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SARCOMAS (SR PATEL, SECTION EDITOR)

Advances in Radiation Therapy for Primary and Metastatic Adult Soft Tissue Sarcomas

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Abstract Soft tissue sarcomas (STS) consist of a heterogeneous group of rare malignancies arising from mesenchymal origin. While surgical resection is the primary treatment for STS, the use of radiotherapy (RT) as an adjunctive modality has been shown to improve oncologic outcomes. Technologic improvements, such as image guidance and intensity-modulated radiotherapy that significantly improve both the precision and delivery of RT, have led to the reduction of long-term RT toxicities without compromising outcomes. This review addresses these technologic advancements as well as discussing the most current updates regarding the use of brachytherapy, charged particles, and novel agents with RT.

Keywords Sarcoma · Radiation therapy · IGRT · IMRT · SBRT · Neoadjuvant radiotherapy · Targeted therapy

Introduction

Soft tissue sarcomas (STS) include a heterogeneous group of tumors arising from connective tissue that can occur at any anatomic location. In 2015, it was estimated that in the USA 11,930 people would be diagnosed with STS and 4870 would die of these diseases [1]. There are more than 50 histologic subtypes of STS; the most common subtypes include high-grade pleomorphic sarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor which in aggregate account for 75 % of all STS [2]. STS patients typically present with a painless, enlarging mass and may be misdiagnosed or correctly diagnosed only following an extended delay. An American College of Surgeons patterns of care study for adult STS found that the most common site of presentation is the extremity (approximately 60 %; lower extremity 46 %, upper extremity 13 %), with other sites being the trunk (18 %), retroperitoneum (13 %), head and neck (9 %), and mediastinum (1 %) [3]. Locally, these tumors typically grow longitudinally along musculoaponeurotic planes, and rarely invade through fascial planes or periosteum [4]. There are numerous histologic subtypes and, of these, five are more likely to be associated with regional lymph node involvement (synovial sarcoma, clear cell sarcoma, angiosarcoma, epithelioid sarcoma, rhabdomyosarcoma) [5]. In the patterns of care study, 23 % of patients presented with distant metastatic disease, mostly in the lung tissue.

Three randomized trials have established conservative surgery combined with radiotherapy as the standard management for most localized high-grade STS of the extremity. The NCI prospective, randomized trial demonstrated that amputation and limb-sparing management produced equivalent survival, thereby establishing limb sparing with surgery and radiotherapy as a new standard of management [6]. The trials by Yang et al. and Pisters et al. showed improved local control with adjuvant radiotherapy [7, 8], as opposed to surgery alone in the limb-sparing context. In both trials, a significant decrease in local recurrences was seen with radiation, without difference in overall survival. In the Pisters trial, there was no

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statistically significant difference in local recurrence for low-grade lesions, suggesting that adjuvant RT can be avoided in favor of close observation for selected patients in expert surgical hands. Since these pivotal trials, developments in the field of radiotherapy have helped to improve outcomes. This review will focus on advances in the field of radiotherapy relevant to localized and metastatic soft tissue sarcoma presentations.

Localized Extremity Soft Tissue Sarcoma

Ideally, localized extremity sarcoma is managed with limb preservation. The goals of this therapy are to affect uncompromised local tumor control while retaining acceptable limb function and cosmesis without causing burdensome symptoms due to treatment in the remaining limb tissues. Limb preservation can be approached by several different pathways: surgery followed by adjuvant radiotherapy, neoadjuvant radiotherapy followed by surgery with or without systemic therapy (neoadjuvant and/or adjuvant), followed by surgery, and surgery alone in selected cases.

Neoadjuvant Radiotherapy Versus Post-operative RT

There are a number of potential advantages of pre-operative radiotherapy for extremity STS. Radial expansion of an intracompartmental tumor causes compression of surrounding structures resulting in the formation of a pseudocapsule around the tumor [9]. Pre-operative RT has been shown in animal models to thicken the pseudocapsule through hyalinization, thus theoretically reducing surgical potential for seeding and histologically positive margins. Moreover, in the post-operative setting, given the larger target volumes and higher doses employed for radiotherapy in this context, the potential for increased late toxicities is increased. This was confirmed by the long-term results of the NCIC SR2 trial which randomized patients to pre-operative versus post-operative radiotherapy in soft tissue sarcoma of the extremities and demonstrated that patients treated with post-operative radiotherapy have more subcutaneous fibrosis (48 vs. 31.5 %), joint stiffness (23 vs. 17.8 %) and extremity edema (23 vs. 15.1 %) compared to the pre-operative radiotherapy [10]. Moreover, patients experiencing a grade 2 or higher toxicity had significantly more physical disability and impairment per the Toronto Extremity Salvage Score (TESS) and the Musculoskeletal Tumor Society Rating Scale (MSTS). However, this improvement in late toxicity from pre-operative management comes at the cost of significantly increasing the patient's risk of acute major wound complications with an absolute difference of 18 % (35 vs. 17 %) in favor of post-operative RT [11].

Radiation Techniques

The NCIC SR2 trial was conducted was conducted in the era of transition away from 2-D planning. The development of ever enhancing computer power in the 1980s and 1990s permitted a series of sequential improvements in radiotherapy planning and delivery. These advances have continued to the current time and now include in roughly historical sequence: 3-D planning, the development of multi-leaf collimators, intensity-modulated radiotherapy (IMRT), and image-guided radiotherapy (IGRT). In addition, the development of magnetic resonance imaging for routine clinical use in the 1980s provided an unparalleled opportunity to visualize both primary soft tissue sarcomas and their radially adjacent regions of edema. In aggregate, these developments result in enhanced dose delivery to tumor regions with reduced margins and improved sparing of normal tissues. In three-dimensional conformal radiation therapy (3DCRT), the planner defines the volume and amount of radiation to be delivered from each treatment field. Indeed, in the SR2 trial, centers were allowed to plan patients using either the older 2-dimensional technique or newer 3DCRT technique. The field margins were larger compared to current standards with an initial volume 5 cm proximal and distal to the tissues at risk [10].

With further radiotherapy advances, margins used for radiotherapy treatment began to evolve. Moreover, with the clinical implementation of magnetic resonance imaging (MRI), a target delineation consensus using fused MRI images was developed by the RTOG Sarcoma Working group [12•]. The GTV was defined based on the T1-weighted gadolinium-enhanced post-contrast images. The clinical target volume (CTV) for intermediate to high-grade sarcomas ≥5 cm was defined as GTV with a 3-cm longitudinal expansion or to the end of a fascial compartment and a 1.5-cm radial expansion including any portion of the tumor not confined by an intact fascial barrier, bone, or skin surface. The final CTV was obtained by augmenting to include any additional tissue at risk for microscopic local tumor spread as defined by hyperintensity on T2-weighted images if not already included in the prior expansion (Fig. 1).

In the early 2000s, intensity-modulated radiation treatment (IMRT) began to be utilized in the clinical treatment of sarcoma. IMRT allows the planner to define not only the orientation and energies of all beams as in 3-D planning. However, additionally specific dose constraints for both normal structures and the target volume are achieved through technique referred to as inverse-planning, which allows the use of specialized computer-aided optimization methods, in which the computer optimally assigns non-uniform intensities to tiny beamlets, or subdivisions of beams, allowing for increased control over radiation dose [13]. These improved dose distributions provide opportunity for sustained or enhanced tumor control with

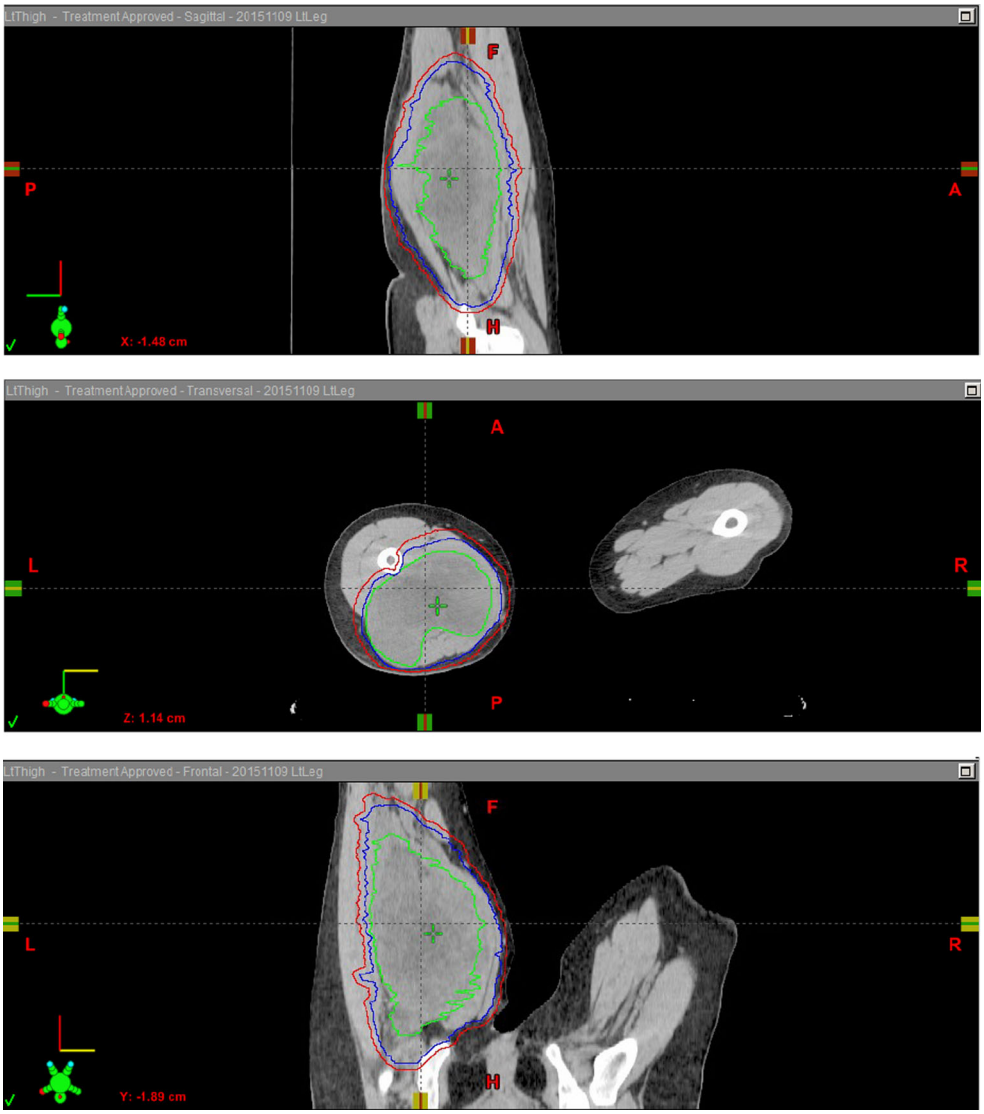

Fig. 1 Example of target volume delineation for the pre-operative treatment of STS of the extremity using daily image guidance. *Green* = GTV, *Blue* = CTV, *Red* = PTV

reduced normal tissue toxicity. In a retrospective study of 41 patients treated with IMRT for STS of the extremity both in the pre-operative and post-operative setting, Alektiar et al. demonstrated a 5-year actuarial local control rate of 94 % with low rate of complications. Additionally, as multiple isocentric gantry angles can be used with IMRT, the extremity can be maintained in a neutral anatomic position, thus providing the patient with a greater level of comfort and less risk of setup inaccuracy compared to 3DCRT treatment [14].

Image-guided radiotherapy is a broad term which universally involves the use of innovative imaging modalities to augment target and normal tissue localization for radiotherapy planning and delivery, by providing opportunity for reviewing and adjusting images taken at the treatment console immediately prior to treatment. With image guidance during treatment, planning treatment volume (PTV) margins can be reduced for setup uncertainty. An additional benefit of IGRT is that if imaging during a course of treatment demonstrates anatomical changes, the radiation treatment plan can be adapted to reflect these changes. O'Sullivan et al. performed a phase II study in order to determine whether image-guided intensity-modulated radiation therapy (IG-IMRT) can reduce morbidity including the high rate of wound complications in the pre-operative setting [15]. In this study, avoidance structures were created which included the skin and subcutaneous tissue to be used for reconstruction. Overall, acute wound complications occurred in 30.5 % which was a 12.5 % reduction from the 43 % seen with pre-operative RT in the NCIC SR2 trial. The authors concluded that this modest change might still be clinically important, if the observation is sustained in future study. Moreover, there was an increase in primary wound closures to 93 % compared to 66 % in the SRT trial, suggesting that would healing is improved by intentionally sparing the skin flap. At a 4-year follow-up, there were no local recurrences near the skin flaps.

RTOG 0630 was a prospective multi-institutional phase II trial of IGRT for STS of the extremity which aimed to assess the impact of reduced treatment volumes on patient toxicities [16••]. Pretreatment MRI of the primary STS within 8 weeks was required to define the GTV and either pre-operative 3DCRT or IMRT could be utilized. For intermediate to high-grade tumors ≥8 cm, the CTV was derived by generating a 3-cm expansion on the GTV (as defined by T1 post-contrast images) in the longitudinal directions (respecting intact natural barriers to local extension) with a 1.5-cm radial margin, then augmented to include suspicious edema as defined by T2 sequences. For low-grade tumors or those less than 8 cm, the CTV expansion was decreased to 2 cm (including suspicious edema) with a 1-cm radial margin. With diagnostic MRI and the use of daily pretreatment IGRT images as guidance, the PTV margin, which takes into account internal organ motion, positioning, and treatment delivery uncertainty, was reduced to 0.5 cm. Please see Fig. 1 for a relevant example of target delineation using these principles. The primary end point was effect of reduced radiation volume through the use of IGRT on radiation morbidity at 2 years from the start of RT. Despite the smaller volumes, local control remained high with a 2-year estimate of 94 %. All failures were in-field and three of the failures had positive margins, a known adverse risk factor for recurrence. Indeed, only 10.5 % experienced at least grade ≥2 toxicity compared with the 37 % of patients in the NCIC SRT trial suggesting that the target volumes used in RTOG-0630 are appropriate for pre-operative IGRT for extremity STS. Please see Table 1 for summary of relevant data regarding toxicities from prospective trials with various radiation therapy techniques.

Brachytherapy

Radiotherapy for extremity STS may be delivered using external beam radiotherapy (EBRT) in the pre-operative setting or post-operatively as either EBRT or brachytherapy (BT). BT and EBRT have not been compared in a randomized controlled study. The major advantage of BT is the ability to deliver highly conformal treatment to the tumor bed with sharp falloff in dose to adjacent organs thus potentially decreasing long-term morbidity. Additionally, BT may be completed in a shorter time period (days rather than weeks) and is thus more convenient for patients. High dose rate (HDR) in comparison to low-dose rate (LDR) BT potentially offers improved dosimetry and enhanced radiation safety for care givers and personnel. Disadvantages of brachytherapy include the inability to target large volumes, potentially higher risk of injury to the nerves in direct contact with the brachytherapy catheters, and the need for high expertise by the treatment team.

The pivotal Memorial Sloan Kettering Cancer Center (MSKCC) trial demonstrated an improvement in local control

Table 1 Toxicity with various radiation therapy techniques

Study	Median follow-up (months)	RT technique	Local control (%)	Wound complication[a] (%)	Fibrosis[b] (%)	Edema[b] (%)	Joint stiffness[b] (%)
PMH phase II [15]	49	Pre-operative IMRT	93.2	30.5	9.3	11.1	5.6
NCIC-SR2 [11]	83	Pre-operative (2D and 3DCRT allowed)	93	35	48	23	23
		Post-operative	92	17	31.5	15.1	17.8
RTOG 0630 [16••]	43	Pre-operative IMRT (75 %) remaining 3DCRT	93	36.6	5.3	3.5	5.3

[a] Based on definition per NCIC-SR2 trial

[b] Based on Common Terminology Criteria for Adverse Events version 3.0, grade ≥2 late toxicity

when comparing limb-sparing surgery alone versus surgery plus radiotherapy-utilized BT as their adjuvant treatment. Results demonstrated that only the use of BT with high-grade lesions yielded an improvement in local control with a 24 % absolute local control benefit [7]. Further studies have shown that monotherapy BT may not be appropriate in the setting of high-grade STS with a positive margin [17]. In 2011, MSKCC published a comparison of adjuvant low-dose rate (LDR) BT as monotherapy to IMRT in primary high-grade sarcoma of the extremity utilizing their prospective database [18]. Despite the fact that IMRT patients had more adverse features such as positive/close margins and larger tumors, the 5-year local control was 92 % for IMRT versus 81 % for BT. On multivariate analysis, IMRT was the only predictor of improved local control. One pitfall of this retrospective analysis might be a lack of imaging-based planning in the BT group when compared with patients treated with MR-based IMRT in the modern era. In addition, 19 % of patients had significant wound complications in the IMRT group compared with 11 % in the BT group and this difference was not statistically significant. Differences in long-term toxicity were not assessed. Results of this comparison study demonstrate that adjuvant brachytherapy must be highly selective and image-based. The type and location of sarcoma as long as its extent of peri-tumor edema are key factors for selection of treatment modality (brachytherapy vs. IMRT vs. 3DCRT). Currently, the American Brachytherapy Society consensus statement concludes that brachytherapy is a useful component of STS treatment with advantages of targeted dose distribution, low integral dose, and shorter treatment times. It is certainly the responsibility of the clinician to select the modality or combination of modalities suitable to the patient and familiar to the treatment team.

STS of the Retroperitoneum

Treatment with aggressive surgical management for retroperitoneal sarcoma (RPS) is essential to achieve long-term survival for patients [19]. Local recurrence rates approach 50 % in comparison to 10 % for extremity sarcomas, likely due to case-specific inability to obtain widely negative surgical margins. As with extremity STS, positive margins and high grade have been shown to be associated with decreased survival [20]. Currently, no randomized data exist to define the role of radiation therapy in the management of RPS. We are still awaiting the results from the EORTC protocol 62092 comparing pre-operative RT plus surgery versus surgery alone for patients with RPS to help better advance our approach to this disease. A number of small prospective or retrospective series have shown a dose-response relationship suggesting improved outcomes with higher doses [21]. For instance, the addition of a BT boost to the area of concern has been shown to increase local control rates over resection and EBRT alone [22]; however, as of yet, this has not resulted in a proven survival [23]. Pre-operative radiotherapy planned with IMRT with or without simultaneous integrated boost (SIB) technique can be used to boost areas anticipated to be at risk for recurrence following resection ("high-risk margins"). In the pre-operative context, in situ tumor displaces adjacent normal abdominopelvic viscera, allowing for optimal sparing of normal tissue structures. Tzeng et al. reported on a cohort of 16 patients with biopsy-proven RPS treated with pre-operative IMRT and simultaneous integrated boost. They showed that 45 Gy in 25 fractions to the entire tumor plus margin and a boost dose of 57.5 Gy to the volume predicted as high risk for positive surgical margins was tolerable with 88 % undergoing complete macroscopic resection, with only two local recurrences at 28 months [24]. However, safety and local control rate need to be established through a large multi-center prospective trial. When planning pre-operative radiotherapy for retroperitoneal sarcoma, close collaboration between the radiation oncologist and surgical oncologist is essential. Issues include designation of areas of concern for high-risk margin status and details of planned surgical resection such as whether either kidney is likely to be resected. Recently a group of the NRG Oncology Sarcoma experts has published their treatment recommendations and consensus for target volume definitions for pre-operative radiotherapy of retroperitoneal sarcoma [25–27].

While IMRT has improved conformality over 3-D and 2-D approaches, the utilization of heavy particle beam therapies (PBT), such as carbon particle treatment offer opportunity for improved therapeutic index through the radiobiologic properties of these particles compared to photons. Moreover, with any charged particle beam therapy, including protons, there is opportunity for dramatically reduced exit dose as a result of the Bragg Peak principle. In 2010, MGH reported their experience treating 28 patients with IMRT or PBRT [28]. Despite the large volumes (median size of 9.75 cm), only 4 of 28 patients had a radiation-related complication. The 3-year local recurrence-free survival for primary and recurrent tumors was 90 and 30 %, respectively. Such retrospective data are very encouraging. We are now awaiting the results from a prospective multi-center phase I/II trial of pre-operative image-guided intensity-modulated proton or photon radiation therapy with simultaneous integrated boost to the high-risk margin for retroperitoneal sarcoma (NCT01659203).

Combined Radiation with Targeted Agents

The primary treatment paradigm in patients with localized STS remains surgery with adjuvant or neoadjuvant radiotherapy. The role of chemotherapy in this setting is a controversial topic and is not the subject of this review. However, a number

of trials have been developed to examine the efficacy and safety of combining targeted molecular agents with radiotherapy. In a phase II trial, Yoon et al. described a cohort of 20 patients with 5 cm or greater intermediate or high-grade STS to neoadjuvant bevacizumab (BV) alone followed by BV plus RT prior to surgical resection [29]. The study demonstrated BV plus RT resulted in ≥80 % pathologic necrosis in 9 of 20 tumors (45 %), over double the historical rate seen with RT alone. In July of 2014, the Children's Oncology Group and the NRG Oncology group opened a joint phase II/III trial to determine the additional benefit of pazopanib, an inhibitor of angiogenesis that targets vascular endothelial growth factor receptor and platelet-derived growth factor receptor, to neoadjuvant RT or chemo-RT in patients with STS of all ages. The rationale of using pazopanib in the localized disease is based on the benefit it has demonstrated in the metastatic setting [30]. The pazopanib neoadjuvant trial in non-rhabdomyosarcoma soft tissue sarcomas (PAZNTIS) trial (NCT02180867) is randomizing patients with T2a/b and grade 3 with upper, lower, or trunk soft tissue sarcomas to study how well pazopanib hydrochloride, combination chemotherapy, and RT work compared to RT alone or in combination with pazopanib hydrochloride or combination chemotherapy in patients with resectable STS. The primary objectives will assess the rates of complete pathologic response and event-free survival. For a more comprehensive discussion of the use of targeted agents in STS, the readers are directed to the review by Wong and colleagues [31•].

Radiotherapy for Metastatic Soft Tissue Sarcoma

Pulmonary metastases are the most common site of metastatic disease and historically have been treated with chemotherapy and or surgery. In those patients presenting with stage IV disease with limited metastases are often recommended to undergo definitive treatment of the primary STS with chemotherapy recommended prior or after resection. Moreover, resection or other ablative treatment is recommended to treat limited metastasis and to render the patient disease free. MSKCC published their experience in treating 719 patients with pulmonary metastases from soft tissue sarcoma of whom 161 underwent surgical resection. The patients treated with complete resection had a median survival of 33 months and a 3-year actuarial survival rate of 46 % compared to median survival of 11 months for patients treated with non-operative therapy [32]. Additionally, they found that resection of metastatic disease is the single most important factor that determines outcome. Moreover, it has been shown that patients with slow growing disease may benefit from repeat surgical resections [33].

Stereotactic body radiation therapy (SBRT) allows for administration of precisely directed, high dose irradiation that tightly conforms to a target while minimizing dose to the surrounding normal tissue Theoretically, SBRT's most important features compared to EBRT are the use of high dose per each radiation fraction, the delivery of one to five fractions over a few days to two and one-half weeks which dramatically decreases the overall duration of treatment, and an improved treatment response [34]. SBRT has been shown in a number of retrospective studies to provide durable local control for pulmonary metastasis from soft tissue sarcoma. A number of small published studies of SBRT for lung metastases originating from a sarcoma have reported a local control rate of 83–100 % with only one grade 3 toxicity [35–37]. In a small, nonrandomized series from Corbin, 20 patients treated with SBRT to one or more nodules had a survival advantage at 2.5 years of when compared to patients who were not treated with SBRT (73 vs. 25 %). Neither the number of pulmonary metastases, nor age predicted for outcome suggesting that older patients or patients with greater disease burden should not be excluded from local therapy. SBRT was the most significant predictor of improved survival in this cohort [35]. Recently, Navarria et al. described results of 28 patients with 51 lung metastases from soft tissue sarcoma who were treated with ablative doses using a variety of SBRT treatment regimens: 30 Gy in one fraction, 60 Gy in three fractions, 60 Gy in eight fractions, and 48 Gy in four fractions. There were no grade III–IV toxicities and the 5-year local control rate was 96 % with overall survival rates at 2 and 5 years of 96.2 and 60.5 %, respectively [38]. Given these data, there is evidence that SBRT of sarcoma oligometastasis should be considered a convenient, safe, and alternative non-surgical modality for treating patients with pulmonary metastatic disease from soft tissue sarcoma.

Conclusion and Future Directions

In conclusion, radiotherapy has an established role in the treatment algorithm for localized STS and is also widely utilized in the setting of metastatic disease. We have seen tremendous development and innovative techniques in the planning and delivery of radiotherapy for STS. Through reduction of field sizes, better conformality, and image-guided treatment delivery techniques, we are able to reduce both acute and long-term morbidity from radiotherapy without compromising local tumor control. In patients in whom local control remains challenging, more aggressive local and systemic treatment is needed for improvement in outcomes. Moreover, as researchers begin to learn more about the

molecular mechanisms involved in each histologic subtype, it is likely that separate treatment algorithms based on molecular markers will begin to emerge.

Compliance with Ethical Standards

Conflict of Interest Philip Blumenfeld, Neilayen Sen, Ross Abrams, Dian Wang declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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