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Sarcoma (SH Okuno, Section Editor)

Soft Tissue Sarcoma and Radiation Therapy Advances, Impact on Toxicity

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Opinion statement

Since adjuvant radiotherapy was introduced in the 1970s for soft tissue sarcoma (STS), sequential clinical trials characterized the toxicities induced by radiotherapy when given post-operatively and pre-operatively. Gradual technological advancements led to more precise radiotherapy delivery through intensity-modulated radiation therapy (IMRT) and more accurate targeting through image-guided radiotherapy (IGRT) to minimize normal tissues from high-dose irradiation. These improvements ultimately reduced the long-term toxicities from radiotherapy. Due to the rarity and complexity of the disease, patients with STS should be treated at institutes where multidisciplinary discussion and care can be provided. Patients with STS should ideally be offered the choice of participating in clinical trials. International phase III trials are ongoing through COG-NRG Oncology (Pazopanib Neoadjuvant Trial in Non-Rhabdomyosarcoma Soft Tissue Sarcomas (PAZNTIS)) to define the role of radiotherapy in combination with pazopanib in the clinical care of extremity STS and through EORTC (STRASS) to define the role of pre-operative radiotherapy in the treatment of retroperitoneal STS. Outside of clinical trials, extremity STS should be treated at centers of expertise where high-quality IMRT–IGRT is administered to lessen acute and long-term toxicities. In patients with extremity STS, pre-operative IMRT–IGRT is preferred as better target delineation and image guidance can be achieved. While acute wound complication remains a concern, patients treated using pre-operative IMRT–IGRT are largely spared of severe chronic irreversible radiation-related side effects such as bone fracture, fibrosis, edema, and joint stiffness that alter limb functions. For STS originating

from the retroperitoneum, if radiotherapy is recommended following multidisciplinary case discussion, pre-operative radiotherapy is preferred over post-operative radiotherapy. Post-operatively, normal radiosensitive organs fill the surgical cavity, which is the targeted volume of radiotherapy; hence, post-operative radiotherapy for retroperitoneal STS is associated with severe to fatal toxicities. Pre-operative radiotherapy has a more favorable toxicity profile as the retroperitoneal STS displaces, and thus spares, normal structures and organs from the high-dose irradiation volume.

Introduction

Soft tissue sarcomas (STS) are rare and heterogeneous malignancies [1•]. Originating most often in the extremities, 46 % are from the lower extremities, 13 % from the upper extremities, 18 % from the torso, 13 % from the retroperitoneum, and 9 % from the head and neck [2]. Due to the disease's rarity and that they present as painless enlarging mass, STS are often misdiagnosed or diagnosed following an extended delay [2]. This frequently results in large masses with a mean size of 9–10 cm at diagnosis [3•]. Known clinical prognostic factors for STS are histological grade, tumor size, depth of invasion, and anatomical location of origin [1•].

Nodal spread is generally rare but in certain histologies such as rhabdomyosarcoma, epithelioid sarcoma, and vascular sarcomas, the rate of nodal metastasis is approximately 15 % [4, 5]. The incidence of distant metastasis at diagnosis is about 10 % and the most frequent site of metastasis is the lung [6].

Despite wide local excision, local recurrence rates range from 20 to 33 % for extremity sarcomas suggesting that microscopic disease remains despite pathologically negative margins [7–9]. This introduces the concept of "reactive zone," an area situated between the tumor's pseudocapsule and normal tissue. This zone consists of granulation-like proliferation tissue such as edema, neovascularization, and potentially satellite tumor cells. It can be represented by T2-weighted hyperintense signal changes surrounding the STS on MRI [9]. In a study by White et al., satellite tumor cells were present up to 4 cm away from the primary tumor in 10 out of their 15 patient cohort. Of the 10 cases with satellite tumor cells, nine were within areas of T2-weighted signal changes surrounding the STS [9]. This could explain the historical need for amputations to yield adequate local control in the absence of adjunctive radiotherapy (RT) [10]. However, a shift towards limb-sparing techniques emerged in the 1970s combining surgery with RT [10], which serves to eradicate microscopic disease at the margin surrounding the macroscopic STS. This review will focus on the acute and chronic toxicities that accompany RT for STS.

Treatment

Radiation techniques

Since the initial introduction of RT to the management of STS, RT techniques have tremendously advanced (Fig. 1). During the last 50 years, treatments have evolved from two-dimensional plans designed from plain radiographs to three-dimensional plans derived from the use of computed tomography (CT). The introduction of CT allowed for the development of three-dimensional conformal radiation therapy (3DCRT), with improved soft tissue visualization, dosimetric planning, and heterogeneity calculations. Nevertheless, 3DCRT uses uniform beams that offer limited freedom in dose sculpting around vital structures [11, 12]. Further progress has led to the now wide-scale implementation of intensity-modulated radiation therapy (IMRT) permitting the delivery of high doses to the tumor while avoiding critical structures using multiple beam directions and segmented or modulated fields [12]. As the precision of

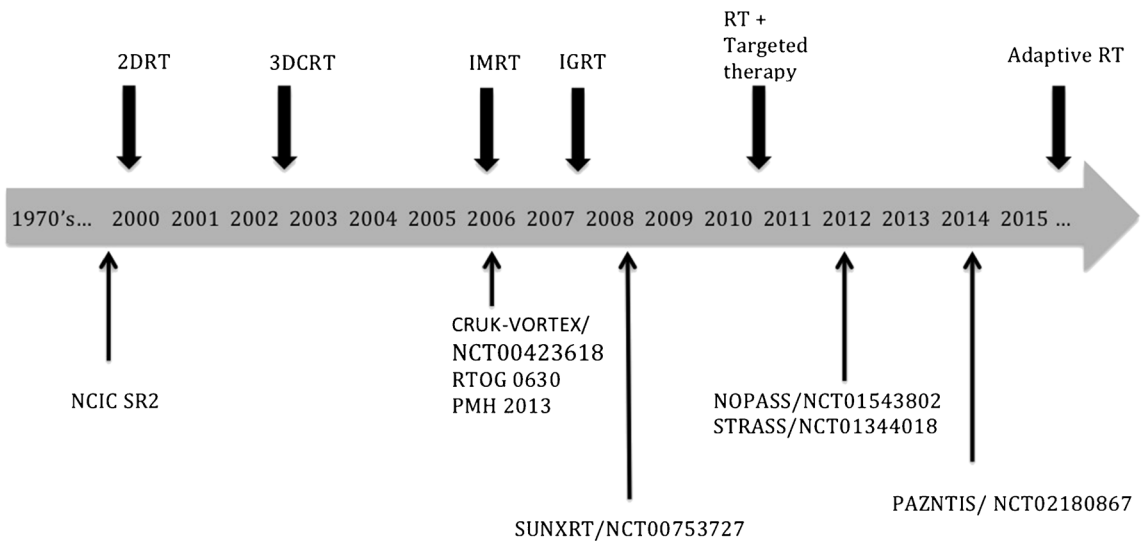

Fig. 1. The evolution of radiation therapy (*RT*) techniques over time modified radiation treatments in soft tissue sarcomas (*STS*). With better imaging and more specialized RT techniques such as intensity-modulated radiation therapy (*IMRT*) and image-guided radiation therapy (*IGRT*), treatment volumes were reduced (RTOG 0630, PMH 2013). Recent publications with modern RT techniques have shown a significant decrease in chronic toxicities (RTOG 0630) possibly in relation to field size reduction. Although pre-operative is associated with less chronic toxicities, the increased risk of acute wound complications is not benign. We await the results of the CRUK-VORTEX trial studying post-operative RT with reduced volumes on toxicities and local control rates. Moreover, the need for RT in the pre-operative setting for STS is still debated as evidenced by the ongoing STRASS randomizing patients between surgery alone and with neo-adjuvant RT. The introduction of targeted therapy in the management of STS brings forth concerns about the toxicity profile when such therapies are combined with RT. Current trials such as SUNXRT, NOPASS, and PAZNTIS are studying sunitinib and pazopanib in combination with RT in the management of STS. In the future, adaptive RT would permit tailored treatment volume that alters according to volumetric changes (increase/decrease) during RT.

delivery of tumoricidal radiotherapy doses was improved, there were increasing concerns in missing the target. To complement and maximize the precision of IMRT, image guidance techniques (IGRT) were conceived to reduce uncertainties in patient positioning, thus allowing physicians to safely reduce the margins used to account for errors [13]. Finally, novel techniques are being developed to account for the movement of tumors during RT (4D-CT) [14] and potential changes in the volume of STS over the course of radiotherapy otherwise known as adaptive radiotherapy [15].

With the gradual introductions of the above techniques, margins used for the treatments of STS also evolved. During the National Cancer Institute of Canada (NCIC) SR2 trial, in which centers used 2D and 3DCRT, RT margins were placed 5 cm longitudinally and 2 cm radially from the gross tumor volume (GTV) to the field edge [16, class I]. Subsequent to the completion of the study, improved resolution and sequences used in diagnostic and RT imaging systems enhanced the appreciation of the tumor, thus reducing the uncertainties on target volume delineation and radiation volumes [17]. The RTOG Sarcoma Working Group subsequently developed a consensus on GTV and clinical target volume (CTV) delineation for large high-grade extremity sarcomas [18••]. The GTV is defined as the tumor volume seen on a T1 contrast-enhanced MRI. The CTV for intermediate- to high-grade sarcomas ≥5 cm is defined as the GTV plus

3 cm longitudinally or to the end of a compartment and 1.5 cm radially including any portion of the tumor not confined by an intact fascia barrier, bone, or skin surface. This should encompass the T2-weighted MRI enhancement where microscopic STS cells may be present [9], but if the T2-enhanced regions is not within the CTV, clinical judgment is to be used to decide whether the entire T2-weighted MRI enhancement should be included [17, 18••]. Although there is no consensus guideline for the target delineation of low-grade tumors, the RTOG 0630 phase II trial defined the CTV as 2 cm longitudinal and 1 cm radial (including suspicious edema) beyond the GTV [19••, class II].

The RTOG 0630 trial aimed at assessing the impact of reduced treatment volumes using the above-described margins on patient toxicities [19••]. This trial required the use of MRI and IGRT to ensure good coverage and accuracy of the RT so that the planning target volume (PTV), which takes into account internal organ motion and positioning errors, could be reduced to 0.5 cm. Although these volumes are smaller then historically used [16], local control remained high (2-year estimate: 94 %). These studies suggest that long-term local control in the range of 90 % can be achieved via conservative surgery and modern precise RT with small margins for errors [8, 16, 19••, 20–22]. The gradual evolution in RT techniques and reduced planning target volumes led to important reduction in RT-related toxicities which will be discussed in the following sections.

STS of the limb and superficial trunk

Acute toxicities

In the treatment of STS, the acute phase toxicities secondary to RT are generally defined as RT or surgery-related side effects found in patients within 120 days of the surgery [16]. The SR2 trial that randomly assigned patients to pre-operative vs. post-operative RT demonstrated that with the smaller volume and lower doses (50 Gy in 25 fractions) of pre-operative RT, the rate of acute grade 2 or greater skin toxicities was 36 % as compared to 68 % ($p<0.0001$) in patients who received post-operative RT (66 Gy in 33 fractions) [16] (Table 1). However, major wound complications defined as those requiring a second operation, prolonged dressing, or readmission were found in 35 % of the patients treated with pre-operative RT compared to 17 % in the post-operative RT cohort. Primary wound closures were more frequently done in the post-operative RT cohort (77 vs. 66 %). Logistic regression suggested that pre-operative RT, larger tumors, and lower extremity STS were significantly associated with higher risk for wound complications. Furthermore, Baldini et al. suggested that diabetics were also significantly more prone to developing wound complications following pre-operative RT [23•, class III].

A phase II trial by O'Sullivan et al. studied pre-operative IG-IMRT for lower extremity STS. Avoidance structures were created in order to decrease the dose to the bone, normal musculature as well as the skin and subcutaneous tissue to be used for reconstruction [24••, class II]. In this trial, the surgeons had to draw and pre-plan their surgical cuts and skin flaps used for the wound closure and define with the radiation oncologists which part of the skin should be spared from IMRT. Reported wound complications rates were 30.5 %, which was not

Table 1. A summary of the acute and late toxicities described in selected studies of extremity soft tissue sarcoma treated with adjunctive radiotherapy

Study		Acute effects			Chronic/late effects (grade ≥2)				
		Major wound (%)	Skin grade ≥2 toxicity (%)	Primary closure rate (%)	Fibrosis (%)	Edema (%)	Joint (%)	Fracture (%)	Total (%)
Pre-op									
NCIC SR2—pre-op [16, 22]		35	36	66	32	15	18		37
NCIC SR2—pre-op [16]	LE	43							
PMH—pre-op [24••]	LE	30		93	9.3	11.1	5.6	0	
RTOG 0630—pre-op [19••]		37			5.3	5.3	3.5		10
RTOG 0630—pre-op [19••]	LE	42			6.0	6.0	4.0		12
Post-op									
NCIC SR2—post-op [16, 22]		17	68	77	48	23	23		
NCIC SR2—post-op [16]	LE	21							
MSKCC—post-op [25•]	Conv	18	49			15	17	9.1	37
MSKCC—post-op [25•]	IMRT	19	32			7.9	14	4.8	31

As complications are more common in lower extremity sarcomas, sub-group analyses were performed on the National Cancer Institute of Canada (NCIC) SR2 study and the RTOG 0630 study. The Princess Margaret Hospital (PMH) prospective study was dedicated to the pre-operative radiotherapy (pre-op) of lower extremity sarcomas. For comparison purpose, toxicity data from a large retrospective study from the Memorial Sloan Kettering Cancer Center (MSKCC) of patients treated largely (88 %) with post-operative (post-op) radiotherapy was included

LE lower extremity subset, *Conv* conventional radiotherapy

statistically reduced from the 43 % reported for lower extremity STS treated under the NCIC SR2. However, the number of primary wound closures was increased to 93 % compared to the 66 % observed in the SR2 trial. This suggested that the skin flap spared from high-dose RT is important to post-operative wound healing. Furthermore, at 4-year follow-up, none of the four local recurrences were near the IMRT-spared skin flaps, thus suggesting that carefully planned reduction of RT volume did not reduce local control.

In the RTOG 0630, wound complications were seen in 36.6 % with all wound complications occurring in the lower extremities (41.9 % (26/62) vs. (0/9) $p=0.02$) [19••]. The lower number of wound complications seen in RTOG 0630 is in concordance with the phase 2 trial from Princess Margaret Hospital (PMH) [24••] with similar number of patients. Both trials largely used IG-IMRT and pre-operative RT at 50 Gy. The difference between the trials was perhaps in the smaller margins of CTV used in RTOG 0630 vs. the PMH trial, which used the conventional SR2-like margins (CTV−4 cm sup/inf). It may be worthwhile examining whether the combination of the two techniques (smaller RTOG 0630 CTV margins + PMH skin flap sparing) would lead to a significant reduction in acute wound complications.

In the post-operative setting, acute radiation effects are best described by Folkert et al. in their retrospective study of 319 consecutive patients from 1996 to 2010 [25•, class III]. Approximately half of the patients ($N=154$) received conventional RT and the other half ($N=165$) received IMRT. In this study, 97 % of the patients treated using conventional RT and 79 % of the patients treated with IMRT received post-operative RT to a median dose of 63 Gy. The wound complication rates from both RT techniques were similar 17.5 % (conventional) vs. 19.1 % (IMRT), which corresponds with the findings from the post-operative cohort of the SR2 study (17 %). However, patients treated with IMRT had significantly less acute grade ≥2 radiation dermatitis (31.5 vs. 48.7 %) and significantly less treatment interruptions ($p<0.001$) than patients treated using conventional RT.

Chronic toxicities

While pre-operative RT potentially leads to re-operations, prolonged wound managements, and re-admissions, many patients recover from these acute toxicities. On the other hand, late and chronic toxicities from RT are permanent side effects and most often define the tolerability of RT regimens (Table 1).

Late toxicity assessment of the NCIC SR2 cohort demonstrated that grade ≥2 toxicities occurred less frequently in patients treated pre-operatively than those who received post-operative RT: fibrosis 31.5 vs. 48 % ($p=0.07$), joint stiffness 17 vs. 23 % ($p=0.51$), and edema 15 vs. 23 % ($p=0.26$). Patients with grade ≥2 fibrosis, joint stiffness or edema had significantly ($p<0.01$) more physical disability and impairment as measured by the Toronto Extremity Salvage Score (TESS) and the Musculoskeletal Tumor Society Rating Scale (MSTS). RT field size was the only factor associated ($p<0.006$) with increased risk of fibrosis and joint stiffness [22]. Of interest, although there was no significant correlation between the timing of the RT and physical impairment, field sizes from post-operative RT were larger than pre-operative RT (416 vs. 333 cm^2, $p=0.01$) despite similar tumor sizes in both treatment arms.

The retrospective study from MSKCC that compared the outcomes (disease and toxicities) of patients treated with mostly post-operative conventional RT

vs. IMRT reported grade ≥2 chronic toxicities in 36.6 and 30.7 % of the patients, respectively [25•]. While there was more nerve damage in patients treated with IMRT than conventional RT (3.5 vs. 2.6 % $p=0.45$), there were fewer joint stiffness (14.5 vs. 17 %; $p=0.40$), edema (7.9 vs. 14.9 %; $p=0.05$), and bone fractures (4.8 vs. 9.1 %; $p=0.18$) in patients treated with conventional vs. IMRT respectively.

Radiation-induced bone fractures are serious complications occurring in 2–20 % of patients treated with limb-sparing surgery and RT [26]. These fractures are accompanied by numerous complications from delayed union to non-union requiring multiple surgeries, endoprosthetic replacement, or even amputation [26]. A study examining the dosimetric parameters and the risk of radiation-induced fractures determined that fracture rates is reduced when the volume of bone receiving ≥40 Gy is less and when the maximum dose to the bone is less than 59 Gy [26]. As post-operative RT requires larger dose (>60 Gy) and often field sizes than pre-operative RT, the above studies suggest that post-operative RT probably incurs higher rates of serious chronic RT-related toxicities with detrimental functional consequences.

The primary endpoint of the recently published RTOG 0630 phase II trial was the rate of grade ≥2 radiation-related toxicities (subcutaneous tissue fibrosis, joint stiffness, or edema) at 2 years (±3 months) from the start of RT [19••]. The chronic toxicities in patients treated with pre-operative RT with modern techniques such as 3DCRT (25 %) and IMRT (75 %) were analyzed and compared to the results from the NCIC SR2 study. At 2-year follow-up, 5.3, 3.5, and 5.5 % of the patients had grade ≥2 subcutaneous fibrosis, joint stiffness, and edema, respectively [19••]. Overall, 10.5 % of the patients in the RTOG 0630 trial developed grade ≥2 toxicities, which was significantly ($p=0.0005$) less than the pre-operative arm of the NCIC SR2, in which 37 % of the patients developed grade ≥2 chronic toxicities at 2-year follow-up [19••, 22]. Similarly, the PMH phase II trial also showed that IG-IMRT reduced the amount of chronic radiation-induced toxicities: 9.3 % subcutaneous fibrosis, 5.6 % joint stiffness, 11.1 % edema, and no fractures [24••]. Functional assessment with TESS and MSTS showed high functional levels. The above studies suggest that the use of modern radiotherapy reduced the chronic toxicities by reducing the volume of normal tissues irradiated at high doses. It is also encouraging to note that the rates of local recurrences in the RTOG 0630 (5/74–6.8 % at a median follow-up of 43.2 months) and the PMH (4/59 pts–6.8 % at a median follow-up of 49 months) trials were equally low [19••, 24••]. However, long-term follow-up on their local control is still needed to validate and ensure that the decreased volumes does not lead to recurrences in the irradiation spared areas, which so far neither trials have observed.

Retroperitoneal sarcoma

In contrast to STS of the extremities, local control for retroperitoneal soft tissue sarcomas (RPS) is about 50–60 % and is in competition with distant metastasis as the primary cause of patient death [27, 28•]. To improve the control of the disease locally, the use of radiotherapy had been explored in several institutions with some describing improved local control with pre-operative RT [29–32] while others observing no benefit for pre-operative RT [33–37]. Two recent prospective trials [28•, 38•, 39] suggested that the local recurrence rates of RPS

is reduced when pre-operative RT is added to surgery. These data need to be validated and thus, surgical resection remains the main treatment for these patients. The American College of Surgeons Oncology Group phase III trial (ACOSOG Z9031) was launched to determine the effect of adding pre-operative RT to RPS treatment, but unfortunately closed prematurely due to lack of patient accrual [39]. However, the EORTC is accruing patients into the STRASS phase III (EORTC 62092–22092; clinicaltrials.gov NCT01344018) trial that randomizes patients to pre-operative RT plus surgery vs. surgery alone for the primary treatment of RPS.

Pre-operative RT has numerous theoretical advantages such as displacement of radiosensitive organs away from treatment fields by the tumor, decreased risk of microscopic seeding during surgical manipulations, increased tumor vascularization, and therefore oxygenation thus increasing radiosensitivity [40]. Furthermore as the tumor is still in place, volume delineation is easier and the GTV can be tracked using IGRT [14]. In addition, a recent publication suggests that pre-operative needle biopsy of RPS did not affect oncological outcomes [41]. The risk of surgical delay from pre-operative RT does not seem to impact the surgical resectability or quality [14]. Post-operative RT is difficult to tolerate as normal radiosensitive organs fill the surgical cavity, which needs to be treated with the full RT dose. In the absence of the STS, IGRT methods cannot be used to target the tumor and reduce RT margins [42]. Furthermore, it is still debated whether local control can be improved with higher doses through brachytherapy boost [38•, class II] or intra-operative RT (IORT) [43]. This might mainly be due to the technical challenge in coverage of large high-risk margins in certain RPS.

Post-operative radiation

Multiple studies have characterized the toxicities from post-operative RT for RPS. The University of Florida published their experience of 40 patients treated with neo-adjuvant ($n=15$) and adjuvant ($n=25$) radiation using 3DCRT. Twelve out of the 15 (80 %) patients who received post-operative RT developed acute grade 1–2 enteritis compared to nine of the 25 patients (36 %) who received pre-operative RT ($p=0.0098$) [44]. In addition, there were significantly more peri-operative complications requiring hospitalization in the group that received post-operative RT as compared to those receiving neo-adjuvant RT ($p=0.0412$).

Pezner et al. reported their results from 33 patients who received up to 60 Gy of post-operative RT with or without IORT. Acute grade 1 to 2 GI toxicities were reported in 79 % of patients and approximately 10 % (three of 33) developed grade 3 to 4 acute GI toxicities [45]. Severe late side effects occurred in five patients (15 %) (one G3 and four G4 GI toxicities). Gilbeau et al. described their experience with 45 patients treated with post-operative RT (40–60 Gy) with or without IORT. Grade 3, 4, and 5(death) GI toxicities occurred in 1, 2, and 2 patients, respectively [46]. Eight patients developed peripheral neuropathy (five of whom received IORT). In a study by Alektiar et al., 32 patients were prospectively treated with high-dose-rate IORT to a dose of 12–15 Gy. Further post-operative RT was delivered to 78 % of patients to a dose of 45–50.4 Gy [47]. Acute complications were seen in 13 patients; 28 % developed grade 3–5 GI toxicities (22 % G3, 6 % G5), 3 % had grade 3 hydronephrosis, 3 % had

grade 3 wound complications, and 6 % had grade 2 neuropathies. A previous randomized trial that compared IORT (20 Gy) plus post-operative RT (35–40 Gy) to post-operative "high-dose" RT (50–55 Gy) demonstrated an overall mortality rate of 9 %, with significantly more acute (12 vs. one patient) and chronic (10 vs. two patients) GI toxicities in patients receiving "high-dose" RT only vs. those who received RT and IORT. However, moderate and severe neuropathy was significantly more frequent in the IORT group (seven vs. 0 patients) [48]. Finally, although uncommon, duodenocaval fistula (DCF) is a late and fatal (40 % mortality) toxicity associated with RPS treatments in combination with irradiation. A review by Perera et al. suggested that nine of the 11 reported RPS patients that developed DCF were treated with surgery and post-operative RT [49].

Pre-operative radiation

Comparatively, Ballo et al. reported their experience, from 83 patients, 50 received a median dose of 50 Gy pre-operative RT and 33 received a median dose of 55 Gy of post-operative RT. Eighteen of these 83 patients also receiving 10–15 Gy of IORT. All patients (n=5) who developed clinically significant radiation-related toxicities were from the post-operative RT cohort; thus, their 5-year complication rate from post-operative RT is 23 % [43]. Similarly, Gieschen et al. described a cohort of 37 patients treated with pre-operative RT (45–50 Gy) with 20 of these patients also receiving IORT (10–20 Gy). Four (11 %) patients developed clinically important late complications which all occurred in patients who received IORT. These complications included neuropathy (3/4), hydronephrosis (3/4), vaginal fistula (1/4), ureteroarterial fistula (1/4), and small bowel obstruction (2/4) [50].

When pre-operative RT alone is given, this regimen seems to be better tolerated. Using the American College of Surgeon database (ACS NSQIP), Bartlett et al. found no increased patient morbidity and mortality within 30 days of surgery following pre-operative RT in comparison to those who only had surgery for RPS [51]. In a review from Australia, Alford et al. found minimal acute toxicities among their 24 patients treated with pre-operative RT (45–50.4 Gy). One patient experienced acute grade 3 bowel obstruction [52] and five patients developed late peripheral neuropathies.

To further reduce toxicities, Bossi et al. treated 18 patients with pre-operative IMRT targeting only the posterior abdominal wall, which was deemed at higher risk of local relapse [53]. Two patients experienced acute grade 3 GI toxicity (long-term toxicities were not described). Yoon et al. reported their experience in 28 patients who received a mixture of radiation treatments that may consist of one or more of pre-operative IMRT, pre-op proton beam RT, post-operative IMRT, and IORT [54]. Late severe RT-related complications occurred in four patients (14 %), three of which received doses greater than 50.4 Gy via IMRT or proton beam RT. A new approach was recently reported in a prospective phase II trial to treat RPS whereby the entire tumor was treated to 45 Gy and the high-risk region received a boost dose to 57.5 Gy using an IMRT-simultaneously integrated boost (IMRT-SIB) technique [55]. More data are expected from an ongoing multi-center phase I/II dose escalation trial of pre-operative RT for RPS using SIB to high-risk volumes (T. DeLaney at Massachusetts General Hospital).

Toxicities from radiotherapy combined with systemic agents

Chemotherapy

The role of adjuvant chemotherapy in adult with resectable STS is controversial and not the subject of the current review [56, 57]. However, the use of neo-adjuvant chemotherapy in combination with RT has been proposed for patients with large high-grade STS [58, 59]. DeLaney et al. reported the long-term results of 48 patients treated with interdigitated neo-adjuvant chemo-radiation therapy [58]. Patients were to receive 6 cycles (three neo-adjuvant and three adjuvant) of MAID chemotherapy (mesna, adriamycin, ifosfamid, and dacarbazine). Patients received RT of 44 Gy/22 fractions in split course of 22 Gy/11 fractions between cycles 1 and 2 and cycles 3 and 4, and surgery was planned at day 80 after the beginning of chemotherapy. Acute wound complications occurred in 12.5 % of patients with leg lesion and in 36 % of patients with buttock/thigh lesions. Late complications included one patient developing fatal myelodysplasia and a 4 % bone fracture rate. Late fibrosis and motor functions were not collected from the patients.

The RTOG 9514 was a phase II trial that was modeled after the above trial for the neo-adjuvant chemo-radiation therapy of high-grade STS [59]. Sixty-six patients were enrolled. There were three deaths, of which two were secondary to acute myelogenous leukemia and one leukopenic sepsis. Grade 4 toxicity occurred in 83 % of the patients, of whom 78 and 19 % had hematological and non-hematological grade 4 toxicities, respectively. Severe wound complications occurred in 11 % of patients, and two amputations were related to the treatment effects.

Targeted therapy

More recently, studies and trials have been developed to examine the efficacy and safety of combining RT with targeted agents. Of the molecular agents, the most targeted agents are anti-angiogenics [60] such as sorafenib, sunitinib, pazopanib, and bevacizumab (NCT00753727, NCT01498835, NCT01543802, NCT01985295, and NCT02180867).

Meyer et al. investigated the combination of 400 mg of daily sorafenib, epirubicin/ifosfamide and pre-operative RT (28 Gy). Grade 3–4 hematological toxicities developed in 15 of the 16 patients, and 38 % of the patients had wound complications [61]. Comparatively, when chemotherapy was omitted and sorafenib was combined with pre-operative RT (50 Gy), grade 3–4 toxicities were reduced to 50 %, and 12.5 % of the patients developed wound complications [62]. The Children's Oncology Group and the NRG Oncology group opened, in July 2014, a joint phase II/III trial to determine the additional benefit of pazopanib to neo-adjuvant RT or chemo-RT in patients with STS of all ages. The Pazopanib Neoadjuvant Trial in Non-Rhabdomyosarcoma Soft Tissue Sarcomas (PAZNTIS) trial (NCT02180867) will measure the pathologic response and event-free survival as its primary endpoints. In the absence of large prospective randomized trials investigating the added toxicities of molecular agents, PAZNTIS will also serve to profile the

adverse events of the treatment regimens when given pre-operatively for the treatment of STS.

Future directions

Radiotherapy is an effective adjunctive treatment that complements conservative STS treatments however, not without its potential side effects. Advancements in radiotherapy and imaging techniques led to methods that reduce the rate of these toxicities. Further advancements in radiotherapy are now aimed at combining IG-IMRT techniques with systemic agents to increase the efficacy of radiotherapy with likely higher rates of serious toxicities. Current research in adaptive radiotherapy will allow for day-to-day field changes to account for volumetric increase or decrease of the target over the course of radiotherapy. MR-guided radiotherapy will further enhance the visualization and accuracy of radiotherapy and when combined with adaptive radiotherapy could perhaps lead to further reduction of radiotherapy field volumes and dose based on MR bio-imaging markers of response. Future improvements in our understanding in the biology of STS will guide the evolution of radiotherapy in STS to yield more efficacious treatments with less side effects than the current techniques and regimens.

Compliance with Ethics Guidelines

Conflict of Interest

Nancy El-Bared, Philip Wong, and 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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•• Of major importance

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