occurring in the seventh decade, but may arise in individuals in their 20s and 30s and uncommonly in the late teens [1, 5].

14.1.2 Aetiology

Melanomas arise as a neoplastic transformation of melanocytes, cells of neural crest origin that migrate during embryo development to the epidermis to reside in the basal layer. The normal function of melanocytes is to produce melanin in response to ultraviolet (UV) radiation, endocrine and paracrine factors. Melanin is then transported to keratinocytes via dendritic processes, where it contributes to the pigment of the skin and acts to scatter and absorb ultraviolet radiation, as well as a scavenger of reactive oxygen species [6]. Melanocytes may be found in mucosal surfaces where, rarely, they may undergo malignant transformation to melanoma. They may also be found in ocular sites such as the conjunctivae and uvea.

14.1.2.1 Environmental

Exposure to UV radiation, whether via sunlight or by the use of tanning beds, is the major risk factor for developing cutaneous melanoma [7, 8]: the lifetime risk appears to be increased with the amount of UV exposure. The pattern of UV exposure may also be important, with some evidence that melanoma risk increases with intermittent episodic, rather than chronic occupational sun exposure [9]. There is also some evidence to suggest that episodes of UV exposure early in life are more important for melanoma risk. For example, incidence rates in adult British migrants to Australia are lower than in Australian-born persons of British descent but appear to increase with duration of residence [10]. The relative importance of life-stage timing of exposure episodes remains unclear, with a recent meta-analysis suggesting that it is the lifetime number of sunburns that increase melanoma risk, not necessarily the age at which they occur [11]. Additional evidence for the role of sunlight exposure in melanomagenesis comes from the frequency of cyclobutane pyrimidine dimer mutations, characteristic of UV exposure [12, 13], in DNA from melanoma [14, 15].

14.1.2.2 Genetic

In general, people with paler skin are at higher risk of developing cutaneous melanoma. Additionally, a family history of melanoma increases the melanoma risk for an individual. Germline mutations in several genes, including CDKN2A and CDK4, are implicated in a minority of familial clusters of cutaneous melanoma, as are other genetic mutations that increase activity of the Ras/RAF/MEK/ERK (MAPK pathway) and PI3K/Akt signal transduction pathways. Mutations of the BRAF proto-oncogene that result in constitutive activation of its gene product (a serine/threonine kinase downstream of Ras) are seen in up to 70% of melanomas. Activating NRas mutations, upstream of BRAF, are seen in up to 15%.

Ras and RAF mutations are rare in acral lentiginous melanoma, which commonly have an activating mutation of the cKIT proto-oncogene [16], a receptor tyrosine kinase that may induce signalling through both Ras and PI3K/Akt pathways.

14.1.3 Radial and Vertical Growth

Although malignant melanomas may arise from melanocytic naevi, they are not a necessary precursor lesion: melanomas may arise from any melanocyte within the epidermis, which has suffered the necessary oncogenic genomic mutations. With the exception of the nodular melanoma subtype, there is an initial radial growth phase in which malignant cells are contained within the epidermis, where there may be accumulation of neoplastic cells at the basal layer of the epidermis which may also extend down appendageal structures, such as sweat glands and hair follicles, in addition to pagetoid spread of cells towards more superficial layers [17]. The radial growth phase may persist for many years before invasive growth develops, as is the case in lentigo maligna. The progression to invasive malignant melanoma is characterized by deeper growth through the basal layer of the epidermis into the papillary dermis.

14.1.4 Subtypes

There are several subtypes of cutaneous melanoma with distinct morphologic and biological characteristics: superficial spreading (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), acral lentiginous melanoma (ALM) and desmoplastic melanoma (DM) [18, 19].

14.1.4.1 Superficial Spreading Melanoma

Characterized by an in situ radial growth phase before dermal invasion develops. It may be slightly elevated with an irregular margin and often has a varied pigmentation with black, brown, tan, grey and violaceous pink in a disorganized fashion.

14.1.4.2 Nodular Melanoma

Presents as a new darkly pigmented nodule with no surrounding in situ melanocytic component. It may bleed or ulcerate and is generally rapidly growing.

14.1.4.3 Lentigo Maligna Melanoma

Presents as an enlarging nodule within a pre-existing lentigo maligna. The in situ lentigo maligna generally has a larger surface area than the in situ component of a superficial spreading melanoma and may have been present for many years.

14.1.4.4 Desmoplastic Melanoma

Arises most commonly in the head and neck region and may lack pigmentation which can delay diagnosis. Neurotropism is common, but not exclusive to, desmoplastic melanoma. It refers to neuronal differentiation of tumour cells and a tendency for perineural invasion. May be seen at some distance from the tumour mass.

14.1.4.5 Acral Lentiginous Melanoma

Arises as a pigmented lesion on the extremities, commonly on the soles of the feet or the palms of the hands. There is an initial radial growth phase. Melanomas in Asian, black or dark brown skin are most often of the acral lentiginous type.

14.2 Staging

The eighth edition of the American Joint Committee on Cancer (AJCC) Tumour-Node-Metastasis (TNM) system, introduced from the first of January 2018, should be used to stage cutaneous melanoma [20]. Melanomas of the uvea and mucosal melanomas arising in the head and neck have their own staging systems, whilst mucosal melanomas arising outside of the head and neck have no AJCC staging system. The AJCC TNM system describes the anatomic distribution of cancer within the body by assigning tumour (T), node (N) and metastasis (M) categories to the pattern of primary, regional and distant disease. The TNM categories can be grouped into prognostic stage groups, which give an indication of prognosis (Fig. 14.1) and guide treatment options. Changes to the eighth edition staging for cutaneous melanoma include the addition of a new M category (M1d) for central nervous system metastases, the stratification of N category for non-nodal regional disease (microsatellitosis, satellitosis, in-transit metastases) by the number of involved regional lymph nodes and the removal of mitotic rate as a determinant of T category [21].

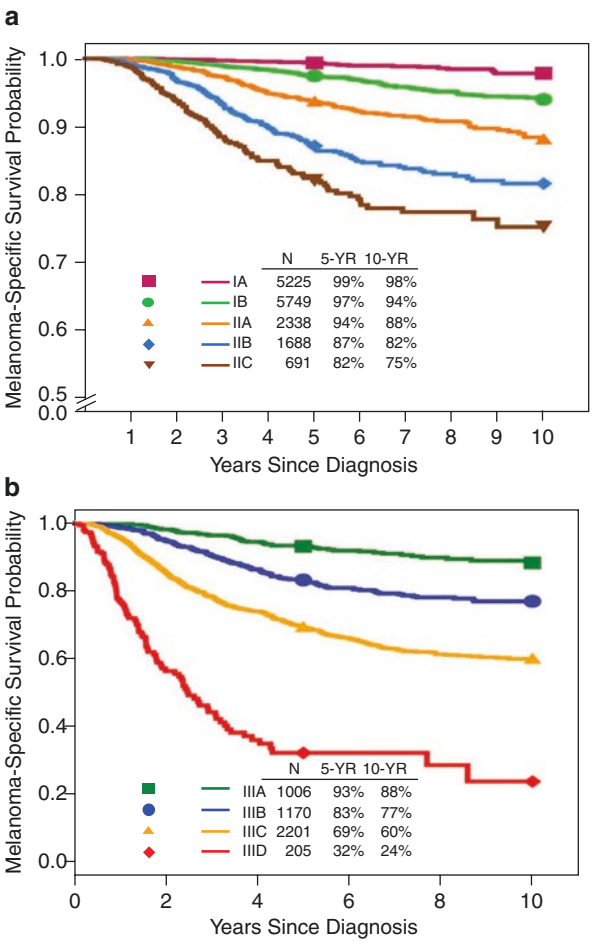

Fig. 14.1 (**a**) Kaplan-Meir melanoma-specific survival curves according to T category stage group for patients with stage I and II melanoma from the Eighth Edition International Melanoma Database. (b) Kaplan-Meier melanoma-specific survival curves according to stage III subgroups from the Eighth Edition International Melanoma Database (Sourced from Gershenwald J.E., Scolyer R.A., Hess K.R., Sondak V.K., Long G.V. et al. Melanoma Staging: Evidence-Based Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual, CA Cancer J Clin 2017;67:472–492)

14.2.1 T Category

The determinants of T category (Table 14.1) are the Breslow thickness, defined as the distance from the granular layer of the epidermis to the deepest extent of the tumour (rounded to the nearest 0.1 mm) and the presence of ulceration, two features which are correlated with the risk of metastasis [22]. It follows that a complete excisional biopsy (rather than incisional punch biopsy or partial thickness shave biopsy) with a 2 mm margin is preferred, because this allows for complete assessment of the depth of the suspicious lesion.

14.2.2 N Category

The determinants of N category (Table 14.2) are the presence and number of regional lymph node metastases; whether regional nodal metastases are clinically occult, clinically detectable or matted, the presence of microsatellites, satellites or in-transit tumour deposits.

14.2.3 M Category

The determinants of M category (Table 14.3) are the absence (M0) or presence (M1) of distant metastasis, the organ or tissue containing the metastasis and the plasma LDH.

Table 14.1 Definition of primary tumour (T)

T category	Thickness	Ulceration status
TX: Primary tumour thickness cannot be assessed (e.g. diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumour (e.g. unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma in situ)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8–1.0 mm	With ulceration With or without ulceration
T2	>1.0–2.0 mm	Unknown or unspecified
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0–4.0 mm	Unknown or unspecified
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Table 14.2 Definition of regional lymph node (N)

N category	Number of tumour-involved regional lymph nodes	Presence of in-transit, satellite and/or microsatellite metastases
NX	Regional nodes not assessed (e.g. SLN biopsy not performed, regional nodes previously removed for another reason)	No
	Exception: Pathological N category is not required for T1 melanomas, use cN	
N0	No regional metastases detected	No
N1	One tumour-involved node or in-transit, satellite and/or microsatellite metastases with no tumour-involved nodes	
N1a	One clinically occult (i.e. detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumour-involved nodes or in-transit, satellite and/or microsatellite metastases with one tumour-involved node	
N2a	Two or three clinically occult (i.e. detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumour-involved nodes or in-transit, satellite and/or microsatellite metastases with two or more tumour-involved nodes, or any number of matted nodes without or with in-transit, satellite and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e. detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Table 14.3 Definition of distant metastasis (M)

M category	Anatomic site	LDH level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle and/or a non-regional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a (1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b (1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c (1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d (1)		Elevated

Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified

Table 14.4 Clinical (cTNM) AJCC prognostic stage groups

When T is…	And N is…	And M is…	Then the clinical stage group is…
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥ N1	M0	III
Any T	Any N	M1	IV

Clinical staging includes microstaging of the primary melanoma and clinical/radiologic/biopsy evaluation for metastases. By convention, clinical staging should be used after biopsy of the primary melanoma, with clinical assessment for regional and distant metastases. Note that pathological assessment of the primary melanoma is used for both clinical and pathological classification. Diagnostic biopsies to evaluate possible regional and/or distant metastases are also included

14.2.4 Clinical and Pathologic Prognostic Stage Groups

Patients can be allocated a clinical prognostic stage group after biopsy of the primary and clinical assessment (including examination, imaging and biopsy) for regional and distant metastases (Table 14.4). A pathologic prognostic stage group (Table 14.5) is allocated after additional staging information from wide local excision, sentinel node biopsy or therapeutic regional lymph node dissection is available.

Table 14.5 Pathological (pTNM) AJCC prognostic stage groups

When T is…	And N is…	And M is…	Then the clinical stage group is…
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b/c, N3b/c	M0	IIIC
T1a/b, T2a	N1a, N2a	M0	IIIA
T1a/b, T2a	N1b/c, N2b	M0	IIIB
T2b, T3a	N1a/b/c, N2a/b	M0	IIIB
T1a/b, T2a/b, T3a	N2c, N3a/b/c	M0	IIIC
T3b, T4a	Any N ≥ N1	M0	IIIC
T4b	N1a/b/c, N2a/b/c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

Pathological stage 0 (melanoma in situ) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use cN information to assign their pathological stage

Pathological staging includes microstaging of the primary melanoma, including any additional staging information from the wide-excision (surgical) specimen that constitutes primary tumour surgical treatment and pathological information about the regional lymph nodes after SLN biopsy or therapeutic lymph node dissection for clinically evident regional lymph node disease

14.3 Initial Assessment

14.3.1 Approach to Pigmented Lesion

The workup of a pigmented lesion typically occurs before a referral to a radiation oncologist, who would normally be consulted after a diagnosis is established. Nonetheless, below is a useful framework, which follows the standard oncologic practice of comprehensive history and clinical examination to guide the choice of further investigations.

14.3.1.1 History

History of the lesion

Table 14.6 Fitzpatrick sun-reactive skin types

Skin type	Typical features	Tanning ability
I	Pale white skin, blue/green eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

Sourced from: Fitzpatrick, The Validity and Practicality of Sun-Reactive Skin Types I Through VI, *Arch Dermatol.* 1988;124:869–871

- Duration
- Rate of change

Symptoms suggestive of metastatic disease

- Nodal masses
- Neurologic deficits
- Pain

Risk factors

- Sun exposure history
- Use of tanning beds
- Personal history of melanoma
- Family history: melanoma, dysplastic naevus syndrome

Past medical history

- Comorbidities
- Other malignancies
- Relative contraindications to radiation therapy: pacemaker, systemic sclerosis/scleroderma, systemic lupus erythaematosus
- Previous radiation therapy

Medications

- Antiplatelet or anticoagulant agents
- Antimetabolites, e.g. methotrexate
- Antineoplastic agents
- Immunosuppressants
- Nephrotoxic or hepatotoxic agents

Social history

- Family history
- Social supports
- Financial supports
- Performance status

14.3.1.2 Examination

General physical inspection

- Complexion, presence and number of pigmented naevi, Fitzpatrick skin type (Table 14.6)
- Evidence of cutaneous UV exposure
- Evidence of previous cutaneous malignancies (excision scar, radiation skin changes)

ABCD suspicious lesion morphologic features

- Asymmetry
- Border irregularity
- Colour heterogeneity
- Diameter >6 mm

Evidence of satellite nodules or in-transit metastases
Examination of regional nodal basins
Complete skin examination

14.3.1.3 Investigations

Complete excisional biopsy of suspicious lesion

14.3.2 Workup of Biopsy-Confirmed Melanoma

14.3.2.1 All Patients

A complete excisional biopsy is the required initial investigation for a suspicious pigmented lesion. It is necessary for diagnosis of melanoma and assignation of T category.

14.3.2.2 Patients with No Clinical Evidence of Regional Nodal or Distant Metastases

Wide local excision of the primary tumour with sentinel lymph node biopsy is the standard of care. In patients with a negative sentinel lymph node biopsy (i.e. stage I and II), systemic staging with cross-sectional imaging is not routinely recommended and is unlikely to alter the disease stage, but may be considered in patients with thicker primary tumors. In patients with positive sentinel lymph nodes, systemic staging with cross-sectional or functional imaging such as computed tomography (CT) or ^{18}[F]fluorodeoxyglucose positron emission tomography (FDG-PET/CT) scan can be considered as a baseline investigation especially in patients with thicker, ulcerated primaries but is not mandatory. In this situation, various studies have reported a yield of detecting clinically occult distant metastatic disease ranging from 0.5 to 3.7% [23–25].

14.3.2.3 Patients with Clinical Evidence of Regional Nodal or Distant Metastases

Biopsy confirmation of clinically suspected regional nodal or distant metastasis by fine needle can be useful to confirm the presence of clinical stage III or IV disease. Whole-body cross-sectional imaging with FDG-PET/CT and dedicated brain imaging, with either contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT), are considered the standard of care. In patients with stage IV melanoma, serum LDH is prognostic and is a component of AJCC eighth edition staging.

14.4 Treatment: Primary Cutaneous Melanoma

14.4.1 Invasive Malignant Melanoma

14.4.1.1 Wide Local Excision

An initial excisional biopsy with 2 mm margin is recommended for the initial assessment of suspicious pigmented naevi. Once the diagnosis of melanoma has been confirmed, wide local excision of the biopsy scar site is the standard of care for primary cutaneous malignant melanoma. The recommended margin of excision depends upon the thickness of the primary tumour (Table 14.7). Several prospective randomized controlled trials have tested wide excision margins (3–5 cm) compared with narrow excision margins (1–2 cm) for primary cutaneous melanoma, with none suggesting a disease control benefit to margins greater than 2 cm. Furthermore, the question of a deep excision margin has not been addressed prospectively but by convention is to the level of the deep fascia, unless a deeper margin is required due to fascial involvement.

In the head and neck, the deep fascial plane may not be clearly defined, and radial margins of up to 2 cm may result in significant loss of function. In some cases, narrower margins may be appropriate and may not necessarily result in poorer disease control [26].

Desmoplastic and neurotropic melanoma has historically been associated with a high risk of local recurrence, prompting recommendations for wider surgical margins in this subtype [27]. More recent evidence suggests that the standard surgical margins used in non-neurotropic melanoma are sufficient in melanomas with neurotropism, as long as adequate pathologic margins are achieved [28].

Table 14.7 Wide excision and sentinel node recommendations by clinical T category

AJCC eighth edition clinical stage group	Recommended excision margin	Sentinel lymph node biopsy
In situ (T0)	0.5–1 cm	No
Stage IA (cT1a)	1 cm	No
Stage IB (cT1b, T2a)	1 cm	Yes
Stage IIA cT2b, 3a)	1–2 cm	Yes
Stage IIB (cT3b, 4a)	1–2 cm	Yes
Stage IIC (cT4b)	2 cm	Yes

14.4.1.2 Radiation Therapy

Radiation therapy as a definitive treatment for a primary cutaneous melanoma can be considered in patients who are unfit for wide local excision due to poor performance status or medical comorbidity, or who refuse surgery. In this case, it is a palliative treatment delivered with the intent of delaying local progression.

14.4.1.3 Adjuvant Therapy

Adjuvant radiation to the primary melanoma excision site may be considered for certain indications (Table 14.8). The most important determinant of local recurrence is an adequate margin of excision. In the case where initial pathological margins are inadequate, repeat excision should be performed to obtain a wider margin. Adjuvant radiation therapy can be considered instead of re-excision, if further surgery would cause unacceptable aesthetic or functional deficit. Narrow margins are most commonly encountered in the head and neck and in desmoplastic and neurotropic melanoma.

In neurotropic melanoma, there is retrospective evidence to suggest that adjuvant radiotherapy may reduce the risk of local recurrence, even in patients with adequate surgical margins, so it is reasonable to consider it in this setting [28–31]. The utility of adjuvant radiation therapy in completely resected neurotropic melanoma in the head and neck is the subject of an ongoing prospective randomized clinical trial (NCT00975520).

Recurrence of primary melanoma following adequate wide local excision should be re-excised with wide margins. Adjuvant radiation therapy can be considered in this setting, given that local scar recurrence may be reflective of locally aggressive tumour biology.

Adjuvant systemic therapy for high-risk stage IIB and IIC melanoma is not currently a standard of care but is being investigated in an ongoing trial (NCT03553836) [32].

Table 14.8 High-risk indications for adjuvant RT in nodal and primary melanoma

Lymph node bed	Indication – any one of:		
	Number of nodes	Size of node	Extranodal extension
Parotid	≥1	NA	NA
Cervical	≥2	≥3 cm	Yes
Axilla	≥2	≥4 cm	Yes
Inguinal	≥3	≥4 cm	Yes
	Indication—Any one of:		
Primary site	Head and neck location		
	Desmoplastic melanoma		
	Neurotropic melanoma		
	Insufficient surgical margin (where further resection would cause unacceptable functional or aesthetic deficit)		
	Local or scar recurrence		

14.4.2 In Situ Melanoma

In situ melanoma, particularly of the lentigo maligna subtype, is also typically treated with surgical excision. A surgical margin of 5 mm is typically recommended; however, due to subclinical melanocytic extension beyond the visible border of the lesion, in a proportion of patients, margins greater than 5 mm may be required for complete excision. Although in situ melanoma is confined to the epidermis, which is much less than 1 mm thick, malignant cells commonly infiltrate along skin appendages, which can sit as deeply as 4.5 mm from the skin surface [33]. In some cases, often due to the performance status of the patient, the size of the lentigo maligna and anatomical locations, such as the face, non-surgical therapy may be preferred. There is no prospective evidence to guide decisions, but radiation therapy is a viable alternative which can provide local control, whilst the use of topical immunotherapy such as the toll-like receptor 7 (TLR7) agonist imiquimod is also described [34]. These two non-surgical approaches are currently being compared in a prospective randomized controlled trial (NCT02394132).

14.5 Treatment: Regional Lymphatics

14.5.1 Approach to the Clinically Involved Nodal Basin

14.5.1.1 Surgery for Resectable Regional Nodal Metastases

Patients with clinically detected regional lymph node metastases (AJCC eighth edition clinical stage group III) that are deemed to be resectable should be offered regional lymph node dissection. There are no prospective randomized controlled data to assess the question of the extent of nodal dissection, but in retrospective studies, inadequate surgery and incomplete nodal dissection have been shown to worsen regional control and survival [35, 36]. Criteria have been proposed to assess the adequacy of cervical, axillary and inguino-pelvic dissections [37].

14.5.1.2 Adjuvant Therapy Following Regional Lymph Node Dissection

Adjuvant radiation therapy can reduce the risk of regional recurrence but does not improve survival in patients with clinically detected cervical, axillary or inguinal lymph node melanoma metastases. This was demonstrated in the long-term results of the prospective randomized TROG 02.01 trial (at a median follow-up 73 months) in which patients with high-risk nodal features (Table 14.8) who received adjuvant radiation therapy to a dose of 48Gy/20# to the surgical bed following cervical, axillary or inguinal/pelvic lymphadenectomy had a reduced rate of nodal relapse (HR 0.52) but no significant improvement in overall survival or relapse-free survival [38]. Patients who received adjuvant radiation therapy were more likely to suffer from subcutaneous fibrosis and, in the lower limb, lymphoedema but without a significant detriment patient-reported quality of life. Thus, in select patients in whom regional recurrence may cause significant morbidity with limited salvage options, and who may not be suitable for surveillance, adjuvant radiation may be considered, but the available evidence does not support its use routinely.

In contrast to radiation therapy, adjuvant systemic therapy has been shown to improve relapse free and overall survival in patients with resected stage III melanoma and should be routinely utilized as standard of care. Adjuvant high-dose interferon alpha (IFNa) is now a largely superseded agent, which has been investigated in a number of historic clinical trials which showed minor effects on RFS with either no effect on OS or minor effect of borderline statistical significance. A meta-analysis of adjuvant IFNa reported improvement in 5 and 10 years RFS and OS with adjuvant IFNa of less than 4% [39]. Adjuvant IFNa was an onerous regimen (4 weeks of induction daily intravenous therapy followed by 48 weeks of maintenance 3 times weekly subcutaneous administration), with a ≥grade 3 treatment-related toxicity rate of 45–67%, including neuropsychiatric, hepatic toxicities and constitutional flu-like symptoms [40, 41]. The CTLA-4 inhibitor ipilimumab at a dose of 10 mg/kg improved 3-year progression-free survival by 12% compared to placebo following surgery for stage III melanoma, with long-term follow-up data, showing a 11% 5-year overall survival advantage (65% vs 54%) [42, 43]. Treatment with ipilimumab at this dose was poorly tolerated with grade 3–4 adverse event rate of 54% (versus 25% in the placebo arm), with a 1.1% rate of treatment-related deaths. There was a high rate of treatment discontinuation, with the average number of cycles of ipilimumab received being only 4, even though the intended treatment duration on trial was for 3 years. Recent interim data from a prospective comparison with a lower-dose regimen of ipilimumab 3 mg/kg has suggested that the dose may be safely reduced, resulting in lower treatment-related toxicity whilst preserving efficacy [44].

Adjuvant ipilimumab too has now been largely superseded due to toxicity, and the current standard of care for resected stage III melanoma is either 12 months of dabrafenib and trametinib for BRAF-mutant patients or 12 months of adjuvant PD-1 inhibitor (with either nivolumab or pembrolizumab) for all comers both BRAF-mutant and wildtype. Although convincing benefit in terms of 40–50% relative reduction in RFS has been shown with both targeted and immunotherapy with limited follow-up, long-term overall survival (OS) data is still pending. A recent update from the CheckMate 238 trial, in which adjuvant nivolumab 3 mg/kg was compared to adjuvant ipilimumab 10 mg/kg in patients with resected stage III or IV melanoma, has demonstrated improved 3-year recurrence-free survival in the nivolumab arm (58% versus 45%) [45]. Interim data from the Keynote-054 prospective trial of adjuvant pembrolizumab versus placebo in stage III melanoma has shown a 12-month disease-free survival rate of 75% in the pembrolizumab arm (versus 61% in placebo arm) [46]. Subgroup analysis from both trials suggests that the benefit of adjuvant PD-1 inhibitors is retained, irrespective of level of PDL-1 expression or presence or absence of BRAF mutations.

In the COMBI-AD trial, adjuvant combination BRAF and MEK inhibition with dabrafenib and trametinib demonstrated improved RFS of 19% (HR 0.47, $P < 0.001$) and an improvement in OS of 9% at 3 years (HR 0.57, $p = 0.0006$, not statistically significant as did not cross prespecified interim boundary) [47]. The evidence for adjuvant systemic agents in stage III melanoma is largely limited to stage IIIB–IIIC patients (AJCC 7) and higher-risk stage IIIA patients with sentinel lymph node deposit >1.0 mm. In BRAF-mutant patients, is it unknown if adjuvant targeted or immunotherapy is a superior strategy in terms of efficacy as the current available

data with limited follow-up shows equipoise. The choice of adjuvant targeted vs immunotherapy thus comes down to a discussion of differing toxicity and patient preference.

14.5.1.3 Neoadjuvant Therapy Prior to Regional Lymph Node Dissection

There is growing interest in the use of neoadjuvant systemic therapy in patients with stage III melanoma for several reasons. Firstly, this approach allows the early treatment of micrometastatic disease with no delay in systemic therapy, which is often better tolerated pre-surgery than post-surgery. For immunotherapy, the presence of in situ macroscopic tumour is attractive as a source of neoantigens to generate a T-cell response. In addition, there is the potential that neoadjuvant systemic therapy may reduce tumour burden prior to surgery and improve resectability, especially in borderline resectable or upfront unresectable patients. Like in many other tumour streams, pathological tumour response post-neoadjuvant therapy may be prognostic and, in future, may conceivably be used to subsequently direct the choice of either escalating or de-escalating further adjuvant therapy [48]. In a pooled analysis of six neoadjuvant systemic therapy trials for patients with resectable clinical stage III melanoma, a pathologic complete response (pCR) was seen in 41% of patients, and no patient who achieved a pCR with immunotherapy had recurred at the time of publication [49]. Notwithstanding these intriguing results, neoadjuvant therapy remains investigational. The effect of neoadjuvant versus adjuvant pembrolizumab is currently being tested in a randomized phase III trial (NCT03698019).

14.5.1.4 Unresectable Regional Nodal Metastases

Patients with unresectable regional lymph node metastases should be offered appropriate systemic therapy with targeted agents or immunotherapy or considered for enrolment in a clinical trial. Patients with initially unresectable metastatic disease confined to the regional nodal bed who have a good response to systemic therapy may then be considered for regional nodal dissection.

In patients who are unable to tolerate systemic therapy or who have progressed despite systemic therapies, radiation therapy is useful for palliation of symptomatic local unresectable disease. These patients should also be considered for enrolment in a clinical trial.

14.5.2 Approach to the Clinically Uninvolved Nodal Basin

14.5.2.1 Sentinel Lymph Node Biopsy

The risk that regional lymph nodes will harbour subclinical metastatic disease increases with the thickness of the primary tumour. All patients with no evidence of regional lymph node metastasis on clinical examination or by imaging and who have a primary melanoma of the trunk or extremities, which is greater than 1 mm thick, should be offered sentinel lymph node biopsy. Patients with melanoma of 0.75–1 mm thick should be offered sentinel lymph node biopsy, if other pathologic

high-risk features, such as ulceration, mitotic figures >1, Clark level IV or V or lymphovascular invasion, are present [50, 51]. Sentinel lymph node biopsy allows for the detection of microscopic nodal disease without the significant morbidity associated with a complete lymphatic dissection. It is therefore an important prognostic tool: in the MSLT-1 trial, sentinel lymph node status was the strongest predictor of 10-year melanoma specific survival [52].

Historically, completion lymphatic dissection was offered to patients with a positive sentinel lymph node in an effort to reduce the risk of distant metastases and death from melanoma. Because of the risk of acute morbidity including wound breakdown, infection, seroma and the risk of late morbidity such as lymphoedema, fibrosis and pain, two prospective randomized controlled trials, the MSLT-2 and the DeCOG-SLT, were designed to investigate the value of completion lymph node dissection compared to close observation of the nodal bed. In the smaller DeCOG-SLT trial, patients randomized to surveillance with 3-monthly clinical examination and ultrasonography did not have worse 3-year distant metastasis-free survival than those undergoing completion clearance of the nodal basin [53, 54]. In interim results from the MSLT-2 trial, patients who were randomized to surveillance with 4-monthly clinical examination and ultrasonography had equivalent 3-year melanoma-specific survival (the primary endpoint) but slightly inferior disease-free survival to those undergoing completion nodal clearance [55]. Lymphoedema occurred in 24% of surgical patients and 6% of observed patients in MSLT-2, whilst the DeCOG-SLT reported a grade 3–4 adverse event rate of 13% in the surgical arm, of which lymphoedema was the most common [54, 55]. On the strength of these findings, national guidelines no longer uniformly recommend completion lymphatic dissection for patients with a positive sentinel lymph node biopsy if close surveillance can be offered [50, 56].

In the head and neck, complex and variable patterns of lymphatic drainage render sentinel lymph node biopsy less reliable than in the limbs or trunk, with false negative rates of up to 20%, compared with 3% in non-head and neck sites [57, 58]. Despite this, patients with head and neck cutaneous melanomas were included in the MSLT-1 and MSLT-2 trials of sentinel lymph node biopsy. Additionally, recent experience suggests that when performed by experienced operators, sentinel lymph node biopsy is prognostic in head and neck cutaneous melanoma and can be performed with a false negative rate of less than 10% [59]. The decision about whether to offer sentinel lymph node biopsy to patients with primary cutaneous head and neck melanoma will depend upon the experience of the surgeon and the institution in performing this procedure. Elective parotidectomy or cervical lymph node dissection is generally not recommended.

14.5.2.2 Adjuvant Therapy Following Sentinel Lymph Node Biopsy

There is no role for radiation therapy to the nodal basin in undissected patients with a positive sentinel lymph node.

The philosophical shift from completion lymphatic dissection to close surveillance in patients with a positive sentinel node will increase the proportion of undissected patients who are considered for adjuvant systemic therapies—a patient group

who (due to mandated completion lymphatic dissection) were not included in the prospective trials, which have established the efficacy of adjuvant immune checkpoint blockade and adjuvant targeted therapy in stage III melanoma [46, 60]. Nevertheless, there is no rational reason why these patients who have not had a completion nodal clearance would not still benefit from adjuvant systemic therapy. The recent re-analysis of Keynote-054 has shown that eighth edition AJCC stage groupings were not predictive of response to adjuvant pembrolizumab, meaning that patients with sentinel lymph node-biopsied but undissected stage IIIIA (AJCC eighth edition) melanoma may yet benefit from this approach [61]. Whether adjuvant immune therapy improves survival in high-risk stage II patients with a negative sentinel lymph node biopsy is being tested in a currently accruing phase III trial [32].

14.5.2.3 Approach to Satellite Lesions or in-Transit Metastases

Satellite or in-transit metastases represent proliferation of melanoma within dermal or subcutaneous lymphatics, the former denoting lesions that occur within 2 cm of the primary tumour and the latter applying to lesions occurring greater than 2 cm from the primary tumour. The management approach to these lesions depends upon their location and extent. For diffuse, non-resectable in-transit metastases in a limb, techniques such as isolated limb perfusion or isolated limb infusion have been reported to have a good response rate but require significant technical expertise to administer. The AJCC eighth edition pathologic stage grouping for in-transit or satellite metastases is at least IIIB, so systemic therapy for non-resectable stage III disease is also appropriate. For less-diffuse distributions, lesion-directed local management is generally preferred. This is commonly achieved with surgical excision, although direct intralesional therapy with PV-10 (Rose Bengal) or the oncolytic virus talimogene laherparepvec (T-VEC) may also be effective. Radiation therapy is an option in this setting; it is most commonly applied to consolidate a partial response following surgical or intralesional therapy or as a palliative measure in the case of more diffuse, unresectable disease. Topical therapy with agents such as imiquimod may also be used.

14.6 Treatment: Distant Metastases and Unresectable Regional Nodal Metastases

14.6.1 Systemic Therapy

Systemic therapies for melanoma come under the three broad headings of cytotoxic therapies, targeted therapies and immunotherapies.

14.6.1.1 Cytotoxic Chemotherapy

Cytotoxic therapies such as dacarbazine have had very limited effectiveness in metastatic melanoma, with poor response rates and no benefit in overall survival. Fotemustine, temozolomide and NAB-paclitaxel have been shown to have similar

efficacy to single-agent dacarbazine. This class of systemic therapies has been largely superseded in the management of metastatic melanoma.

14.6.1.2 Targeted Therapies

The development of targeted therapies, which inhibit BRAF oncogenic signalling, have significantly improved upon historic systemic therapies in those patients with BRAF V600-mutant melanoma. Single-agent dabrafenib and vemurafenib have demonstrated improved progression-free survival and overall survival compared to dacarbazine [62, 63]. Patients can often display striking initial reduction in tumour burden within days to weeks of commencing a BRAF inhibitor, but in the majority of cases, these responses are not durable and are followed by disease progression. Resistance mechanisms to BRAF inhibition often stem from bypass pathways, which result in the restoration of downstream MAPK signalling, providing a therapeutic rationale for concurrent blockade of BRAF and MEK, which is downstream of BRAF, in the MAPK pathway [64]. This has been borne out clinically, with upfront dual blockade of BRAF and MEK, giving further improvement in PFS and OS compared to single-agent BRAF inhibition. The combination of a BRAF and MEK inhibitor is also better tolerated than single-agent BRAF inhibition, with reduced cutaneous toxicities, in particular reduced incidence of cutaneous squamous cell carcinomas (SCCs), due to the suppression of paradoxical MAPK activation in BRAF wild-type cells in cutaneous tissue. The median progression-free survival of patients with V600-mutant melanoma treated using this approach is 9.3–11.4 months, with a median overall survival of 25 to 33 months [65–68]. With long-term follow-up, the 5-year overall survival of metastatic melanoma patients treated with first-line dabrafenib and trametinib is 35% [69].

14.6.1.3 Immunotherapy

Immunotherapy is an emerging field of systemic therapy in which components of the patient's intrinsic immune system are influenced to improve its ability to identify and destroy cancer cells. There are many potential mechanisms through which immune function might be exploited in cancer therapy, but contemporary clinical immunotherapy of melanoma is synonymous with T-cell checkpoint inhibition by CTLA-4 or PD-1 antagonists. Ipilimumab, a monoclonal antibody with affinity for CTLA-4, was the first immune checkpoint inhibitor to show improved survival in patients who had progressed on cytotoxic therapy [70]. Further experience has shown that single-agent ipilimumab achieves durable survival in approximately 20% of melanoma patients, which plateaus after 3 years and is sustained with up to 10 years of follow-up [71]. Pembrolizumab and nivolumab are monoclonal antibodies with an affinity for the PD-1 receptor expressed on T-cell lymphocytes. The initial experience with nivolumab in ipilimumab and/or BRAF-inhibitor pre-treated patients showed an improved objective response rate for nivolumab compared with cytotoxic chemotherapy [72]. Subsequently, PD-1 blockade with pembrolizumab has demonstrated superior progression-free survival and overall survival with lower rates of immune-related toxicity than ipilimumab [73]. Due to their differing but

complementary modes of action, there is a theoretical rationale for combination immune checkpoint inhibition in melanoma. This was definitively tested in the phase III Checkmate 067 trial, where the 5-year overall survival with ipilimumab + nivolumab (52%) and nivolumab alone (44%) were significantly superior to ipilimumab alone (26%) [74]. Combined immune checkpoint blockade is associated with significantly higher rates of treatment-related toxicity, with grade 3 or 4 adverse events occurring in 59% treated with ipilimumab + nivolumab arm, compared to 21% of those receiving nivolumab alone, or 28% of those receiving ipilimumab (28%) [75].

14.6.2 Local Therapy for Extracranial Oligometastases

14.6.2.1 Surgical Metastasectomy

Prior to the availability of effective systemic therapies for melanoma, complete surgical resection of de novo and recurrent metastatic disease represented a viable treatment option for certain suitable stage IV patients [76]. In a selected patient group, this approach has been demonstrated in two prospective trials to achieve long-term survival, even in the absence of systemic therapies [77, 78]. Similarly, in the same era, a retrospective analysis of patients in the MSLT-1 trial who subsequently developed metastases found that those who received metastasectomy had significantly better survival than those treated with systemic therapy alone [79]. Buoyed by these findings, a clinical trial to compare upfront metastasectomy with best systemic therapy was initiated in 2009 but was terminated in 2013 after accruing 12 patients. In the current environment of highly effective systemic therapies, the role of surgery for metastatic disease is not clear. The majority of stage IV patients will not require surgery; however, it is reasonable to offer surgery in select oligometastatic or oligoprogressive lesions that are refractory to systemic therapy. The decision to offer surgery in this setting is generally best decided after discussion in a multidisciplinary team meeting. A recent retrospective analysis of patients with oligoprogression during treatment with immune checkpoint inhibitors found that local therapy (including metastasectomy) can result in durable progression-free survival [80]. Factors that influence a decision to proceed with metastasectomy include the performance status of the patient, the burden of comorbidities, the presence of absence of other metastatic sites, the disease-free interval and pace of progression, the expected morbidity of the procedure and the remaining systemic therapy options.

14.6.2.2 Radiation Therapy

Historically, in the treatment of extracranial melanoma metastases, radiation therapy has been reserved for palliation of symptomatic lesions or to prolong local control in unresectable sites. Although, historically, melanoma was believed to be a radioresistant tumour, there is no reason to adopt a nihilistic approach to palliative treatment—a good proportion of patients will obtain some benefit from palliative radiation therapy [81]. Radiobiologically, melanoma is believed to have a low α/β ratio, and be more sensitive to large doses per fraction, although this is not

supported by a trial that compared moderate hypofractionation of 50Gy/20# delivered once daily with 32Gy/4# delivered once weekly, in which a complete response rate of approximately 23% was seen in each arm [82]. Practically speaking, moderately hypofractionated treatments are often used for melanoma and are convenient for patients in addition to affording a possible radiobiological advantage over standard fractionation.

In the last decade, the emergence of immunotherapy and stereotactic ablative radiation therapy (SBRT) have changed the landscape of radiation therapy in metastatic melanoma in two ways: firstly, because SBRT might be employed as an alternative to metastasectomy in the treatment of oligometastases and, secondly, because the incompletely characterized interactions of radiation therapy dose and timing in potentiating the effect of targeted therapies and immunotherapy have implications for combining these with radiation. Preliminary experience with combination of SBRT to multisite metastases, from a variety of primary tumour sites with concurrent and sequential ipilimumab and with sequential pembrolizumab, do not suggest increased toxicity [83, 84]. Retrospective evidence also suggests that tumour response might be enhanced by the addition of radiation therapy. In a retrospective study, SBRT to soft tissue melanoma metastases, given prior to immunotherapy, led to an enhanced response at the treated site, an effect that was not observed in bone metastases or when SBRT was administered concurrently with immunotherapy [85]. Additionally, there are case reports of abscopal effects (regression of distant, unirradiated tumours) when SBRT is given prior to or concurrently with immunotherapy [86, 87].

14.6.3 Approach to Brain Metastases

Brain metastases are a common complication of metastatic melanoma, with an incidence of around 50% in patients with stage IV disease [88]. They confer a poor prognosis if untreated, with a median survival of 3–4 months, and represent the worst prognostic metastatic group (stage M1D) in AJCC eighth edition staging. The landscape of brain metastasis management has shifted dramatically from a historical standard of surgery and/or whole-brain radiotherapy (WBRT) to increased utilization of stereotactic radiosurgery in the upfront and post-operative settings and effective systemic therapies with central nervous system penetrance [89–96]. The treatment of melanoma patients with brain metastases can be highly complex and should ideally be discussed by an expert multidisciplinary team, including a radiation oncologist, medical oncologist and neurosurgeon, to determine the optimal combination or sequencing of both local and systemic therapies.

Surgery remains the mainstay of initial treatment, where a tissue diagnosis is needed, or for larger lesions with symptomatic mass effect. Historical trials have demonstrated a survival advantage for resection followed by WBRT in the setting of a solitary metastasis, compared with biopsy and WBRT, of which the most significant landmark trial was by Patchell et al. [91]. Recurrence rates following surgery alone are relatively high—up to 57% even for completely resected lesions; thus,

adjuvant post-operative stereotactic radiotherapy to the resection cavity should be strongly considered and is a much preferable alternative to WBRT [93].

Surgery may be omitted in many patients in lieu of stereotactic radiosurgery (SRS) alone, particularly those in whom the diagnosis of metastatic disease has already been confirmed and where rapid relief of mass effect is not required. The essential role of SRS in modern brain metastasis management has been demonstrated in multiple randomized trials, which have compared WBRT with SRS, and observation with SRS in both definitive and post-operative settings [92, 93, 95, 97]. These have shown high rates of local control and significantly improved quality of life and neurocognitive function with SRS followed by MRI surveillance, with no survival disadvantage when compared with WBRT. Randomized data to date has focused on patients with 1–3 brain metastases, with non-randomized evidence, suggesting similar benefits for patients with 4–10 brain metastases [98, 99]. Randomized trials are underway to further investigate this [100].

Given its general lack of efficacy and significant toxicity, WBRT has fallen out of favour in the treatment of melanoma brain metastasis. A recent landmark randomized multicentre phase III, single histology study has shown that adjuvant WBRT, following local treatment (comprising stereotactic radiosurgery, surgical resection or both) to 1–3 melanoma brain metastasis, does not improve overall survival, distant intracranial control or preservation of performance status [101].

Upfront systemic therapy with or without local therapy is an effective option for carefully selected patients with melanoma brain metastases, where there are reasons to avoid upfront local therapy, such as rapidly progressive extracranial disease, poorer performance status or contraindications to surgery or SRS. For BRAF-mutant disease, earlier studies of single-agent BRAF inhibitors demonstrated response rates of between 18 and 39%, with an intracranial PFS of 4 months or less [102, 103]. For combination BRAF and MEK inhibition with dabrafenib and trametinib, intracranial response rates are significantly higher, ranging from 44 to 60% [104]. For BRAF-mutant patients, rapid intracranial response and symptomatic relief can be achieved with targeted therapy using combination BRAF and MEK inhibitors, even for patients with bulky multifocal brain metastasis. However, this is generally a palliative approach as intracranial progression-free survival remains modest at 5–7 months. Thus, MRI surveillance should be adopted if patients may be candidates for salvage local therapy (SRS or surgery).

Combination immunotherapy with ipilimumab and nivolumab can achieve disease control in patients with small volume, asymptomatic brain metastasis, with response rates of between 46 and 55% and 12-month intracranial PFS of 53%. The higher end of response rates tends to occur in patients who have not previously been exposed to targeted therapies [96, 105]. However, patients with bulky symptomatic disease who are steroid dependent remain a challenge, with poor outcomes even with combination immunotherapy, and thus upfront local therapy should be instigated.

It is important to note that the rates of ≥grade 3 toxicity for combination immunotherapy is significant, at up to 55%. For patients who are not candidates for combination immunotherapy, outcomes are poorer. Single-agent anti-PD1 yields

intracranial response rates of 21% with a 12-month PFS of 20% [104]. Single-agent anti-CTLA4 (ipilimumab) has a response rate of 24% and median intracranial PFS of 6 weeks, dropping to 10%, if steroids are needed for symptoms [106]. Regardless of the choice of systemic therapy, close MRI surveillance should be adopted so that salvage local therapies, such as stereotactic radiosurgery, can be instigated on a timely basis for refractory lesions. In the setting of asymptomatic small volume brain metastasis who are going to be treated with upfront combination immunotherapy, it is unclear whether SRS should be best used upfront or as a salvage option, with a randomized trial underway designed to answer this important question (NCT03340129).

In summary, the management of melanoma brain metastases is optimally performed in the setting of a multidisciplinary team environment. Recognition of the roles of surgery, radiotherapy (specifically radiosurgery) and systemic therapy, either alone or in combination with one another, is essential. Further research is underway to determine the best sequencing and combination of these treatments.

14.7 Head and Neck Mucosal Melanoma

14.7.1 Pathology, Epidemiology and Staging

Mucosal melanoma is a separate entity from cutaneous melanoma, with a distinct set of genetic alterations [107]. Being not caused by UV radiation, these tumours have a lower tumour mutational burden profile than cutaneous melanoma. It is decidedly less common, accounting for less than 1% of new melanoma diagnoses in the United States. Mucosal melanoma has a poor prognosis, possibly due to delayed diagnosis and poorer response to systemic therapies: a recent retrospective analysis of head and neck mucosal melanomas from the United States National Cancer Database reported a 5-year overall survival probability of 27.4% [108]. Mucosal melanomas have a significantly lower incidence of actionable BRAF mutations than cutaneous melanomas and are also less sensitive to immunotherapy. The AJCC eighth edition TNM staging system for head and neck mucosal melanoma allocates a tumor category T3 to primary head and neck mucosal melanomas limited to the mucosa or immediate underlying soft tissue, whilst T4 denotes tumours with involvement of deeper structures or overlying skin: there is no T1 or T2. Nodal category N1 or N0 describes the presence or absence of regional lymph node metastases [109].

14.7.2 Treatment

There is no high-level data on which to base management recommendations, but excision of the primary tumor with clear margins (where this is functionally and aesthetically acceptable) and neck dissection (where there is clinically detected lymph node metastasis) are preferred. National guidelines recommend elective neck dissection for non-sinonasal head and neck mucosal subsites, because of the higher risk of nodal

metastases [110]. Adjuvant radiation therapy should always be strongly considered, because it may reduce the risk of locoregional recurrence [111]. Whether this affects overall survival is unclear: An analysis from the National Cancer Database reported that the addition of adjuvant radiation therapy follow surgery was associated with improved overall survival in sinonasal mucosal melanoma [112], but a retrospective report on head and neck mucosal melanoma from the DAHANCA group reporting no significant effect on disease progression or survival [113]. Definitive radiation therapy should be reserved for those who refuse surgery or in whom surgery would not be feasible due to the extent of disease or medical comorbidity.

14.8 Other Mucosal Melanoma

14.8.1 Pathology, Epidemiology and Staging

Non-head and neck mucosal melanomas are rare. They arise most commonly in the anorectal region and in the lower genitourinary tracts of males and females. They may also arise in the lower respiratory tract and along the length of the upper gastrointestinal tract, but these sites are rarer still. No specific risk factors have been identified. There is no staging system in common usage.

14.8.2 Treatment

There is a lack of high-quality evidence to guide treatment recommendations. In general, wide local excision is the mainstay of treatment for non-metastatic, resectable primary disease. Adjuvant radiation therapy may be recommended on a case-by-case basis for risk factors for local recurrence, such as narrow or involved surgical margins.

14.9 Ocular Melanoma

14.9.1 Pathology, Epidemiology and Staging

Ocular melanoma comprises both uveal and conjunctival melanomas, which are genetically quite different. Conjunctival melanoma has a distinct genetic profile that is nonetheless similar to cutaneous melanoma in that it commonly harbours mutations in Ras and RAF genes [114]. Uveal melanoma has a genetic profile that is very

different from cutaneous, conjunctival or mucosal melanomas, in that over 90% of uveal melanomas are associated with mutation of the GNA11 or GNAQ genes [115]. Uveal melanoma has its own TNM staging system in the AJCC eighth edition cancer staging manual [20].

14.9.2 Treatment

The treatment of ocular melanoma should be performed in a high-volume unit, where the relevant expertise is available. Conjunctival melanoma is commonly treated by local resection with any of several adjuvant therapies, including cryotherapy, plaque radiation therapy, brachytherapy or external beam radiotherapy or topical chemotherapy. More locally advanced tumours may require enucleation or exenteration. Uveal melanoma of a certain thickness may be treated with plaque brachytherapy, for example, I-125 or Pd-103, to achieve local control whilst avoiding nucleation. Thicker uveal melanomas may be treated with proton or heavy ion radiation therapy, photon stereotactic radiation therapy or enucleation. Uveal melanomas typically metastasize to the liver, often as the sole site of metastasis. In general, they do not harbour BRAF mutations and, furthermore, are insensitive to immunotherapy due to their very low tumour mutational burden. Consequentially, metastatic uveal melanomas have a dismal prognosis with no effective systemic treatment options currently available.

14.10 Radiation Therapy Techniques

14.10.1 Considerations in Selecting a Radiation Technique

Several different radiation therapy (RT) techniques can be employed in the treatment of melanoma – it is the responsibility of the radiation oncologist to select an appropriate modality for the particular situation. For example, superficial or orthovoltage radiation therapy may be appropriate for the definitive treatment of lentigo maligna but is unlikely to be sufficiently penetrative for post-operative treatment of neurotropic melanoma. A useful first step in deciding on treatment modality is to define the clinical target volume: complex three-dimensional volumes with adjacent organs at risk may be best suited to intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) techniques, whereas more superficial volumes may be more elegantly treated with techniques, such as electrons or superficial X-rays (Table 14.9).

Table 14.9 Comparison of radiation therapy techniques

Technique	Advantage	Disadvantage	Clinical example
Superficial X-rays	Sparing of deeper structures Narrow penumbra Simple clinical set-up Shielding easier to fabricate than for electrons	Risk of undertreatment with greater depth of target volume Treatment time can become lengthy with larger field sizes and harder beams Absorbed dose is significantly affected by contour irregularity and variations in source-to-surface distance (SSD) across the treatment field due to shorter SSD	Palliative treatment of in-transit metastases
Electrons	Rapid dose fall-off at depth allows sparing of deeper structures More deeply penetrating than superficial or orthovoltage Treatment volume can be marked clinically, rather than in the treatment planning system	Wider penumbra (less suitable for targets near the eye) Shielding blocks are more complex to fabricate than for superficial or orthovoltage Absorbed dose is significantly affected by obliquity, surface irregularity, air gaps and tissue inhomogeneity Skin-sparing effect of lower energy beams means that build-up of appropriate thickness is required to treat the skin	Adjuvant therapy for neurotropic melanoma of the parietal scalp
Megavoltage (MV) X-ray three-dimensional conformal radiation therapy (3D-CRT)	Higher-energy photon beam increases the percentage dose delivered at depth Computer planning provides visual confirmation of treated volume	Unmodulated beams limit the achievable conformality of the treated volume to the target volume Skin-sparing effect of MV beam means that build-up of appropriate thickness is required to treat the skin and superficial tissues	Adjuvant therapy to axilla following dissection for multiple nodes with extranodal extension

MV intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT)	Higher-energy photon beam increases the percentage dose delivered at depth Computer planning provides visual confirmation of treated volume Inverse planning and beam modulation allow for high conformality of treated volume to target volume	Highly conformal treated volume increases the potential for geographic miss compared to 3D-CRT Skin-sparing effect of MV beam means that build-up of appropriate thickness is required to treat the skin and superficial tissues Daily image matching required for safe delivery Higher integral dose than other techniques	Adjuvant therapy to parotid and cervical lymph nodes following parotidectomy for nodal metastasis
Surface brachytherapy	Potential for highly conformal radiation treatments across complex surfaces with greater sparing of adjacent organs at risk than other techniques Reduced percentage depth dose compared to teletherapy due to inverse-square law	Requires expertise in radiation oncologist and radiotherapists for treatment planning, physics for calibration of the source Complex transport, storage and handling requirements for radioactive source	Definitive treatment of large lentigo maligna e.g. where obliquity, surface irregularity and adjacent organs at risk demand compromises with photon or electron techniques

14.10.2 Simulation

Simulation approaches will differ, depending on the radiation technique to be employed and the site to be treated. Some suggested approaches for adjuvant RT to the resected primary and nodal bed (Table 14.10) and for definitive RT to lentigo maligna (Table 14.11) are tabulated.

14.10.3 Daily Treatment Position and Image Verification

This will vary somewhat between departments and should be tailored to the treatment technique that is selected. Patient position, immobilization devices, couch height and position will be recorded at the time of simulation and can be reproduced at the time of treatment, with the help of the in-room laser localization system. Highly conformal approaches, such as VMAT and IMRT, should have daily image verification with online correction. This is not necessary for less conformal approaches, such as three-dimensional conformal radiation therapy (3DCRT) and electron therapy, which may have first week daily imaging than weekly imaging with offline trend review.

14.10.4 Treatment Planning, Volume Delineation and Recommended Dose

14.10.4.1 Adjuvant Radiation Therapy for High-Risk Nodal Metastases

The highest-quality evidence base (TROG 02.01 prospective RCT) for post-operative radiation for high-risk regional nodal metastases (see Table 14.8) allowed clinically marked electron fields, to treat the unilateral parotid and neck, and two-dimensional field-defined or 3DCRT megavoltage X-ray techniques, to plan axillary or inguinal radiation treatments [38]. The majority of radiation centres have moved away from these techniques, which have been replaced by IMRT and VMAT which offer the potential to reduce the burden of toxicity associated with these treatments by reducing doses to organs at risk whilst maintaining planning target volume (PTV) coverage [116]. A general approach to defining volumes for conformal treatments to the nodal bed in the adjuvant setting in melanoma, adapted from the International Council on Radiation Units (ICRU) report 62 and informed by the TROG 02.01 prospective trial, is set out below [38, 116, 117]:

- *High-risk target volume (HRTV)*: Define the preoperative nodal disease, with the aid of co-registered preoperative imaging.
- *Clinical target volume (CTV)*: HRTV (adapted to post-operative anatomical boundaries—bone, muscle, fascia, skin) plus 1 cm isotropic expansion plus the elective nodal groups (see Table 14.10) plus the surgical scar.

Table 14.10 Example of simulation approaches for adjuvant RT to resected primary melanoma and regional nodal bed

	PORT following wide local excision of neurotropic melanoma of head and neck	PORT following parotidectomy and neck dissection for parotid and cervical nodal metastasis	PORT following axillary dissection for high-risk nodal metastasis	PORT following inguinal dissection for high-risk nodal metastasis
Proposed CTV	Surgical bed plus 1.5 cm isotropic margin Respect anatomical boundaries	Surgical bed plus Elective nodal levels – Ib–V. – Pre- and post-auricular. – Deep parotid. Surgical scar plus 1.5 cm Indications to include primary site: – Abutting field. – Excised within 1 year of nodal metastases. – T3.	Surgical bed plus Axilla levels I – III Supraclavicular fossa Surgical scar plus 1.5 cm Indications to include primary site: – Within 5 cm of field. – Excised within 1 year of nodal metastases.	Surgical bed plus Femoral, inguinal, external iliac nodal regions (up to 5 cm margin on cephalad extent of surgical bed) Surgical scar plus 1.5 cm Indications to include primary site: – Within 5 cm of field. – Excised within 1 year of nodal metastases.
Technique	Electron VMAT/IMRT/3DCRT	VMAT/IMRT	VMAT/IMRT/3DCRT	VMAT/IMRT/3DCRT
Position	Comfortable, reproducible position that minimizes obliquity and contour irregularity. – Supine, with or without neck rotation. – Prone permissible to treat scalp vertex.	Supine Neck neutral	Supine Arm akimbo	Supine Hip slightly abducted and externally rotated Male genitalia taped to contralateral side

(continued)

Table 14.10 (continued)

	PORT following wide local excision of neurotropic melanoma of head and neck	PORT following parotidectomy and neck dissection for parotid and cervical nodal metastasis	PORT following axillary dissection for high-risk nodal metastasis	PORT following inguinal dissection for high-risk nodal metastasis
Immobilization	Head and neck support – Personalized, e.g. with two-part foam, if using position other than supine with neutral neck. Thermoplastic mask	Head and neck support Thermoplastic mask	Personalized torso and arm support – E.g. with vacuum bag.	To improve reproducibility of this unstable position, use bilateral personalized thigh, knee and lower leg supports, e.g. with two-part foam or vacuum bag
Clinical markup	Approximate position of tumour before resection Scar CTV	Parotidectomy scar Neck dissection scar +/− primary site scar	Axillary dissection scar +/− primary site scar	Inguinal dissection scar +/− primary site scar
Bolus	Sufficient thickness that scar and skin within CTV receive prescription dose	Bolus to include scar plus 1.5 cm margin in treated volume Consider expanding bolus to cover regions where involved lymph nodes were superficial or if there was extranodal extension		

Table 14.11 Electron and superficial/orthovoltage technique for definitive treatment of lentigo maligna

	Superficial/orthovoltage	Electron
Proposed CTV	Visible extent of lentigo maligna plus 0.5–1 cm radial, 0.5 cm deep	
Position	Stable, comfortable position Minimize beam obliquity Minimize SSD variation across the field (e.g. using lead cut-out to flatten lateral nose)	Stable, comfortable position Minimize beam obliquity
Immobilization	Patient in comfortable position, field defined by surface shielding Patient observed during treatment	Head and neck support Consider thermoplastic mask
Clinical markup	Border of lentigo maligna Field edge = CTV (defined by surface shielding)	Border of lentigo maligna Field edge = CTV + PTV + consideration of penumbra
Radiation quality	Choose appropriate half-value layer (HVL) for the field size to achieve 90% of peak dose at 5 mm depth Typically in the range of 2–4 mm Al	Choose appropriate beam energy to achieve 90% of peak dose (R90) at deep border of dermis Typically 6 MeV (with 1 cm bolus)
Bolus	No build-up Pack air cavities adjacent to CTV (e.g. nasal vestibule, Conchal bowl, ear canal) to ensure adequate scatter conditions to minimize lateral electronic disequilibrium	Build-up to include skin in treated volume, usually 0.5 to 1 cm with 6 MeV electron beam energy Pack air cavities adjacent to CTV (e.g. nasal vestibule, Conchal bowl, ear canal) to ensure adequate scatter conditions to minimize lateral electronic disequilibrium
Shielding	Lead cut-out to define field boundary (custom or library) Internal/external eye shield for medial canthus, lower eyelid lesions Nasal shield for ala nasi lesions Intra-oral shield for lesions of lip and cheek Posterior-auricular shield for ear helix lesions	Cerrobend block to define treatment mortal, mounted in electron cone on linac gantry (surface lead shielding for electrons is also possible for lower beam energies)
Prescription point	Typically prescribed to peak dose	

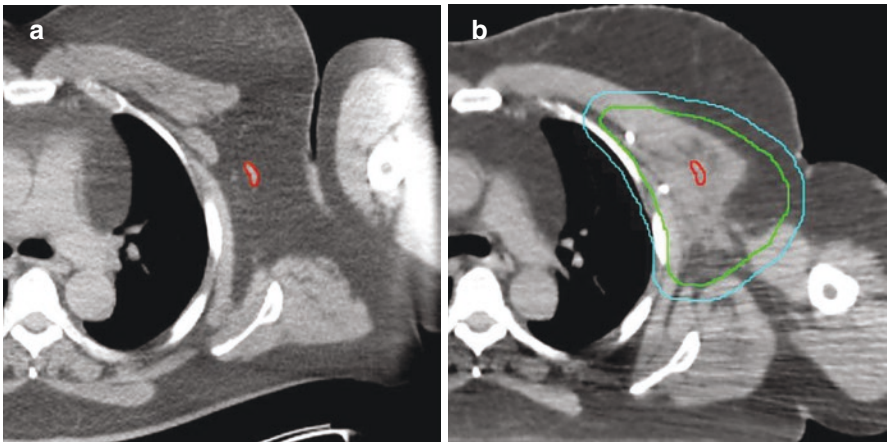

Fig. 14.2 PORT volumes for left axilla following level I–III axillary dissection. Pathology findings were metastatic melanoma in 3 of 22 lymph nodes, largest deposit 13 mm, no extranodal spread. (**a**) Axial slice of preoperative PET/CT (PET component not shown) showing HRTV (red). (**b**) Axial slice of post-operative planning CT at the same level, showing position of HRTV (red) and the CTV (green) and PTV (light blue). These volumes are the minimum recommended and could also be expanded to include the level II and III nodes medial to pectoralis minor
PORT = post-operative radiation therapy; PET/CT = positron emission tomography/computed tomography; HRTV = high-risk target volume; CTV = clinical target volume; PTV = planning target volume

– *Internal Target Volume (ITV)*: CTV plus a margin to account for physiologic movements (e.g. respiration). May not always be necessary.
– *Planning target volume (PTV)*: CTV (or ITV if this has been delineated) plus an expansion to account for daily positional uncertainty (department and anatomic site specific).

The preferred dose in the setting of adjuvant treatment to the regional nodal bed is a single-phase prescription of 48Gy/20#/5pw, which is supported by level II evidence [38]. Other options include 50Gy/25#/5pw or 30Gy/6#/2pw [118, 119]. Higher-dose schedules such as 60Gy/30#/5pw may also be employed but may be associated with higher levels of toxicity in the axilla and groin. A clinical example of PORT volume delineation following axillary dissection for high-risk melanoma metastases is depicted in Fig. 14.2.

14.10.4.2 Adjuvant Radiation Therapy for High-Risk Primary Cutaneous Melanoma of the Head and Neck

A general approach to defining volumes for conformal treatment to the primary site in the adjuvant setting for melanoma, adapted from the ICRU reports 62 and 71 and the currently recruiting TROG 08.09 clinical trial (NCT00975520), is set out below [117, 120].

- *HRTV*: Define the preoperative site of the melanoma (if known), adapted to post-operative anatomy, plus the surgical bed and the overlying primary site scar (excluding scars related to local flaps).

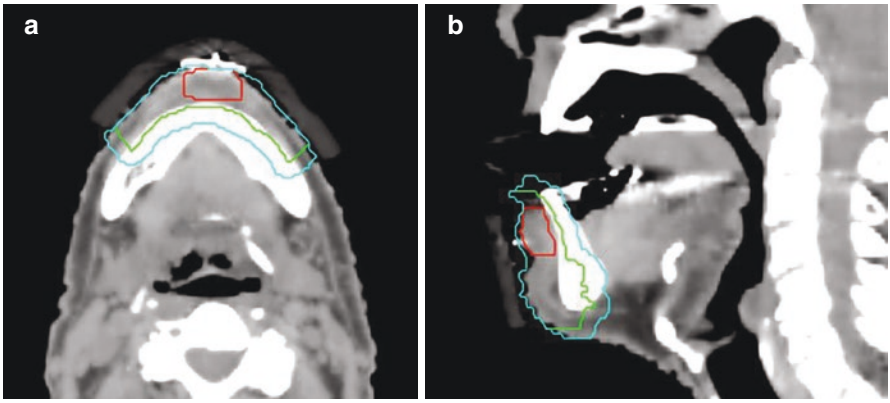

Fig. 14.3 PORT volumes for a patient with a 9 mm Breslow thickness neurotropic melanoma of the lower lip excised with 8 mm margins. (**a**) Axial slice showing HRTV (red), extending deeply to the cortex of the underlying mandible; a wide margin to CTV (light green), extending to the skin surface; a 0.5 cm margin to PTV (light blue). Note the wire to mark the position of the scar and the overlying 1 cm thick bolus to ensure treatment dose at the skin surface. (**b**) Sagittal slice showing the HRTV; CTV extending superiorly to the skin surface of the vermilion lip; PTV. Note the bolus to cover the craniocaudal extent of the PTV and the open mouth with tongue depressor to spare radiation toxicity to the upper lip
HRTV = high-risk target volume; CTV = clinical target volume; PTV = planning target volume

- *CTV*:
  - Neurotropic melanoma of the head and neck.
  - HRTV +1.5 cm isotropic expansion, respecting anatomic boundaries
  - Non-neurotropic head and neck melanoma with involved or narrow surgical margin.
  - HRTV +1 cm isotropic expansion, respecting anatomic boundaries
- *PTV*: CTV plus an expansion to account for daily positional uncertainty (department specific).

Acceptable radiation dose-fractionation regimens include standard fractionation 60–66 Gy/30–33#/5pw, moderate hypofractionation of 48 Gy/20#/5pw or hypofractionated 30 Gy/6#/2pw. A clinical example of volume delineation is depicted in Fig. 14.3.

14.10.4.3 Definitive Radiation Therapy for Lentigo Maligna

If a superficial X-ray technique is used, a clinical markup of the GTV is performed (consider dermatoscopic evaluation or the assistance of a dermatologist in defining the GTV). The GTV is then expanded to a CTV to account for subclinical disease. Electron treatments may also be marked up clinically, but if a Cerrobend block in the electron applicator is used to define the field, rather than surface shielding, then a PTV expansion is required in this case. The details of superficial X-ray and electron simulation approaches are compared in Table 14.11.

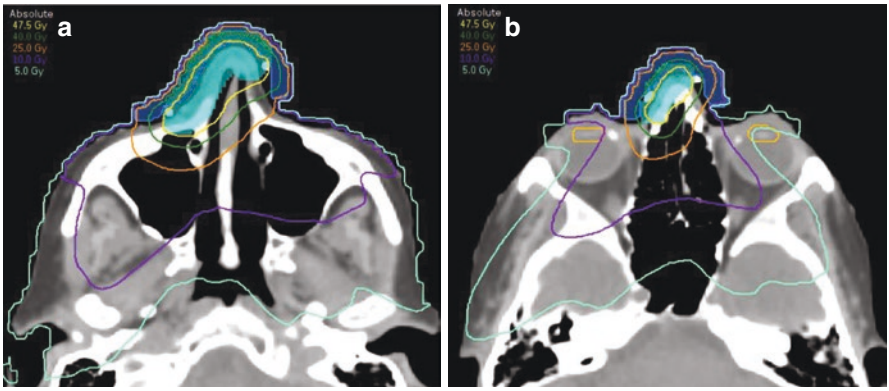

Fig. 14.4 VMAT plan prescribed to 50Gy/20# for lentigo maligna over dorsum of nose, with PTV marked clinically at time of simulation and wired. (**a**) Axial slice at level of cheek showing 95% coverage of PTV without compromise. Isodose lines are shown as indicated. PTV = light blue shading; 1 cm thick bolus = dark blue shading. (**b**) Axial slice at level of lens. Note some compromise of 95% coverage of PTV at the right border and sparing of ipsilateral lens by 10Gy isodose line
VMAT Volumetric modulated arc therapy, *PTV* Planning target volume

Alternatively, for larger or more complex lentigo maligna, computer-planned conformal electron, 3DCRT or IMRT/VMAT approaches may be used (Fig. 14.4). Simulation should be performed as previously described (Table 14.11). A general approach to defining volumes for definitive conformal treatment of lentigo maligna (with electron, 3DCRT or IMRT/VMAT) is set out below:

– *GTV*: The clinical extent of the lentigo maligna
– *CTV*: GTV plus minimum 0.5–1 cm radial expansion plus 5 mm deep
– *PTV*: CTV plus an expansion to account for daily positional uncertainty (department specific)

Typical doses include 60 Gy/30#/5pw, 54 Gy/27#/5pw, 50 Gy/20#/5pw and 45 Gy/15#/5pw. If invasive disease is suspected in a patient who is not a candidate for surgical resection, dose escalation to 60–66 Gy/30–33#/5pw can be considered.

The use of surface brachytherapy has been reported for the definitive treatment of lentigo maligna and for the palliative treatment of in-transit metastases [121, 122]. This technique has theoretical dosimetric advantages, because of the proximity of the source to the target resulting in rapid dose fall-off according to the inverse-square law, but requires specialist expertise to plan and deliver (Table 14.9) and is not available in the majority of radiation therapy centres.

14.10.4.4 Definitive Radiation Therapy for Mucosal Melanoma of the Head and Neck

A general approach to defining the target volumes for definitive treatment of mucosal head and neck melanoma is set out below.

- *GTV:* The clinical extent of the primary melanoma and any nodal metastases
- *CTV:* GTV plus minimum 0.5 cm isotropic expansion
  - Anatomical barriers such as bone and air gaps may be cropped from this volume at the discretion of the radiation oncologist
- *PTV:* CTV plus an expansion to account for daily position uncertainty (department specific)

Appropriate doses range from 66 to 70 Gy EQD2 for radical treatments or 48 to 50 Gy/20#/5pw or 30Gy/6#/2–3pw for high-dose palliative treatments.

14.10.5 Dose Specification

14.10.5.1 Megavoltage (MV) Energy Photon Treatments (3DCRT, IMRT/VMAT)

The International Council of Radiation Units (ICRU) reports 50/62 and 83 specify minimum requirements for the prescription, planning and reporting of 3DCRT and IMRT treatments, respectively. In 3DCRT, using unmodulated beams with a generally homogenous distribution of dose within the treated volume, the dose is prescribed to a clinically relevant point. In IMRT and VMAT, due to the potential for heterogeneity of dose distribution within the PTV, because of complex fluence patterns generated by heavy modulation of the radiation beam, dose statistics that describe the pattern of coverage of the PTV are reported and are used to specify the prescription [123]. These include:

- D98: Minimum dose received by 98% of the PTV (near-minimum). Recommend greater than 95% of prescribed dose.
- D50: Minimum dose received by 50% of the PTV (median). Recommend 100% of prescribed dose.
- D2: Minimum dose received by 2% of the PTV (near-maximum). Recommend less than 107% of prescribed dose.

The purpose of the PTV is to reduce the likelihood that the CTV will receive an inadequate dose due to errors in patient position. Due to the potential for dose heterogeneity within the PTV in intensity-modulated treatments, it is possible to achieve the above parameters but still have suboptimal dose to the GTV and

CTV. Thus, it is essential to visually inspect the dose distribution for adequate target coverage and presence of cold spots. It is also useful to report dose statistics for the CTV to ensure a clinically meaningful dose distribution.

14.10.5.2 Electron Treatments

The ICRU report 71 describes the minimum requirements for prescribing, recording and reporting electron beam therapy [120]. In practical terms, the dose should be reported at the ICRU point—a point in a region of uniform dose that is clinically relevant, preferably on the central axis—typically the peak dose (Zmax). The dose is typically prescribed to Zmax but may also be prescribed to the 90% isodose deep to the peak (R90), although in this instance, it must be remembered that the maximum absorbed dose will be ~110% of the prescribed dose.

14.10.5.3 Superficial (Kilovoltage Energy) Photon Treatments

Superficial and orthovoltage X-rays reach peak absorbed dose at the skin surface. It is generally the convention to prescribe to the peak dose and select a beam hardness that will afford 90% coverage of the deep margin of the CTV. The source to surface distance, applicator size, field size, field shape and energy of the beam will affect the percentage depth dose (PDD), so the departmental reference should be checked to ensure the correct half value layer beam is selected for these parameters.

14.11 Principles of Stereotactic Ablative Radiation Therapy for Extracranial Oligometastases

Historically, stereotactic radiation therapy was used intracranially and referred to the use of a three-dimensional coordinate system to localize targets. Contemporary extracranial stereotactic ablative radiation therapy (SBRT) treatments can be recognized by the following principles [124, 125]:

- High doses per fraction, for one or several fractions, to treat small fields with steep dose gradients
- Motion management
- Image guidance
- Specialist expertise in planning, quality assurance and treatment delivery

14.11.1 Highly Hypofractionated Treatment to Small Fields with Steep Dose Gradients

Small fields and steep dose gradients allow for the safe delivery of ablative doses of radiation to the intended target whilst sparing adjacent normal tissues from severe late radiation effects. A feature of SBRT treatments is the prescription to a low isodose of 70–90%, giving rise to a heterogenous dose distribution within the PTV with a central peak of ~125–140% of the prescribed dose. Processes other than

mitotic catastrophe caused by non-repair or mis-repair of double-strand DNA breaks may contribute to cell death at these high radiation doses, and normal means of cellular recovery, such as repopulation, re-assortment and re-oxygenation, may not occur in the same way as following fractionated radiation therapy. Thus, there is some debate as to whether the linear quadratic model is accurate for calculating biologically effective doses, when such large radiation doses are delivered. Nevertheless, the available clinical data suggest that currently used stereotactic treatment regimens are very effective in achieving local tumour control and are tolerable when treating small targets with small margins achievable due to motion management and image guidance.

14.11.2 Motion Management

Motion management refers to reproducible, comfortable patient set-up to limit error due to position uncertainty and techniques to account for variation of the position and deformation of the clinical target volume (CTV) due to physiological organ motion. Organ motion typically results from excursion of the diaphragm during the respiratory cycle, which is most pronounced in thoracic and upper abdominal organs. The least invasive approach is to simulate and treat the patient during free breathing, using four-dimensional computed tomography (4D-CT) to define the target volume in all phases of the respiratory cycle, but this will lead to a larger irradiated volume. The addition of abdominal compression can reduce diaphragmatic excursion but may be uncomfortable and may not always improve the spatial relationship between target volumes and organs at risk. More invasive approaches include breath-hold techniques such as deep inspiration breath-hold and end expiratory breath-hold. An example is active breathing control, which may reduce the ITV but requires patients who are able to follow breathing instructions and hold their breath for moderate periods. Respiratory-gated or real-time tumour tracking free-breathing solutions are also available that track non-tumour surrogates such as fiducial markers, but the accuracy of these approaches can be affected by patients with irregular breathing cycles.

14.11.3 Image Guidance

Pretreatment and mid-fraction image guidance with linear accelerator gantry-mounted kV cone beam CT (CBCT) is the most commonly used image guidance technique. Protocols for the timing of additional CBCT (post-position shift and/or post-fraction) and the action levels for online correction will be determined by individual departments based on the anatomical tumour location. For some target sites, such as spine, a robotic treatment couch with six degrees of freedom is essential to enable fine rotational and translational adjustments. Potential sources of error when relying on CBCT image guidance include poorer image quality than diagnostic CT, inter-observer variation in image interpretation, mis-binning of 4D CBCT (where

this is available) and inadequacy of surrogates for tumour position (such as the use of liver contour for intrahepatic targets): the anticipated magnitude of these uncertainties for a given patient treatment scenario should inform the planning target volume (PTV) margin. Linear accelerator-integrated magnetic resonance imaging (MRI) is beginning to be introduced into clinical practice and has the potential to improve the accuracy of image guidance in soft tissues.

14.11.4 Quality Assurance

High-level quality assurance (QA) is essential to the safe implementation of SBRT and should be addressed at every stage of the patient journey. Clinical QA includes appropriate patient selection, correct dose prescription, accurate target and organ delineation. These should be peer reviewed before the commencement of treatment. General physics QA for SBRT is a complex topic and is beyond the scope of this chapter. A comprehensive approach to planning and treatment for SBRT, including physical QA, is detailed in the ICRU report 91 [125]. In broad terms, tight mechanical tolerances of the linear accelerator gantry, couch and on-board imaging and the accurate calibration and dose measurement for small field photon beams are required. Patient-specific QA is essential prior to delivery of SBRT.

14.12 Patient-Specific Radiation Quality Assurance for Modern Techniques

Patient-specific quality assurance (QA) should be performed for IMRT, VMAT and SBRT plans prior to commencing treatment. These should include measurements of dose and fluence pattern in a clinically appropriate phantom with an appropriate dosimeter to confirm the monitor unit calculation and multi-leaf collimator sequencing. A physical check to avoid collisions of the gantry with the treatment couch should be performed when non-coplanar beams are used.

14.13 Normal Tissue Complications From Radiation Therapy for Melanoma

Radiation toxicity is classified as early (occurring during treatment and resolving within 3 months) or late (occurring or persisting after 3 months). Early responding tissues typically have a threshold dose, below which acute toxicity is uncommon and above which the risk of toxicity is near certain. Good examples are epithelial surfaces, such as aerodigestive mucosa and the epidermis, which begin to show clinical radiation toxicity following 10–20 Gy of standard fractionation radiation therapy, worsening in severity with increasing dose. These tissues are typically hierarchical in arrangement, and the toxicity is largely a product of stem cell death leading to progressive hypoplasia. Late responding tissues may have a flexible tissue

architecture, and the mechanism of toxicity is due to the combined effects of parenchymal cell loss, endothelial dysfunction leading to microvascular insufficiency and radiation-induced fibroblastic proliferation. The probability of late radiation toxicity, and the severity of the toxicity, increases with absorbed dose. In tissues that have a parallel arrangement of functional subunits, the volume of irradiated tissue is also important in determining the likelihood and severity of toxicity. A good example in the setting of radiation therapy for melanoma would be the parotid gland, in which the probability of permanent xerostomia is increased significantly with mean doses above 20–25 Gy [126]. In tissues that have a series arrangement of functional subunits, the volume of tissue irradiated is less important (although not immaterial) than the maximum absorbed dose. A good example is the spinal cord, where maximum doses that exceed 45 Gy and above lead to increasingly high probabilities of radiation myelopathy [127]. Several grading scales are in use to quantify the severity of a toxicity, including the Radiation Therapy Oncology Group (RTOG) and Common Terminology Criteria for Adverse Events (CTCAE) systems.

14.13.1 Factors Affecting Risk of Normal Tissue Complications

The risk of toxicity is affected by patient, tumour and treatment factors.

14.13.1.1 Patient Factors

This encompasses intrinsic radiation sensitivity (which is impossible to quantify if the patient has never received radiation therapy, but a qualitative estimate may be made by assessing the severity of late effects in a previously irradiated patient) and prior radiation dose to relevant organs at risk.

14.13.1.2 Tumour Factors

Tumour factors include the size and location of the tumour or planning target volume and its proximity to relevant normal tissues.

14.13.1.3 Treatment Factors

Treatment factors include the total dose, dose per fraction, use of beam modifiers such as bolus, type of radiation used and the quality of the radiation plan (e.g. the presence of clinically significant hotspots).

14.13.2 Early Radiation Toxicity Following Radiation Therapy for Melanoma

14.13.2.1 Head and Neck

When treating cutaneous melanoma of the head and neck, typical early toxicities include erythaema and desquamation of the skin (onset of cutaneous early effects seen from 10–20 Gy), temporary or permanent alopaecia of hair or facial hair and dry skin due to effects on sebaceous and sweat glands (onset from approximately

10 Gy). If parotid or deep cervical nodal volumes are to be treated, mucositis (onset from 10 to 20 Gy), xerostomia (onset from 10 to 15 Gy; minor salivary glands in oral cavity, major salivary glands including parotid and submandibular) and dysgeusia (onset 20–30Gy; taste buds in oral tongue) are possible. Lhermitte's phenomenon—electric shock-like sensations caused by a transient demyelination in the spinal cord (a subacute radiation toxicity)—may be seen but is unlikely with unilateral neck irradiation typically delivered in cutaneous melanoma (onset possible with doses above 35 Gy).

The early effects of irradiation of the eyelids and surface of the eye include temporary kerato-conjunctivitis (onset from 10–20 Gy), temporary eyelash loss (10–20 Gy) and erythaema, oedema and moist desquamation of the skin of the eyelids.

14.13.2.2 Axilla

When treating the axilla, common early radiation toxicities include erythaema and desquamation of the skin, permanent alopaecia of axilla hair and dry skin due to effects on sebaceous and sweat glands. Radiation pneumonitis (a subacute radiation toxicity) is unlikely with a traditional 3DCRT MV photon technique, using an anterior-posterior/posterior-anterior beam arrangement, but with newer techniques such as VMAT, the dose to lung should be monitored: the typical dose/volume limits for the combined lungs in radical primary lung cancer radiation therapy are V20Gy <30% and V30Gy <20% (for a ≤20% chance of symptomatic pneumonitis), but much lower lung dose/volume parameters will be achievable when treating the axilla in this setting [128].

14.13.2.3 Groin

When treating the groin, common early radiation toxicities include erythaema and desquamation of the skin, temporary or permanent alopaecia of pubic and body hair and dry skin due to effects on sebaceous and sweat glands. Other potential early effects include radiation bladder toxicity, such as frequency, dysuria and urgency, and rectal toxicity such as tenesmus and faecal urgency.

14.13.3 Late Toxicities Following Radiation Therapy for Melanoma

14.13.3.1 General

In general, more deeply penetrative MV energy X-rays are used to treat the nodal regions, and so the potential late effects may affect deeper organs and structures than those seen in the superficial or electron treatments used for lentigo maligna or neurotropic primary melanoma. Despite this, if the skin is included in the target volume by the application of tissue-equivalent bolus, then cutaneous atrophy, telangiectasia and permanent alopaecia may be seen. More severe late cutaneous effects such as slow healing or non-healing ulcer occur most commonly following trauma to irradiated, hypoperfused skin. An example of this would be a biopsy to an

Table 14.12 Late effects following lymph node dissection and adjuvant radiation therapy

	Lymph node dissection alone		Lymph node dissection plus adjuvant RT		p value for differences in grades 2–4 between groups
	Grade 1	Grades 2–4	Grade 1	Grades 2–4	
Head and neck					
Subcutaneous tissue fibrosis	55%	34%	39%	54%	0.15
Nerve damage	48%	45%	50%	43%	0.88
Joint in treated area	31%	24%	68%	7%	0.081
Pain	59%	10%	54%	25%	0.15
Axilla					
Subcutaneous tissue fibrosis	54%	27%	44%	49%	0.042[a]
Nerve damage	78%	15%	64%	19%	0.59
Joint in treated area	66%	12%	55%	21%	0.26
Pain	66%	17%	60%	24%	0.45
Groin					
Subcutaneous tissue fibrosis	50%	34%	33%	60%	0.045[a]
Nerve damage	78%	19%	52%	26%	0.5
Joint in treated area	38%	13%	45%	13%	0.96
Pain	34%	31%	55%	23%	0.44

Selected adverse events by lymph node field from the TROG 02.01 trial
Adapted from *Henderson* et al. *Adjuvant lymph-node field radiotherapy* versus *observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial; Lancet Oncol 2015; 16: 1049–60*
[a]Statistically significant increase in rate of grade 2–4 in subcutaneous tissue fibrosis in patients having adjuvant RT to the axilla or groin

irradiated skin graft on the scalp. Second malignancy such as angiosarcoma or basal cell carcinoma is a rare but material risk.

Deep to the skin, the subcutaneous tissue may develop fibrosis. Surgical dissection of the cervical, axillary and inguinal lymph nodes may also cause subcutaneous fibrosis, but the addition of adjuvant radiation therapy significantly increases this probability in the axilla and the groin (Table 14.12).

Unless otherwise specified, the dose limits here are presented as equivalent dose in 2 Gy per fraction according to the linear quadratic formalism (EQD2). Commonly, adjuvant radiation therapy for melanoma is prescribed in a moderately hypofractionated regimen, such as 48 Gy/20#. Organ at risk (OAR) doses for such treatments should be converted to EQD2 using an appropriate α/β ratio for late responding tissue, such as 2 or 3, in order to compare them with recommended dose/volume limits.

14.13.3.2 Head and Neck

Fibrosis of the soft tissues of the neck of varying severity is commonly seen following adjuvant radiation therapy. Persistent xerostomia may be seen although is uncommon with unilateral neck irradiation in which the minor salivary glands in the oral cavity and the contralateral parotid and submandibular glands may be effectively spared. Hearing impairment following adjuvant radiation therapy to the neck in melanoma is uncommon, where it is usually possible to keep the mean dose to the ipsilateral cochlea less than 35–45 Gy [129]. The risk of mandibular osteoradionecrosis increases in regions of the mandible where the biologically effective dose (BED) exceeds 102 Gy_2 and is increased further by subsequent surgical trauma, such as tooth extraction, in these areas [130]. Brachial plexus radiation tolerance is poorly defined, and much of the data informing current practice comes from older two-dimensional radiation techniques. Nevertheless, radiation brachial plexus injury is essentially not seen at doses below 50 Gy and rare with point doses up to 60–66 Gy [131, 132]. Radiation myelopathy of the spinal cord is rare with doses below 50 Gy, with a probability of 0.03% at 45 Gy, increasing to 0.2% at 50 Gy and 6% at 60 Gy. Some recovery of radiation tolerance is seen with time, at least 25% after 6 months [127]. Carotid artery stenosis is a recognized late effect of radiation therapy to the neck, although dose-volume parameters are unclear [133]. Hypothyroidism is not uncommon following radiation therapy to the neck; the risk might be reduced by limiting the volume of the thyroid gland receiving 30–35 Gy [134].

The late effects of irradiation of the orbit can cause several complications [135]. Fibrosis of the skin and subcutaneous tissue of eyelid can result in ectropion or entropion. Permanent loss of eyelashes may be seen after 30 Gy. The lens is very radiosensitive, and cataracts can be caused by a single dose of 2 Gy or 8 Gy over multiple fractions. When radiation-induced corneal injury occurs, it is mostly indirect and as a result of secondary keratitis sicca due to a dry eye: this can be avoided by keeping the lacrimal gland to a mean dose of less than 30 Gy. A chronic watery eye (epiphora) may be cause by nasolacrimal duct stenosis, which may be more likely when a BED greater than 100 Gy_3 is delivered to this structure [136]. Subacute anterior uveitis may be seen with doses of 60–80 Gy, and neovascularization of the iris may cause glaucoma. Late retinal radiation toxicity is unlikely with doses of less than 45 Gy, and late toxicity of the optic nerve is unlikely with doses of less than 54 Gy.

14.13.3.3 Adjuvant Treatment of Axilla

Fibrosis of the soft tissues of the axilla is very common following adjuvant radiation therapy and is significantly worse than in those patients who have lymph node dissection alone (Table 14.12). Rates of upper limb grade 3 lymphoedema appear not to be significantly increased compared to axillary dissection alone in those who receive adjuvant radiation therapy [38]. The brachial plexus enters the axilla by passing between the scalenus anterior and scalenus medius muscles. As is the case in cervical nodal radiation, the risk of plexopathy is low with doses in the range used for adjuvant radiation therapy.

14.13.3.4 Adjuvant Treatment of Groin

The proportion of patients with grades 2–4 fibrosis of the soft tissues of the groin are significantly higher with adjuvant radiation therapy following inguinal lymph node dissection (Table 14.12). Rates of grade 3 lower limb lymphoedema appear not to be significantly increased in patients receiving adjuvant radiation therapy, but in the TROG 02.01 trial, these was a statistically significant difference in the increase in mean limb volume, with larger change seen in the adjuvant radiation therapy group [38]. Radiation therapy to the long bones of the lower limb can increase the risk of pathologic fracture and avascular necrosis. Various dose/volume limits have been proposed. In the TROG 02.01 trial, a femoral neck maximum dose of 40 Gy was recommended, although higher doses to small volumes are probably safe [137, 138]. In males, there is a risk of temporary oligospermia with a testis dose of 0.1 Gy. Azoospermia of several years' duration is seen after 2 Gy, with a high risk of irreversibility. Hypogonadism is seen at doses greater than 20 Gy. In post-pubertal premenopausal females, sterilization and induction of menopause may be precipitated by a dose to the ovaries of 14–30 Gy, with the tolerance decreasing with advancing age [138].

14.13.4 Strategies to Minimize Radiation Toxicity

14.13.4.1 Patient Factors

Careful selection of patients

- Will avoid unnecessary toxicity in poor performance status or medical comorbidity

  Understanding the evidence supporting radiation therapy

- Will allow the multidisciplinary team and the patient to proceed with radiation or to exclude it where it is limited benefit.

14.13.4.2 Treatment Factors

A clear conception of the target volume and accurate delineation of that volume (both at clinical markup and in the treatment planning system)

- May or may not reduce the toxicity of the treatment but is critical because it will improve the therapeutic ratio by ensuring that at risk sites are adequately treated

  Appropriate selection of radiation modality

- Will limit irradiation of deeper structures where the target is superficial; will limit the effects of tissue inhomogeneity and contour irregularity
- Will allow for more conformal treatment of complex volumes, where there are adjacent organs risk

Appropriate use of shielding and bolus

- Bolus to air gaps will minimize lateral electronic disequilibrium and improve target coverage and will improve the therapeutic ratio
- Surface build-up of the correct thickness will treat skin where this is desired and improve the therapeutic ratio
- Appropriate placement and thickness of coated lead shielding (e.g. oral/buccal, external eye, internal eye, nasal vestibule) will limit dose to adjacent organs at risk in superficial X-ray and low energy electron treatment

Accurate delineation of organs at risk

- Is critical where steep dose gradients are needed to achieve OAR dose limits and adequate PTV coverage

Careful attention to plan review

- Appropriateness of radiation technique, adequacy of target coverage according to relevant ICRU guidelines; optimization of OAR radiation dose/volume parameters (i.e. is this the best plan that can be achieved?), avoidance of hotspots adjacent to organs at risk (even within the PTV e.g. adjacent to brachial plexus) and minimization of low-dose wash to sensitive structures, e.g. brain, breast, lung and gonadal tissue

Regular treatment review

- Will allow for timely symptomatic treatment of expected acute treatment toxicities
- Will allow for treatment to be paused or stopped, if early radiation toxicity is excessive

14.14 Summary for Role of RT in Melanoma

We are witnessing a period of rapid change in melanoma treatment, which has been largely driven by new systemic therapies that have improved survival in the palliative treatment of stage IV disease and the adjuvant treatment of stage III disease. At the same time, high-level prospective randomized evidence has demonstrated the absence of survival benefit associated with locoregional therapies for stage III disease, such as adjuvant irradiation of a dissected lymphatic basin and completion lymphatic dissection for a positive sentinel lymph node. Although one might infer from these results that continued improvements in systemic therapy are destined to replace local therapies entirely, two observations stand in opposition to this notion. Firstly, radiation therapy avoids the not-insubstantial systemic toxicities associated with immune and targeted therapies and thus may still be preferred in certain select

situations, such as in the adjuvant treatment of high-risk primary melanoma of the head and neck, as a definitive treatment for unresectable lentigo maligna and as a palliative treatment for symptomatic metastases refractory to systemic therapy. Secondly, the emergence of stereotactic radiation therapy as a well-tolerated ablative alternative to metastasectomy may allow for novel and potentially synergistic combinations of radiation therapy and systemic therapies. Future efforts to improve tumour control and extend patient survival in this recalcitrant disease will require the judicious combination of radiation therapy with surgery and systemic agents.

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Merkel Cell Carcinoma

15

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15.1 Introduction

Merkel cell carcinoma (MCC) is a rare, cutaneous malignancy of neuroendocrine origin first described in 1972 as "trabecular carcinoma" of the skin [1]. MCC is an aggressive primary skin cancer with metastatic potential, and its incidence and mortality are increasing worldwide in the last few decades [2–4]. Higher rates of MCC are seen in Australia and New Zealand [5, 6]. Population-based studies show its incidence in 2013 to be estimated at 0.7 cases per 100,000 person-years in the USA, which corresponds to approximately 2500 cases. Overall incidence in the last few decades has risen exponentially with increasing age, UV exposure, immune-senescence and when considering the overall aging population in the USA and projected census data, the incidence is predicted to be approximately 3300 cases in 2025 [4]. Despite its rarity, MCC is associated with a disease-specific mortality three times that of malignant melanoma (46% vs 15%, respectively) [7, 8]. MCC also has a poor prognosis with 5-year overall survival (OS) rates ranging between 23 and 80% [3, 7, 9, 10].

The cell of origin in MCC is controversial. It historically has been believed that MCC arises from cells in the basal layer of the epidermis named Merkel cells [11].

The recent discovery of Merkel cell polyomavirus (MCPyV) and its association with approximately 80% of MCCs in the USA strongly suggests a viral etiology [12, 13]. Interestingly, only about 25% of MCC in Australia has been attributed to MCPyV [12]. It has been postulated that MCPyV-positive (VP-) and MCPyV-negative (VN-) MCCs may arise from two different cells of origin, dermal fibroblasts and epidermal keratinocytes, respectively [14, 15]. Studies involving exome sequencing analyses show that MCPyV-positive and MCPyV-negative MCCs show distinct genomic signatures [16].

15.1.1 Clinical Presentation

MCC tumors are frequently misdiagnosed and often confused with cysts, lipomas, or other benign processes. MCCs appear as benign red or violaceous, spherical, firm, and rubbery nodules with a smooth surface that are typically painless [17]. The five common clinical features typical of MCC are represented by the acronym "AEIOU": asymptomatic/lack of tenderness, expanding rapidly in less than 3 months, immunosuppression, older than 50 years, and on UV-exposed skin [17]. Approximately 90% of patients will have three or more of the aforementioned features [17]. MCC is typically located in areas most exposed to the sun and is most predominant in the head and neck region (43%), followed by the upper limbs and shoulders (24%), lower limbs (15%), and trunk 11% [18]. VP-MCC may be more likely to be involved in sun-protected areas. Despite its benign appearance, MCC is highly aggressive and has the propensity for in-transit cutaneous metastases (found between the primary tumor and regional nodal basin) via intradermal lymphatic vessels [19, 20]. Additionally, MCC can metastasize early, both locoregionally and distantly. At presentation, localized disease represents 65% of cases, regional disease 26%, and distant metastatic disease 8.4% [18].

15.1.2 Risk Factors and Pathogenesis

Risk factors associated with MCC include ultraviolet (UV) exposure in persons of fair skin, age, immunosuppression, and MCPyV infection and clonal integration into the genome. Large database studies using the Surveillance, Epidemiology, and End Results (SEER) and the National Cancer Database (NCDB) have shown that incidence of MCC was highest in Caucasian men and the most common anatomic location affected is the head and neck region (43%) [4, 7, 18].

Large population studies also have shown a link between immunosuppression and MCC. It has been observed that MCC has a higher incidence in the severely immunosuppressed [17]. In HIV patients, the relative risk for developing MCC is 13.4-fold higher in comparison to the general population [21]. After solid organ transplantation, the overall risk of MCC increases by 23.8-fold [22]. Furthermore, after diagnoses of multiple myeloma, chronic lymphocytic leukemia, and non-Hodgkin lymphoma, a three- to sevenfold increase in MCC has been observed [23]. The mechanism by which immunosuppression yields higher rates of MCC is currently an active area of research.

Infection with the ubiquitous MCPyV, discovered in 2008 by Feng et al., is another known risk factor contributing to the pathogenesis of MCC. MCPyV can integrate its viral DNA into the tumor genome and result in oncogenic gene expression [13, 24]. Through whole genome sequencing, it is evident that MCPyV may be able to control cellular processes and produce a tumorigenic phenotype and perhaps inhibit tumor suppressors [25]. A meta-analysis of 23 studies found a cumulative prevalence of MCPyV in 79% of MCC tumors in comparison to 12% in control skin samples [26]. Additionally, tumor burden in MCC seems to be correlated with antibodies against MCPyV oncoproteins, and this may be prognostic [27]. MCPyV DNA-positive tumors are associated with better overall survival, less regional nodal metastases, and are more typically located on the limbs [28].

In terms of prognosis, both initial tumor size and clinical nodal disease predict for worse outcomes [29]. Other negative prognostic factors include lymphovascular invasion (LVI) and p63 expression [30, 31]. Conversely, the presence of tumor infiltrating lymphocytes (TIL) is associated with a more favorable prognosis and improved disease-specific survival (DSS) [32].

15.1.3 Staging

The current American Joint Committee on Cancer (AJCC) eighth edition TNM classification is based on a National Cancer Database (NCDB) analysis of MCC patients diagnosed between 1998 and 2012. In this study, prognostic differences due to clinical and pathologic staging were evaluated, and survival estimates were compared by the extent of disease. The 5-year OS estimate for local disease was 51%, 35% for nodal disease involvement, and 13.5% when distant disease was present [18]. The most recent clinical and pathologic staging representing the AJCC eighth edition are delineated as follows in Table 15.1 [33]:

Table 15.1 Clinical and pathologic staging of MCC (AJCC 8th edition)

T		Clinical nodal		Pathologic nodal	
T1	≤2 cm	**cN1**	Regional nodes	**pN1**	
T2	2–5 cm			pN1a	Clinically occult nodes
T3	>5 cm			pN1b	Clinical apparent nodes
T4	Bone, muscle, cartilage, fascia	**cN2**	In-transit mets, − nodes	**pN2**	In-transit mets, − nodes
M1a	Mets to skin, distant nodes	**cN3**	In-transit mets + nodes	**pN3**	In-transit mets + nodes
M1b	Mets to lung				
M1c	Other				
MCC clinical stage groups					
	T1	**T2**	**T3**	**T4**	
cN0	I	IIA		IIB	
cN1–3	III				
M1	IV				
MCC pathologic stage groups					
	T1	**T2**	**T3**	**T4**	
pN0	I	IIA		IIB	
pN1a	IIIA				
pN1b-N3	IIIB				
M1	IV				

15.2 Management Principles

15.2.1 Initial Diagnosis

Initial diagnosis of MCC is generally made by histologic examination of a biopsy of a new cutaneous nodule that shows high-grade neuroendocrine carcinoma cells in the dermis or hypodermis. The differential diagnosis includes other small round blue cell tumors or blastic lymphomas. Immunohistochemistry (IHC) reveals expression of epithelial markers (pancytokeratin AE1/AE3) as well as neuroendocrine markers (chromogranin A, synaptophysin, CD56, and insulinoma-associated 1 (INSMI)). Expression of cytokeratin 20 (CK20) (with a characteristic perinuclear dot-like pattern) and concurrently negative for thyroid transcription factor-1 (TTF-1) distinguishes MCC from metastatic small cell tumors [15].

Once an initial diagnosis is made, if feasible, the quantitation of MCPyV oncoprotein antibodies via a clinically validated assay (AMERK; now listed on NCCN guidelines) may be considered, given their possible prognostic value [20]. Patients should also undergo full clinical nodal evaluation by a physician. Imaging including CT of the chest, abdomen, and pelvis, positron emission tomography (PET) scan, or magnetic resonance imaging (MRI) may be useful in determining regional disease or metastases.

15.2.2 Treatment

Despite the poor prognosis, the rarity of MCC has hindered conducting prospective, randomized trials to better guide treatment. Nonetheless, the mainstay of treatment for early-stage MCC is surgery. If nodes are clinically negative, treatment includes a wide excision with 1–2 cm margins with a sentinel lymph node biopsy (SLNB) for determination of clinically occult regional disease [9]. Following surgery, PORT is typically recommended to optimize local control. Surgical margins may be less relevant if postoperative radiation therapy (PORT) is being considered. Some academic centers also acknowledge primary RT as a valid option for definitive therapy of MCC.

SLNB can detect occult nodal disease in up to one-third of patients [29, 34, 35]. Even in small primary tumors (<0.5 cm), there is a 14% risk or regional nodal involvement; thus, pathologic nodal evaluation with a SLNB should be considered even for small primary tumors, and SLNB remains part of the treatment paradigm in early-stage MCC [20, 36, 37]. The false-negative rate for a SLNB can be high (17%), and thus, a negative SLNB should not definitively exclude adjuvant therapy, especially in the setting of higher-risk features of the primary site [34].

For clinically node-positive MCC, the diagnosis should be made using fine needle aspiration (FNA) or core biopsy. If positive, and overt metastatic disease is ruled out by imaging, treatment options include nodal dissection (limited or full) and/or RT to the regional nodal basin [20].

For all MCC patients, a multidisciplinary consultation and enrollment in clinical trials is of utmost importance when feasible and available. Adjuvant treatment will be further addressed in more detail in the subsequent sections.

15.2.3 Current Role of Adjuvant Therapy in MCC

15.2.3.1 Radiation Therapy

MCC is known to be a radiosensitive disease, much like other small round blue cell tumors, and PORT is typically recommended in order to prevent locoregional recurrence (LRR) and for improved DSS [38–40]. Radiotherapy may also be used as definitive therapy for patients that are not adequate surgical candidates [20]. Much of the evidence for radiation in MCC is derived from retrospective analyses. Due to disease rarity, there is a lack of randomized controlled trials in this setting, and selection biases can obscure study conclusions.

Overall, the evidence suggests that PORT likely provides a local regional control (LRC) benefit in the setting of MCC and, though the data is conflicting, it may also provide an OS and DSS benefit as well. A French prospective clinical trial randomized stage I MCC patients to receive either wide local excision alone or wide local excision in combination with adjuvant regional radiation to 50 Gy. This trial closed early due to lack of accrual; however, it showed that patients treated with adjuvant radiation had lower regional recurrence risk (17% vs 0%) but there was no survival advantage to radiation [41]. Retrospective studies show that adjuvant radiation

yields better outcomes. One single-institution study evaluated 171 patients with MCC and showed that RT was associated with improved LRC, DSS, and OS [42]. Additionally, a large NCDB study of 6908 MCC patients showed that surgery followed by adjuvant RT for localized disease had a significant OS advantage (stage I, HR 0.71; $P < 0.001$; stage II, HR 0.77; $P < 0.001$). However, in patients with regional nodal disease, neither adjuvant RT nor adjuvant chemotherapy conferred the same survival benefit [43]. Furthermore, in a meta-analysis evaluating surgery alone and surgery in combination with adjuvant RT, statistically significant reductions in local (HR 0.27; $p < 0.001$) and regional recurrence (HR 0.34; $p < 0.001$) were observed in patients treated with surgery followed by RT. In this study, however, no significant OS or cause-specific survival associated with adjuvant radiation was observed [44]. In another SEER analysis in 2013, in which 747 patients treated between 1998 and 2006 were included, adjuvant radiation was shown to improve OS in patients with MCC. However, the data did not show improvement in DSS, suggesting that the benefit in OS may not have been due to radiation alone and may have been the result of selection bias or other unknown factors [45].

Despite the general acceptance that adjuvant radiation is beneficial, it is of note that in one single-institution study of 251 patients with stage I through IV MCC, no benefit in local control with the routine use of either definitive or adjuvant radiotherapy was found [9]. However, in this study, it is worth noting that the primary tumors were small (median of 1.5 cm), tumors were mostly in non-head and neck locations, and the details of radiation and dosage are not provided [9]. A subsequent SEER study with 1665 patients showed that adjuvant radiation was associated with better overall survival for all sized tumors but particularly for those greater than 2 cm [10]. Nonetheless, adjuvant radiation after wide local excision is typically recommended unless tumors are small (<1 cm), and there are no additional pathologic risk factors (LVI, immunosuppression), at which point close observation may be reasonable in non-head and neck locations [20]. For primaries located in the head and neck region, a single-institution retrospective study described a local failure rate of 26% with surgery alone in highly selected non-immunosuppressed patients with favorable stage I tumors of <2 cm resected with negative margins and a negative SLNB. Addition of PORT was associated with a reduced risk of local recurrence (26% vs 0%) [46]. Thus, in the head and neck locations, PORT is generally indicated.

15.2.3.2 Adjuvant Systemic Therapy

Presently, no randomized controlled trials have been performed to evaluate the benefit of adjuvant systemic therapy in patients with MCC. The role of chemotherapy in this setting is controversial. In most analyses, adjuvant chemotherapy fails to show an improvement in OS, and it is associated with increased morbidity and decreased quality of life and, therefore, generally not recommended as first-line treatment by guidelines [9, 47–49]. Furthermore, treatment with chemotherapy may affect response rates to subsequent immunotherapy should a patient recur or have metastatic disease. Data from the phase II prospective JAVELIN Merkel 200 trial showed that the response rate of patients to immunotherapy (avelumab) who had previously received chemotherapy was 28% in

comparison to a response rate of 62% in those that had not received prior systemic therapy [50, 51].

Given the outstanding success of systemic immunotherapy in metastatic MCC (discussed below), several adjuvant trials are underway in the USA in patients with high risk of MCC recurrence. These include the phase III ADAM trial for highest-risk MCC (patients with clinically detected lymph node metastases; avelumab vs placebo; NCT03271372) and the phase III STAMP trial for stages I–III MCC (pembrolizumab vs observation; NCT03712605) (clinicaltrials.gov).

Cancer immunotherapy for MCC is a topic of wide interest and has been proven to be effective in the metastatic setting (discussed in section Metastatic Disease). In the adjuvant setting, however, current ongoing prospective clinical trials will further investigate adjuvant immunotherapy with checkpoint inhibitors, including a phase II trial using nivolumab (human monoclonal antibody against protein programmed death receptor 1 (PD-1)) (NCT02196961), a phase II trial using avelumab (human monoclonal antibody against the protein programmed death-ligand 1 (PD-L1)) (NCT03271372), and a phase I trial examining adjuvant nivolumab with radiation in comparison to ipilimumab alone (monoclonal antibody that targets cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)) (NCT03798639) (clinicaltrials.gov).

15.2.3.3 Metastatic Disease

MCC is considered a chemosensitive malignancy. Cytotoxic chemotherapy (with platinum-etoposide and other regimens) is associated with high initial response rates, although responses are not durable and chemoresistance develops early [37]. Hence, chemotherapy has been replaced as the standard-of-care therapy for metastatic MCC by immunotherapy agents including avelumab and pembrolizumab, which are now FDA approved and regarded as the recommended first-line treatment in the metastatic setting [20].

Pembrolizumab treatment has shown evidence of a benefit in patients with recurrent or metastatic MCC. In a multicenter phase II prospective trial, pembrolizumab was shown to have an objective response rate of 56% in this setting, with responses seen in both VP-MCC and VN-MCC patients [52]. In longer follow-up, these response rates have remained stable, and tumor control with pembrolizumab monotherapy has been durable [53]. This has led to FDA approval of pembrolizumab for treatment of advanced MCC in 2018.

The US Food and Drug Administration (FDA) has also approved avelumab in March 2017 for treatment of metastatic MCC based on the results of the phase II JAVELIN Merkel 200 trial, part A. This trial showed that, in patients that had prior chemotherapy treatment, treatment with avelumab in 88 patients revealed a progression free survival (PFS) and an OS of 26% and 62%, respectively [50]. Results from part B of the trial, in a preplanned analysis of 29 patients who had not received prior treatment, show that avelumab administration is associated with a 62% objective response rate and is well tolerated [51].

Despite the outstanding success of immunotherapy in a significant proportion of patients with metastatic MCC, many patients do not respond (primary resistance) or progress after initial benefit (acquired response). Future approaches include further

studies on how to best exploit the immunogenicity of MCC tumors for ameliorated treatment approaches. Many trials are currently underway, and they include novel drug targets, vaccines, neoadjuvant, and adjuvant approaches [54].

15.2.3.4 Role of Radiation

Radiation may be used in the metastatic setting for symptom palliation and local control. Palliative dose of either 30 Gy in 10 fractions or 8 Gy in 1 fraction can be considered. In one study, single-fraction radiation therapy (SFRT) of 8 Gy in 1 fraction showed excellent palliation and was associated with a 94% response rate. Local control at a median follow-up time of 9 months was 77% [55]. Importantly, SFRT has minimal toxicity, is cost-effective, and may be practically convenient for patents. Therefore, when clinically appropriate, SFRT may be considered for palliation.

In addition to its use for palliation, RT is also being investigated for synergy with immunotherapy to overcome resistance to the latter. With RT, there is exposure of more antigens due to cell death, and this may lead to immune activation. A current phase II trial is evaluating the response rate of using nivolumab and ipilimumab with or without the addition of stereotactic body radiation therapy (SBRT) in patients with recurrent and metastatic disease (NCT03071406, clinicaltrials.gov). Interestingly, intratumoral G100, a TLR4 agonist, was found to induce an antitumor immune response in both the locoregional (3 patients) as well as the metastatic setting (7 patients). In the metastatic setting, there was a durable response in two of seven patients, and this holds promising for possible future clinical trials [56]. Additionally, a case report where two patients with progressive MCC were treated successfully with high linear energy transfer neutron radiation therapy (NRT) shows potential promise in conjunction with immunotherapy as options in the refractory setting [57]. More work will need to be done with heavy particles as we continue to learn about this aggressive disease.

15.3 Radiation Therapy Techniques and Planning

Radiation therapy treatment for MCC can be technically challenging, given the heterogeneity in disease location and presentation. The head and neck anatomic location is common in MCC, and this site is particularly challenging to treat and may be associated with worse outcomes [58]. In head and neck MCC, it may be difficult to incorporate the necessary margins for adequate microscopic coverage and also include all regional disease. Also, a SLNB in the head and neck is controversial due to variable lymphatic drainage in this anatomic region. However, radiation therapy, especially in the head and neck, is indicated and seems to result in good local control both in the adjuvant or definitive setting [46, 59].

As summarized previously, adjuvant radiation is typically indicated unless a primary tumor is <1 cm and has low-risk factors including a non-head and neck location. Other indications for radiation include a positive or close margin, LVI, lymph node involvement, head and neck location, and immunocompromise [20]. Also,

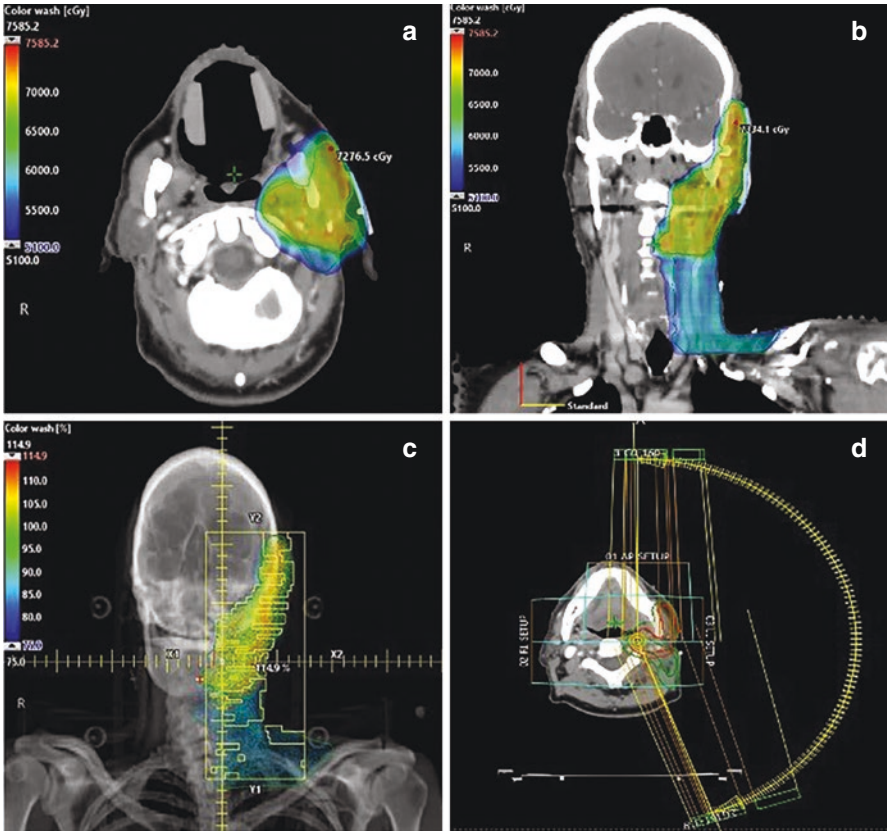

Fig. 15.1 A pT2N1M0 stage IIIB MCC patient treated in the adjuvant setting with RT to a dose of 60 Gy to the primary and node positive region, 54 Gy to the lower neck/next LN draining echelon. (**a**) Axial with view of mouthpiece/stent. (**b**) Coronal view. (**c**) Treatment field. (**d**) Axial view showing arc length and design. Patient treated with volumetric arc therapy

given the ability of MCC to affect all parts of the body, dose tolerances to organs at risk should be followed closely and be based on literature established values for each subsite of treatment. Because MCC is a biologically aggressive disease, adjuvant RT should be expedited as is technically and clinically feasible. Figure 15.1 provides an example of adjuvant radiation treatment to the head and neck of a patient with MCC after surgical resection.

15.3.1 Radiation Technical Considerations

Because there is wide variability of anatomic sites that can be affected, radiation with either electrons or photons is recommended. Photon radiation therapy can include either three-dimensional conformal radiation therapy (3D-CRT), volumetric modified arc therapy (VMAT), or image modulated radiation therapy (IMRT). Below are recommendations for technical considerations:

- Treatment setup and reproducibility are of utmost importance; input from medical dosimetry and medical physics is vital.
- Electrons:
  - En face electron treatment.
  - Energy 6–9 MeV to ensure enough dose to deep margin.
  - Prescribed to 90% isodose.
  - Near nose: pack nose with wet gauze or bolus material, external lead shielding to minimize scatter outside the RT field.
  - Near eye: consider internal shielding to protect the cornea and lens with ceramic-coated lead lens cup during treatment and anesthetic drops and eye lubrication for daily placement.
- Use bolus over treatment area to ensure adequate skin dose.
- In the adjuvant setting, wire surgical scar to help with primary tumor target delineation.
- Head and neck treatment:
  - Immobilization with head and neck Aquaplast mask.
  - Consider usage of mouthpiece or stent for tongue deviation to decrease toxicity.
- Use IMRT or VMAT to cover regional nodes, especially in the head and neck.
- Upper or lower limbs: ensure proper treatment immobilization for reproducibility.

15.3.2 Target Delineation

Current guidelines recommend adjuvant radiation to the postsurgical bed, any in-transit metastases, and regional draining lymph nodes. A 5 cm margin around the surgical bed or the primary tumor is recommended, when anatomically attainable [20]. Head and neck margins, particularly around the eyes, will undoubtedly be less due to anatomic constraints and depend on individual clinical scenario. Table 15.2 outlines currently accepted recommendations for target delineation.

15.3.3 Dose Treatment Recommendations

In terms of RT dosing, there is little evidence for precise dosing recommendations in MCC; however, current guideline recommendations to both the primary tumor and regional nodes are summarized in Table 15.3 and are based upon tumor burden [20].

Table 15.2 MCC radiation target delineation guidelines

Target	Definition
GTV	Gross disease
CTV	
Primary	GTV or scar +3–5 cm (anatomy permitting)
Regional nodes/in-transit mets	Per individual clinical context
PTV	Per institutional standards

Table 15.3 MCC radiation dose recommendations

Primary tumor	Dose (2 Gy fractions)
Definitive radiation alone	60–66 Gy
Adjuvant radiation	
Surgical margins negative	50–56 Gy
Surgical margins microscopically positive	56–60 Gy
Surgical margins grossly positive	60–66 Gy
Metastatic disease, palliation	30 Gy in 10 fx, SFRT (8 Gy in 1 fx)
Regional lymph nodes	**Dose (2 Gy fractions)**
SLNB negative	Observation (or RT if high risk)
SLNB positive	50–56 Gy
No SLNB or pathologic node evaluation	
cN0, but high risk	46–50 Gy
cN+	60–66 Gy
Lymph node dissection with multiple nodes, or ECE[a]	50–60 Gy

[a]ECE: extracapsular extension

15.4 Summary

- Merkel cell carcinoma is a rare cutaneous malignancy of neuroendocrine origin.
- It typically occurs in elderly patients in areas of the body with frequent sun exposure, most commonly in the head and neck region.
- MCC is also associated with higher incidence rates in immunocompromised patients.
- There is a strong association of MCC with the Merkel cell polyomavirus (MCPyV).
- Primary treatment for MCC is wide local excision with margins of 1–2 cm and SLNB.
- Adjuvant radiation is typically recommended; unless the tumor is small with adequate margins and low-risk factors, then observation may be considered.
- Radiation dosing recommendations are based on disease burden and extent of resection.
- Radiation therapy treatment setup and technical considerations can be challenging, given the wide range of possible anatomic areas affected by MCC.
- Immunotherapy is the first-line treatment in metastatic disease. A less protracted radiation regimen or SFRT may also be considered for palliation.

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Treatment of Cutaneous Lymphomas: Topical, Systemic, and Radiation Therapies

16

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16.1 Introduction

Cutaneous lymphomas are a highly heterogeneous group of non-Hodgkin's lymphomas (NHL) derived from either B or T lymphocytes and are defined by their predominant involvement of the skin. There is a higher frequency of cutaneous T-cell lymphomas (CTCL) (~75%) compared to cutaneous B-cell lymphomas (CBCL) (~25%) [1]. They can be further classified into several specific subtypes based on the European Organization for Research and Treatment of Cancer-World Health Organization (EORTC-WHO) classification and may have vastly different disease presentations, clinical courses, and treatment approaches (Table 16.1) [1, 2].

The most common cutaneous lymphoma is mycosis fungoides (MF), which accounts for 50% of all cutaneous lymphomas with an incidence of around 1/100,000 persons/year [1]. There is a male:female predominance of 2:1 with a median age of 57 years. The diagnosis of MF can be delayed for long period of time, sometimes even on the order of several years, with a waxing and waning course of rashes clinically consistent with eczema or psoriasis before a more definitive diagnosis is made. Patients normally present with patches or plaques, but tumor-stage disease or more diffuse involvement of the entire skin surface by erythema and scale (i.e., erythroderma) may be present at diagnosis.

Table 16.1 Cutaneous lymphoma classification

Cutaneous T-cell lymphomas
Mycosis fungoides (MF)
– Folliculotropic MF
– Pagetoid reticulosis
– Granulomatous slack skin
Sezary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous CD30+ lymphoproliferative disorders
– Primary cutaneous anaplastic large cell lymphoma
– Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Chronic active EBV infection
Cutaneous γ/δ T-cell lymphoma
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
Primary cutaneous acral CD8+ T-cell lymphoma (provisional)
Primary cutaneous CD4+ small−/medium-sized pleomorphic T-cell lymphoproliferative disorder (provisional)
Primary cutaneous peripheral T-cell lymphoma, NOS
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicular center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
EBV+ mucocutaneous ulcer (provisional)

Skin biopsy in early-stage lesions may not be diagnostic; in established lesions there are small- to medium-sized atypical cells with indented nuclei present within the epidermis (epidermotropism) and aligning the dermal-epidermal junction. Intraepidermal lymphocytes can become much more pronounced in plaque-stage disease and form aggregates (Pautrier's microabscesses). In tumor-stage disease, neoplastic lymphocytes may evolve into a more dermal distribution with loss of epidermotropism. There are three distinct variants of MF recognized by the EORTC-WHO based on pathologic and clinical features: pagetoid reticulosis, granulomatous slack skin, and folliculotropic MF. Folliculotropic MF is characterized by a predominance of T lymphocytes involving the pilosebaceous unit. Clinically, patients will have a higher involvement of the head and neck area with associated alopecia. The folliculotropic nature of the disease results in a lower efficacy of skin-directed therapy and the need for deeper targeting therapies, as discussed further below.

Sezary syndrome (SS) is a distinct form of CTCL characterized by the presence of diffuse erythroderma, generalized lymphadenopathy, and blood involvement as defined by the peripheral blood presence of distinct malignant lymphocytes with cerebriform nuclei (Sezary cells) ≥ 1000/uL, an expanded CD4+ T-cell population with a CD4:CD8 ratio ≥10, or an expanded CD4+ T-cell population with loss of one or more T antigens.

All patients with a diagnosis of MF or SS should undergo careful staging with a comprehensive skin examination performed by a dermatologist with documentation of the extent of disease by percent body surface area involved, biopsy of any clinically enlarged lymph nodes (>1.5 cm) present on exam to distinguish between disease involvement versus dermatopathic change, and peripheral blood flow cytometry to assess for circulating lymphoma cells (Tables 16.2 and 16.3). Imaging assessment with CT or PET scans at baseline are not routinely recommended for patients with early-stage disease but should be considered for tumor or erythrodermic disease, unexplained symptoms, or laboratory abnormalities at the time of diagnosis.

The clinical course of MF is typically indolent. Patients with localized skin involvement can be managed with skin-directed treatments and can have a life expectancy comparable to age-matched persons without MF. However, 24% of patients with generalized patch−/plaque (T2)-stage disease progress to higher stages with the potential need for systemic treatments for disease control [3]. In addition, large cell disease transformation may occur, defined by the presence of >25% of large lymphocytes, and is associated with a poorer prognosis. In contrast to MF, SS is a more aggressive disease with a median overall survival of only 32 months [1].

Primary cutaneous CD30-positive lymphomas account for approximately 25% of all CTCLs and include primary cutaneous anaplastic large cell lymphoma (pcALCL) and lymphomatoid papulosis (LyP) [4]. Primary cutaneous ALCL is the second most common type of CTCL and normally affects the trunk, face, and extremities. It typically presents as a solitary lesion but can be multifocal in 20% of cases and disseminated in 10% of cases. LyP is characterized by the appearance of papulonodular or papulonecrotic skin lesions on the trunk and limbs. These lesions

Table 16.2 TNMB staging of MF/SS

Skin	T1	Limited patches, papules, and/or plaques covering <10% of the skin surface
	T2	Patches, papules, and/or plaques covering ≥10% of the skin surface
	T2a	Patch only
	T2b	Plaque +/− patch
	T3	One or more tumors (≥ cm in diameter)
	T4	Confluence of erythema ≥80% body surface area
Node	N0	No abnormal lymph nodes; biopsy not required
	N1	Enlarged lymph nodes with either no or occasional and isolated atypical lymphocytes
	N2	Aggregates of atypical lymphocytes but with preserved nodal architecture
	N3	Partial or complete effacement of lymph node architecture by atypical lymphocytes
	NX	Abnormal lymph nodes without histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement with histologic confirmation
	MX	Abnormal visceral site without histologic confirmation
Blood	B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes of <250 cells/μL are atypical (Sezary) cells or <15% CD4+/CD26− or CD4+/CD7− cells of total lymphocytes
	B1	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sezary) cells or >15% CD4+/CD26− or CD4+/CD7− cells of total lymphocytes but do not meet criteria of B0 or B2
	B2	High blood tumor burden: ≥1000/μL Sezary cells determined by cytopathology of ≥1000 CD4+/CD26− or CD4+/CD7− cells/μL or other abnormal subset of T lymphocytes by flow cytometry with clone in the blood same as that in the skin. Other criteria for documenting high blood tumor burden in CD4+ MF/SS include CD4+/CD7− cells ≥40% and CD4+/CD26− cells ≥30%

Table 16.3 Clinical staging of MF and SS

Clinical stage	T (skin)	N (node)	M (visceral)	B (blood)
IA	T1	N0	M0	B0–1
IB	T2	N0	M0	B0–1
IIA	T1–2	N1–2	M0	B0–1
IIB	T3	N0–2	M0	B0–1
IIIA	T4	N0–2	M0	B0
IIIB	T4	N0–2	M0	B1
IVA_1	T1–4	N0–2	M0	B2
IVA_2	T1–2	N3	M0	B0–2
IVB	T1–4	N0–3	M1	B0–2

typically heal spontaneously over the course of a couple of weeks to a few months but can have a persistently relapsing course. Although LyP itself is a benign condition with a nearly 100% disease-specific survival rate, there is an increased risk of development of other types of lymphoma, in particular MF, pcALCL, and Hodgkin's lymphoma, in up to 18–24% of cases [5, 6].

The primary cutaneous B-cell lymphomas (CBCL) can be classified into three subtypes: primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT), primary cutaneous follicular cell lymphoma (PCFCL), and primary cutaneous marginal zone lymphoma (PCMZL). As its name suggests, PCDLBCL, LT involves the lower extremities in 72% of cases, but dissemination outside this location is frequently seen [7]. It is a disease of the elderly with a median age of onset of 76 years and 5-year disease-specific survival of 41%. These clinical features are in far contrast to both PCFCL and PCMZL, which typically present with solitary or several nodules or plaques of the head or trunk. Prognosis can vary and is based on the cutaneous lymphoma international prognostic index (CLIPI) with elevated lactate dehydrogenase (LDH), >2 skin lesions, or nodular lesions serving as negative prognostic signs. In the absence of these, 5-year progression-free survival (PFS) is 91%, while if 2 or 3 are present, the 5-year PFS decreases to 48%.

Consensus guidelines have been previously published on the management of cutaneous B-cell lymphomas by the EORTC Cutaneous Lymphoma Group [8]. For localized disease, excision or localized radiation to the involved site may result in cure [9].

16.2 Management Approaches

16.2.1 Primary Cutaneous B-Cell Lymphomas

16.2.1.1 Radiotherapy

Involved-site radiation therapy (ISRT) is recommended as the appropriate field for targeting solitary or regional primary cutaneous B-cell lymphoma [9]. Since the involved skin is the target, the volume would be the clinically evident disease (palpable or visible) with adequate margins. If there is questionable subclinical disease or questions on depth of involvement, imaging studies such as CT should be used to determine the depth of involvement.

PCMZL and PCFCL: Optimal dose for solitary or regional disease will be 24–30 Gy as recommended by the International Lymphoma Radiation Oncology Group (ILROG) as well as NCCN [9, 10], but doses can range from 20 to 45 Gy in literature [11, 12]. Surface margin of 1.0–2.0 cm is recommended by ILROG and NCCN [9]. Margins in depth should include any subclinical at risk areas. This margin is theoretically the same as the surface margin, but it should be adjusted based on the location of the lesion as well as the anatomic boundary of the subcutaneous tissue. Typically, treatment with 6–9 MeV electron with appropriate surface bolus provides an adequate depth of treatment for a superficial lesion. Sometimes photon beam treatment is needed when lesions are large, extensive, and/or with irregular surfaces.

Low-dose treatment (4 Gy in 1–2 fractions) is a reasonable dose regimen in the palliative setting. Recent data suggested that this dose may achieve a complete remission rate as high as 72%, with 30% of lesions requiring re-treatment within a median period of 6.3 months [12].

PCDLBCL, LT: Given its more aggressive course similar to systemic DLBCL, combination chemotherapy is typically required. In most cases, disease is localized to the skin of the legs and can be treated similar to limited stage systemic DLBCL with three cycles of R-CHOP followed by involved-site radiation therapy (ISRT). For patients who cannot tolerate combination chemotherapy, either radiation to the sites of disease or single-agent rituximab is an option.

ISRT of 30–40 Gy is recommended based on ILROG and NCCN guidelines [9, 10]. Setup and margin consideration are similar to PCMZL and PCFCL described above, but pre-chemotherapy disease volume should be used for planning.

Relapsed Disease: Local recurrence after 24–30 Gy (PCMZL or PCFCL) or 30–40 Gy (PCDLBCL, LT) treatment is rare. Local recurrence is more commonly seen after a palliative dose of 4 Gy, in which case the same dose (4 Gy) can be repeated or a definitive course of RT can be delivered. Recurrences near the margin of the original disease may occur, and re-treatment of recurrent lesion with ISRT to the same definitive dose will be acceptable. Biopsy is recommended as the new lesion could represent a different histology.

16.2.1.2 Other Therapies

Local cutaneous BCL has been shown to have high response rates to local intralesional therapies, which can lead to long-term disease clearance. Intralesional interferon-α has been used successfully in both PCFL (primary cutaneous follicular center lymphoma) and PCMZL with CR rates at 100%, with only 28% (PCFL) and 25% (PCMZL) of patients relapsing locally and no extracutaneous relapses seen in either case [13, 14]. Intralesional rituximab has also been shown to have significant activity, with CR rates of 83% in PCFL and 89% in PCMZL [15, 16]. However, in both diseases, nearly half of patients eventually relapsed, some at a cutaneous site different from the treated site.

Patients with multifocal PCFCL and PCMZL in the absence of symptoms may be observed until lesions become symptomatic. For symptomatic multifocal disease, single-agent IV rituximab (375 mg/m^2 weekly for 4–8 weeks) has been shown to have CR rates of 75% (n = 28) and 67% (n = 3) in PCFCL and PCMZL, with relapse rates of 50% and 19% in responding patients, respectively, will all relapses confined to the skin [8]. Similarly, in a retrospective study of 75 patients with PCBCL of different histologies treated with four cycles of IV rituximab, an ORR of 97% and a CRR of 83% were seen with a 5-year DFS of 57% [17]. For patients with limited disease control with rituximab, chemoimmunotherapy incorporating bendamustine (BR) or anthracycline-based regimens (R-CHOP) is reasonable.

16.2.2 Cutaneous T-Cell Lymphoma (CTCL) Including Primary Cutaneous CD30-Positive Lymphomas (Such as pcALCL and LyP) and Mycosis Fungoides (MF)

In general, topical therapies serve an important role in patients with early-stage disease (i.e., stage IA, IB, and IIA) for local disease control and palliation of symptoms. Notably, the majority of patients with early-stage disease can be controlled

with skin-directed therapies alone without the need for systemic agents [18]. In addition, in the uncommon event that a patient presents with localized, unilesional CTCL, radiation can be curative. However, if disease progression or presentation with advanced-stage disease occurs, managing disease with localized therapy may be impractical due to the extent of disease involvement, and more broadly acting treatments, such as total skin electron beam therapy (TSEBT) or systemic modalities may be required. Topical therapies are frequently continued as adjunctive treatments when systemic treatments are initiated if they help improve overall disease control or offer symptom palliation.

16.2.2.1 Radiation Therapy (RT)

pcALCL and LyP: Solitary or grouped lesions (most commonly presented) can be treated with ISRT alone or surgery +/− ISRT [10]. For curative intent, the recommended dose will be 24–36 Gy in 2 Gy fractions. Field setup and margin consideration are similar to above described in cutaneous B-cell lymphoma. For palliation, 2 Gy × 2 is recommended.

16.2.2.2 Mycosis Fungoides

For patients with disease limited to patches and plaques without any extracutaneous involvement, skin-directed therapy (topical therapy, phototherapy, or RT) is generally preferred over systemic therapy. Comprehensive total skin electron beam therapy (TSEBT) may be used to treat diseases with extensive but superficial involvement.

Local Palliation: Ultralow dose (2 Gy × 2 or 4 Gy × 1) is typically insufficient to achieve a desirable response with a complete response (CR) rate <30%, and higher doses (8–12 Gy in 1 fraction, or 4 Gy × 2–3) are recommended. This higher palliative dose may render a CR rate of >90% [9, 19]. Radiation field should include the lesion(s) of interest plus 1.0–2.0 cm margin.

Unilesional Treatment: A fractionated course of RT 24–30 Gy [9, 10] is recommended for this condition. Local recurrence is rare when dose is >24 Gy [19, 20]. A fractionated approach should be considered based on condition of skin, prior RT to the site and if future re-treatment, including TSEBT would be considered in the future. Radiation field should include the lesion(s) of interest plus 1.0–2.0 cm margin.

TSEBT: Doses used for TSEBT have been transitioned from the past standard of 36 Gy, which is known to render a higher CR rate [21] to the current dose of 10–12 Gy [22]. This is because relapse after the standard 36 Gy was still common even after CR. Lower TSEBT doses have the benefit of shorter duration of treatment, more tolerable and reversible radiation toxicities, and the opportunity for re-treatment if needed [22].

TSEBT is a complex treatment and requires strong dosimetry and physics support. Various techniques have been developed to allow total skin coverage [23]. The most commonly used technique (developed at Stanford) utilizes a 6-field large electron field approach, where the body is facing different angles offset by 60 degrees from each other. This technique requires the patient to be treated standing, assuming multiple different positions to expose maximal body skin surfaces (Fig. 16.1).

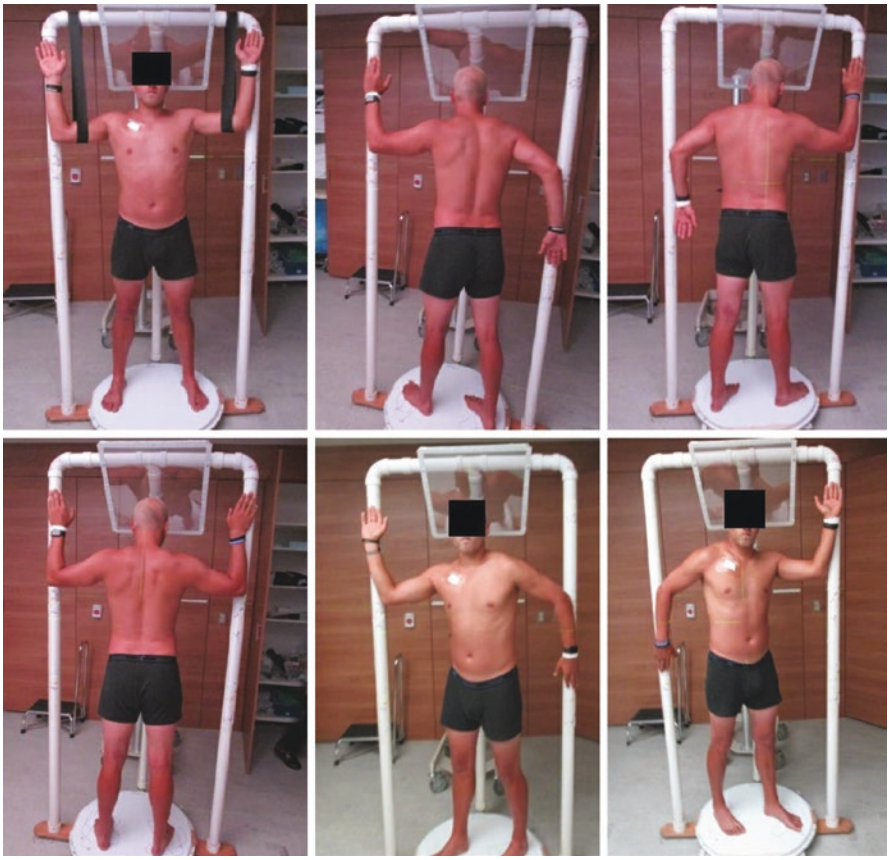

Fig. 16.1 Patient positions during total skin electron beam therapy (TSEBT) with the 6-field technique. The anterior, right posterior oblique, and left posterior oblique fields are treated on day 1 (top row). The posterior, right anterior oblique, and left anterior oblique fields are treated on day 2 (bottom row). The platform is custom designed for treating TSEBT patients

In addition, unexposed or partially exposed areas, especially if they are involved by mycosis fungoides, require supplemental treatment. This may include the top of the scalp, axillae, soles, perineum, as well as areas under the breasts or panniculus. Careful measurement of radiation doses at the skin surface with devices, such as optically stimulated luminescent detectors (OSLDs), at various potentially underdosed locations is critical during the first several treatments in order to ensure adequate dose delivered.

TSEBT is commonly prescribed at 100 cGy per day for better tolerance. For the sake of workflow, many facilities uses a 2-day cycle to deliver 200 cGy (6 fields) over 2 days at 200 cGy per fraction (i.e., treat 3 fields on day 1 and 3 fields on day 2). Techniques for degrading electron beams to make them suitable for total skin treatment are also variable. The goal is to achieve dose homogeneity in the coronal plane, a Dmax at the skin surface (where the dose is prescribed), and an 80% dose at 0.7–1.0 cm depth.

16.2.2.3 Topical Therapies

Topical steroids are the most widely used treatment for early-stage CTCL. They are highly active with overall response rates (ORR) of 94% and 82% and complete response rates (CRR) of 63% and 25% for T1 and T2 disease, respectively [24]. Detailed instructions on proper application techniques have been previously published [25]. Class I steroid creams or ointments, such as clobetasol, are initially preferred with twice daily application liberally to involved areas. If response is not seen within 3 months of regular application, an alternate therapy should be considered. Side effects include irritant dermatitis, purpura, skin atrophy, and striae. Adrenal suppression can be seen on laboratory evaluation, but actual clinical hypoadrenalism is rare.

Topical mechlorethamine is a nitrogen mustard (NM) that acts by alkylation of CTCL cells leading to apoptosis as well as stimulation of an anti-CTCL reaction by resident immune cells in the skin. ORR of 93% and 72% and CRR of 65% and 34% are seen in T1 and T2 disease, respectively [26], with 5-year freedom from progression (FFP) rates of 92% and 83%. Interestingly, most patients that achieve a CR with NM can achieve disease control with NM upon relapse and thus do not require other therapies. The most common side effect is irritant dermatitis with a higher rate with aqueous preparations than ointments, as well as a higher frequency when applied to intertriginous areas or the genitals. Allergic contact dermatitis can also occur. Interestingly, it was observed that contact hypersensitivity reactions were associated with a greater clinical response, presumably due to an increased Th1-mediated anti-CTCL response [27]. Systemic absorption of mechlorethamine does not occur. The risk of secondary malignancies with mechlorethamine is unclear as conflicting data has been reported.

Carmustine is another NM topical alkylating agent. ORR and CRR of 98% and 86% for T1 disease and 84% and 47% for T2 disease have been reported [28]. Long-term follow-up of 188 patients has shown that carmustine was able to control disease by itself in 91% of patients with T1 disease and 62% of patients with T2 disease [27]. Side effects include erythema (especially in the body folds), telangiectasia, and irritant and allergic dermatitis. Mild depression of white blood cell and hemoglobin counts can occur in small proportion of patients (5% in general body surface treatment). No increased risk for secondary skin malignancies has been reported.

A single-institution retrospective review of 148 patients from Stanford with either T2 or T3 MF who received TSEBT with or without a nitrogen mustard as adjunctive therapy has shown that treatment with adjuvant nitrogen mustard resulted in a longer freedom from relapse in patients with T2 disease compared to observation after TSEBT, although the result was not statistically significant ($p = 0.068$) [29].

Retinoids are vitamin A derivatives that bind to the retinoic acid receptor α (RARα) and/or RARX family of receptors leading to diverse transcription changes. This can result in direct antiproliferative and apoptosis in CTCL cells themselves or immune-mediated anti-CTCL responses. Bexarotene is a RXR agonist with a topical 1% gel formulation that has been FDA approved for the treatment of stage IA–IB CTCL. This is based on a phase III trial in which patients with disease refractory to prior topical treatments demonstrated an ORR of 44% and a CRR of 8% [30].

Local skin reactions at the application site were relatively high, with rash (56%), pruritus (18%), and contact dermatitis (8%) being the most frequent. A common practice is to alternate the use of bexarotene with topical steroids, thus reducing the local skin irritation of bexarotene and the skin atrophy effect of steroids for the most optimum skin side effect profile. Although bexarotene remains the only FDA-approved topical retinoid for CTCL, other topical retinoids have been used off-label, including tretinoin and tazarotene, with an overall similar side effect profile.

Imiquimod is a nucleoside analog which activates Toll-like receptor 7 (TLR7) and TLR8 leading to localized inflammatory responses with increased concentrations of IFNα, TNFα, IL-1, and IL-6. Small case reports with patients with localized disease with disease previously treated with prior therapies have demonstrated complete responses in both MF and CD30-positive CTCL [31, 32]. Side effects were mainly irritation and pruritus at the application site.

16.2.2.4 Phototherapy

Phototherapy is an extensively used therapy for multiple commonly occurring skin diseases, including eczema and psoriasis, that has activity in CTCL as well. Phototherapy can be used either by itself for early-stage (IA–IIA) disease or in combination with systemic treatments in advanced-stage CTCL. Both narrowband ultraviolet B (nbUVB) and psoralen + ultraviolet A (PUVA) are options, with PUVA being preferred when deeper lesions are present, such as thick plaques or folliculotropic disease, given the deeper penetration of this modality. The psoralen, most commonly 8-methoxy psoralen, is either applied to the skin directly (in localized disease) or taken orally (in more diffuse disease). It becomes intercalated in DNA and activated by UVA, resulting in DNA photo-adducts and apoptosis. When given orally, psoralen can cause nausea and abdominal pain.

UV therapy can be either directed to a particular body part, such as the hands and feet, or given broadly to most of the skin. Detailed guidelines have been published previously regarding the administration, dosing, and schedule of therapy [33]. CRR of PUVA therapy are 85% and 65% for stage IA and IB, respectively, while CRR ranged from 54% to 90% for nbUVB in a series of small studies involving patients with stage IA and IB disease [33]. Maintenance therapy after a CR can result in a more durable control and is therefore commonly advocated if feasible for the patient. Common side effects of phototherapy are erythema and pruritus. For PUVA therapy, photodamage is more frequent than UVB and is seen in 27% of the patients [34]. PUVA therapy also increases the risk for secondary skin cancers with an overall incidence of 26% in CTCL patients who received PUVA [34]. Due to these added toxicities of PUVA compared to nbUVB, some providers may initially start with nbUVB and move to PUVA if disease control is not adequate, especially in a patient with a prior history of skin cancers without deep skin lesions. Randomized comparisons between these two modalities have not been performed.

16.2.2.5 Systemic Therapies for CTCL

Systemic biologics, chemotherapy, photopheresis, and/or allogeneic transplant are used to treat advanced-stage disease, specifically with Sezary syndrome.

Multiple oral retinoids have activity in CTCL and have long been used as systemic treatments in advanced-stage CTCL. In a phase II/III study of oral bexarotene in 94 patients with stage IIB–IVB, ORR of 45% (300 mg/m^2/d) and 55% (>300 mg/m^2/d) were seen [35]. The median duration of response was 7–9 months. In early-stage, relapsed/refractory disease, the ORR were 54% (300 mg/m^2/d) and 67% (>300 mg/m^2/d) [36]. The most frequent drug-related adverse events were hypertriglyceridemia, hypercholesterolemia, central hypothyroidism, headache, and leukopenia. In practice, bexarotene is typically initially dosed at 150 mg/m^2/d and escalated up or down based on clinical response and toxicity to a maximum of 650 mg/m^2/d. Oral isotretinoin and acitretin are other systemic retinoids that have been used off-label for CTCL.

Interferon-α (IFN-α) results in potent stimulation of both CD8+ T cells and NK cells leading to CTCL cytotoxicity. In addition, CTCL growth-promoting Th2 cytokines are suppressed by IFN-α. In a small study of both previously untreated ($n = 28$) and treated patients ($n = 15$), IFN-α was given daily with dose escalation from 3 to 18 million units (MU). ORR and CRR were 79% and 36% in the untreated group and 67% and 6.5% in the previously treated group [37]. Of note, patients who achieved a CR had a durable response on the order of 18 to 40 months. IFN-α2a is the more generally used IFN-α in CTCL clinical practice. Administration schedules and dosing have been variable from trial to trial, but expert recommendations on dosing have been published [38, 39]. Short-term side effects include fevers, chills, arthralgias, myalgias, and malaise, which usually improve after the first week of treatment. Long-term chronic side effects include fatigue, anorexia, weight loss, and mood and cognitive changes.

IFN-α has been given concurrently with TSEBT and has been found to be safe, but the efficacy of combined therapy has been inconsistent with no clear proven benefit. A retrospective study comparing 31 patients treated with TSEBT and 19 patients with TSEBT and IFN-α has shown CRR of 65% and 58% ($p = 0.6$), respectively [40]. In another retrospective study, a CRR of 35% was seen in the TSEBT group ($n = 11$) and 63% in the TSEBT + IFN-α ($n = 30$), respectively, but this difference was not statistically significant [41].

IFN-γ1b has also been shown to have activity in CTCL. In a study of 16 patients who had prior systemic treatment failure (some with IFN-α), an ORR of 31% was seen, all of which were partial responses with a median duration of response of 10 months [42]. Side effects included fever, weight loss, mild neutropenia, elevated LDH, and elevated hepatic transaminases.

Methotrexate is an antimetabolite and immunosuppressant that acts by competitively inhibiting dihydrofolate reductase (DHFR) leading to reduction of tetrahydrofolate thus inhibiting nucleotide synthesis and thus DNA and RNA production. A retrospective review of 69 patients (most with patch/plaque disease, $n = 60$) treated with oral low-dose methotrexate found an ORR and a CRR of 33% and 12%, respectively, with a median time to treatment failure of 15 months [43]. Another retrospective study of patients with primary cutaneous CD30-positive lymphoma and LyP achieved long-term control in 87% of patients with a median duration of continuation of therapy of 39 months [44]. Thus, low-dose methotrexate is an oral

treatment option in both MF and CD30-positive lymphoproliferative disease. Side effects of methotrexate include fatigue, nausea, increased transaminase levels, weight loss, diarrhea or gastrointestinal cramping, anemia, and leukopenia.

Pralatrexate is a synthetic antimetabolite that, like methotrexate, also inhibits DHFR but is internalized into cancer cells at a much higher rate, given its enhanced ability to bind to reduced folate carrier (RFC) and folylpolyglutamate synthase (FPGS) [45]. It is administered intravenously (IV) rather than orally. Given its activity in relapsed/refractory nodal peripheral T-cell lymphoma, it was studied in heavily pretreated patients (median prior systemic treatments = 4) with MF, SS, and primary cutaneous ALCL. At a dosage of 15 mg/m^2 IV weekly on a 3-week on/1-week off schedule, an ORR of 45% was seen. The most common toxicities were mucositis, fatigue, nausea, edema, epistaxis, pyrexia, anorexia, and skin toxicity. Both folic acid (1 mg daily) and vitamin B12 injections (every other month) are given while on pralatrexate therapy.

Acetylation of histones results in chromatin conformational changes predominantly to a more open state for greater accessibility for transcription factor binding. The histone deacetylases (HDACs) are a family of enzymes responsible for removing these histone acetylation marks and have been found to be essential for the survival of many T-cell lymphomas. Romidepsin is an inhibitor of the zinc-dependent class I HDACs. Two large multicenter single-arm clinical trials of patients with CTCL of romidepsin given IV at 14 mg/m^2 weekly on 3-week-on/1-week-off schedule have shown OR (CR) rates of 33% (6%) and 25% (4%) and median durations of response of 15 and 11 months, respectively [46, 47]. The most common adverse events (AEs) were GI toxicity and asthenia, with the incidences of ≥grade 3 AEs and discontinuations the highest during cycle 1 for patients with CTCL [48]. Vorinostat is an oral HDAC inhibitor that targets the zinc-dependent class I, II, and IV HDACs. In two phase II studies of vorinostat given at 400 mg daily in heavily pretreated patients with CTCL, ORR (CR) of 31% (0%) and 30% (1.3%) were seen, with median response durations of 3.7 months and 6 months, respectively [49, 50]. Side effects included fatigue, diarrhea, nausea, anorexia, dysgeusia, weight loss, and thrombocytopenia.

Brentuximab vedotin (BV) is an antibody-drug conjugate that targets CD30. It is covalently bound to the microtubule inhibitor monomethyl auristatin E (MMAE). Binding of BV to CD30-positive lymphoma cells results in internalization of MMAE leading to mitotic inhibition and apoptosis. Two phase II trials and a more recent phase III study demonstrated significant activity in patients with MF/SS. In the first phase II study enrolling 32 patients with stage IB–IVB with failure of at least one prior systemic therapy, an ORR of 70% was observed with one patient having a CR [51]. A higher response rate was seen in patients with >5% CD30 expression. In another phase II study of patients (n = 48) with CD30-positive cutaneous lymphoproliferative disorders or MF, ORR and CR of 73% and 35% were seen, with no association between CD30 expression and response rate [52]. In the phase III ALCANZA study, patients with CD30-positive MF and pcALCL were randomized to either BV 1.8 mg/kg every 3 weeks or physician's choice of therapy. The ORR was 56.3% for BV versus 12.5% for physician's choice therapy with a

median PFS of 16.7 months and 3.5 months, respectively. This study led to the FDA approval of BV for patients with CD30-positive MF and pcALCL who have received prior systemic therapy. The most common adverse reactions (>20% of patients) include peripheral sensory neuropathy, anemia, nausea, diarrhea, fatigue, and neutropenia.

Mogamulizumab is a humanized IgG1 antibody that targets the C-C chemokine receptor 4 (CCR4), which is expressed on malignant T cells in many types of T-cell lymphomas, including CTCLs. Binding of CCR4 to the cell results in significant antibody-dependent cytotoxicity through enhanced binding of effector cells to a defucosylated Fc region of mogamulizumab. In addition, mogamulizumab depletes CCR4-expressing Treg cells within the CTCL microenvironment, likely enhancing an anti-CTCL immune response [53]. A phase III study (MAVORIC) randomizing previously treated patients with CTCL ($n = 372$) to either mogamulizumab or vorinostat demonstrated an ORR of 28% versus 4.8% and a median PFS of 7.7 months versus 3.1 months in favor of mogamulizumab. The most common treatment-emergent AEs were infusion-related reactions (33.2%) and skin eruptions due to drug (23.9%). Serious adverse events included pyrexia (4%) and cellulitis (3%). The trial led to the approval of mogamulizumab for relapsed/refractory MF/SS in 2018.

Alemtuzumab is an anti-CD52 antibody that has been shown to have activity in MF and SS patients. In a phase II study ($n = 22$) of advanced MF and SS patients treated with alemtuzumab, an ORR and a CRR of 55% and 32%, respectively, were seen [54]. Alemtuzumab has been found to induce longer-term remissions in some SS patients and thus may serve as a reasonable option for treatment refractory SS [55]. As alemtuzumab depletes both T cells and B cells due to the common expression of CD52 on both lymphocyte populations, there is a very high risk of opportunistic infections including CMV reactivation, requiring antiviral, antifungal, and *Pneumocystis* prophylaxis.

Chemotherapy, in general, does not provide durable responses in CTCL patients. In two retrospective studies, the median time until another treatment is required for disease control after chemotherapy has been reported to be 3.9 months and 5.1 months [56, 57]. Combination chemotherapy is generally reserved for aggressive, life-threatening disease that requires rapid control. Single-agent chemotherapy has shown activity in heavily pretreated patients and thus is an option after other targeted therapies have been given. Gemcitabine was given as monotherapy (1000 mg/m^2 on days 1, 8, 15 of a 4-week cycle) in a heavily pretreated population of MF and pcALCL ($n = 25$, median prior therapies = 5) [58]. An ORR of 68% and a CRR of 8% were found. Pegylated liposomal doxorubicin (Doxil) was studied in a small group of ten patients as a second-line agent. Doxil was given at a dose of 20 mg/m^2 once a month (with a maximum of eight infusions given). An ORR 80% and a CRR of 60% with a median DFS of 13.3 months were noted [59]. A retrospective review of 34 CTCL (mostly MF) patients treated with Doxil as second-line therapy found an ORR of 88.2% and a CRR of 44% with a median DFS of 13.3 months [60]. Adverse events were seen in 41.2% but were temporary and generally mild.

Extracorporeal photopheresis (ECP) is a procedure in which a patient's leukocytes are removed from circulation by apheresis, treated ex vivo with 5-methoxypsoralen, and returned back to the patient [61]. The principle behind ECP is that the killed CTCL cells injected back in the patient will provide antigens that are taken up by antigen-presenting cells (APCs) to induce an anti-CTCL immune response in the skin. It commonly takes 6–8 months after the start of ECP before a response is observed. ECP has traditionally been used as an initial therapy to achieve disease control in SS patients with an overall response rate from combined reported series of 42.9% and a CRR of 9.5% in patients with T4 (erythrodermic) disease [62]. ECP has since been applied to earlier stages of disease with similar ORR and higher rates of CR [62]. Controversy surrounds whether or not detectable CTCL cells in the peripheral blood are absolutely required for a response to ECP. However, especially with the advent of newer agents in the treatment of non-erythrodermic relapsing CTCL, the role of ECP in the early-stage patient is less clear. ECP is generally very well tolerated with uncommon side effects mainly associated with the apheresis procedure itself, such as hypotension, bleeding at the access site, and line-associated infections.

ECP's role as an adjunctive therapy to TSEBT has been retrospectively evaluated in CTCL patients with erythrodermic disease [63]. A comparison of patients receiving TSEBT alone versus patients receiving ECP given concurrently with, or immediately after, TSEBT has shown a significant 2-year PFS difference of 36% versus 66%, respectively. An improvement in overall survival (OS) has also been noted. Thus, ECP in combination with TSEBT is one of the recommended first-line treatment options in the current National Comprehensive Cancer Network (NCCN) guidelines for SS patients.

Allogeneic stem cell transplant (HCT) has been shown to have a graft versus lymphoma effect with durable responses seen in heavily pretreated patients. In a retrospective analysis of HCT outcomes in advanced-stage primary CTCL ($n = 37$, 54% of which had disease transformation), the estimated 2-year OS and PFS were 57% and 31%, respectively, with weak residual tumor burden prior to transplant associated with improved PFS [64]. In another retrospective study of the European Group for Blood and Marrow Transplantation database of 60 patients with MF/SS who underwent HCT, a 5-year median PFS and an OS of 32% and 46%, respectively, were found [65]. The associated non-relapse mortality rate at 7 years was 22%.

In a study of 19 patients who underwent TSEBT prior to HCT, the overall intent to treatment response rate was 68% with a CR rate of 58% [66]. At 19 months of follow-up, the non-relapse mortality (NRM) was 27% with four patients dying from infections and one from lung cancer. Only two patients died from disease, and 11 patients remained in CR. These results demonstrated that incorporating TSEBT into pretransplant therapy has overall acceptable safety with NRM not significantly different compared to that found in prior CTCL HCT studies, at least at this duration of follow-up. However, a randomized comparison is needed to prove the benefit of TSEBT in patients undergoing allogeneic transplant.

In keeping with the fact that combination chemotherapy seldom produces long-term responses in CTCL, autologous stem cell transplant has generally not lead to durable responses in CTCL in the limited number of patients in which this approach was taken, with a median time until disease progression of only 2.3 months [67].

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