



## REVIEW

# The role of radiotherapy in the management of localized soft tissue sarcomas

Siaw Sze Tiong<sup>1</sup>, Colleen Dickie<sup>1</sup>, Rick L. Haas<sup>2</sup>, Brian O'Sullivan<sup>1</sup>

<sup>1</sup>Department of Radiation Oncology, Princess Margaret Cancer Center, University of Toronto, Toronto M5G 2M9, ON, Canada; <sup>2</sup>Department of Radiotherapy, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam 1066, CX, The Netherlands

### ABSTRACT

The combination of radiotherapy (RT) and function-preserving surgery is the most usual contemporary approach in the management of soft tissue sarcomas (STS). Pre- and postoperative RT result in similar local control rates, as shown by a landmark trial in extremity STS. In this review, the role of RT in the management of extremity STS will be discussed, but STS in other sites, including retroperitoneal STS, will also be addressed. The focus will consider various aspects of RT including strategies to reduce the volume of tissue being irradiated, dose, scheduling, and the possible of omission of RT in selected cases. Finally, technology advances through the use of intensity-modulated radiotherapy (IMRT), image-guided IMRT, intraoperative radiotherapy (IORT) and particle therapy will also be discussed.

### KEYWORDS

Sarcoma; radiotherapy; retroperitoneal sarcoma; surgery; extremity sarcoma

## Introduction

The management of soft tissue sarcomas (STSs) has evolved in recent decades towards combined modality treatment [i.e. surgery and radiotherapy (RT)], to permit optimum structure and function preservation. Local control (LC) rates with surgery and RT exceed 90% for extremities, but are lower (approximately 60%) for retroperitoneal sarcomas (RPS), and also remain challenging in other sites where anatomic constraints predominate that decision-making. This may be especially so in areas such as the head and neck where aesthetic concerns also influence management beyond tumor control and anatomic function. The management of sarcoma continues to evolve with potential integration of systemic treatment into the treatment paradigm, including chemotherapy and/or targeted agents, which is outside the scope of this review. This paper will discuss the rationale for the use of RT in the management of localized STSs, common types of RT including planning and delivery considerations, the timing and dose of RT in the adjuvant setting, and how RT target volumes are defined.

## The rationale for the use of RT

Surgery is the mainstay of treatment for resectable STSs. Surgery alone may be an option which can achieve wide margins (e.g. traditionally 2 cm, as described by Karakousis<sup>1</sup>), without sacrificing critical structures (bones, nerves, or vessels)<sup>1</sup>. Most often, surgery alone is advisable for small (< 5 cm) superficial and/or low-grade sarcomas, while observing certain caveats discussed later (see “Can radiotherapy be avoided” section). If a wide resection is not possible, level 1 evidence supports the combination of surgery with RT. The original premise for limb preservation is underpinned by the landmark study at the US National Cancer Institute (NCI) conducted by Rosenberg et al.<sup>2</sup>. Patients were randomized to receive either amputation ( $n=16$ ) or limb-sparing surgery with adjuvant RT ( $n=27$ ). In the Rosenberg study, both groups also received postoperative chemotherapy with doxorubicin, cyclophosphamide, and high-dose methotrexate. There was no apparent statistically significant difference in overall survival or in local recurrence between the arms (100% LC for surgery vs. 85% for the surgery plus radiation group,  $P=0.06$ ). Two subsequent prospective randomized trials<sup>3,4</sup> have shown significant improvement in LC with the addition of adjuvant RT to limb-sparing surgery. In the first study, Yang et al.<sup>4</sup>, also at the US NCI, randomized 141 patients (91 with high-grade tumors, 50 with low-grade tumors) to receive adjuvant external beam

Correspondence to: Brian O'Sullivan

E-mail: brian.osullivan@rmp.webmail.uhn.on.ca

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radiotherapy (EBRT) or not. Patients with high-grade tumors also received chemotherapy. RT improved LC for both high-grade sarcomas (10-year LC rates of 78% vs. 100%,  $P=0.03$ ), and there was a non-statistical improvement in low-grade sarcomas (10-year LC rates 68% vs. 95%,  $P=0.067$ ). This benefit was confirmed in a recent update, with a median follow-up of 17.9 years<sup>5</sup>. In the other trial, Pisters et al.<sup>3</sup> evaluated postoperative brachytherapy (BRT) in 164 patients randomized to receive BRT versus surgery alone, and also demonstrated a benefit in LC in the BRT group (81% vs. 67%,  $P=0.03$ ) for high-grade lesions. The impact of adjuvant RT using brachytherapy in low-grade lesions remains controversial and EBRT may represent a preferred option in patients whose tumors require adjuvant RT (see “BRT” section).

## Common types of RT

Various types of RT are available for clinical application and require careful consideration of issues surrounding the choice of target volumes, organs at risk, and planning technique. EBRT is widely used, but other modalities exist including brachytherapy, intraoperative radiation therapy (IORT) and hadron treatment (i.e., protons and carbon ions).

### External beam intensity modulated radiotherapy (IMRT)

IMRT offers superior dose conformity, and improvement of the therapeutic ratio by reducing dose to normal structures

while maintaining local tumor control<sup>6</sup>. The original concern with the use of IMRT was whether more conformal treatment volumes would result in an increase in local recurrence rates. Several retrospective reviews have validated the safety of IMRT and have demonstrated excellent LC<sup>6,7</sup> with minimal dose to critical structures. For example, Alektiar et al.<sup>7</sup> showed a 5-year actuarial LC rate of 94%, which compared favourably with historical controls (5-year LC 82%). In addition, IMRT demonstrated improved LC in comparison to brachytherapy (5-year local control for IMRT 92% vs. 81% for BRT,  $P=0.04$ )<sup>8</sup>.

The role of preoperative image-guided radiotherapy (IGRT) using IMRT or conformal RT to achieve reduction of RT related morbidities was investigated in two recently completed prospective phase 2 trials, one from Princess Margaret Hospital (PMH) (NCT00188175) and the other from the Radiation Therapy Oncology Group (RTOG 0630: NCT00589121)<sup>9,10</sup>. See **Table 1**<sup>9,10</sup> for the comparison of certain aspects of both trials. Acute wound healing complication rates were reduced for lower extremity sarcomas using image guided-IMRT in the PMH trial (30.5%) in comparison to the Canadian Sarcoma Group NCIC CTG SR2 trial<sup>12</sup> that used conventional 2D and 3D RT (43%) and is discussed later (see “Timing and dose considerations for the application of adjuvant RT” section). Similarly the IGRT RTOG 0630 trial reported a significant reduction of late toxicities in comparison to the NCIC-SR2 trial (10.5% vs. 37% in SR2). The reduction in RT related toxicities seen in both trials could be attributed to the purposeful reduction of the clinical target volume (CTV) defined in the RTOG trial (longitudinal margin of 3cm from

**Table 1** Summary of the details of RTOG 0630 and PMH-IMRT trial<sup>9,10</sup>

Item	RTOG 0630	PMH-IMRT-LE-STs
Technique	3D or IMRT	IMRT alone
Anatomic site	Upper or lower extremity	Lower extremity
Chemotherapy	Cohort A: (closed Jan 2010)-induction chemotherapy (50 Gy)-concurrent chemotherapy (44 Gy)	No chemotherapy
Image guidance	2D or 3D daily image guidance	3D daily online cone-beam CT
Post-op boost (+margins)	External beam radiotherapy or brachytherapy (LDR, HDR, or IORT)	No postoperative boost
Primary end-point	Reduction of late morbidity at 2 years by RTOG/EORTC criteria (> grade 2 lymphedema, subcutaneous fibrosis, joint stiffness)	Reduction of wound complications by the SR2 criteria at 120 days
Secondary end-points	Similar between both studies	Similar between both studies
Target definitions	CTV high grade: 3 cm longitudinally; 1.5 cm axially	CTV 4 cm longitudinally; 1.5 cm axially. “Flap” is contoured as a region of interest.

the gross tumor for high-grade lesions, compared to 2 cm for low grade lesions *vs.* 4cm longitudinal margins as originally used in the SR2 trial) or to the highly conformal targeted RT approach used in both the PMH and RTOG studies. IMRT may also have the potential to reduce the risk of bone fractures. Dickie et al.<sup>13</sup> reported an algorithm of dose constraints on bone with the use of IMRT. This will be described in more detail later (see “Risk of radiotherapy dose on bone fracture” section). Longer follow-up will confirm if the risk of fracture can be reduced using bone avoidance objectives for RT planning.

## BRT

BRT theoretically offers several potential advantages over EBRT. It permits dose intensification to target volumes while limiting dose to normal tissues due to the inherent rapid dose fall-off properties. It also has a shorter overall treatment time in comparison to conventional EBRT, thus limiting tumor cell repopulation. As mentioned earlier, Pisters and colleagues<sup>3</sup> demonstrated, in a randomized trial, that adjuvant BRT provided superior local disease control compared with surgery alone, (5-year actuarial LC rate of 81% in the BRT group *vs.* 67% in the surgery alone group,  $P=0.03$ ). This benefit was limited to high-grade tumors and low grade lesions requiring adjuvant RT may be preferably treated with EBRT. Furthermore, BRT may be less ideal for upper extremity lesions or more proximal limb regions, where the implant geometry is suboptimal<sup>14</sup>.

Most published work on BRT utilizes low dose rate (LDR) techniques. The utility of LDR BRT has also been investigated in deep cavity sarcomas, *i.e.*, RPS. Fairweather et al.<sup>15</sup> reported on the safety and efficacy for permanent Iodine-125 mesh BRT after resection of deep cavity (retroperitoneum, thoracic, abdominal, pelvic and deep truncal) STSs. In their study, the majority of patients (74%) also received EBRT. In-field recurrences were observed in 19.5% ( $n=9$ ). Complications have been observed in 22 patients; and half of them experienced grade III/IV complications requiring percutaneous intervention or reoperation. Therefore, the authors have concluded that although mesh BRT appears effective in reducing local recurrences, it should be utilized with caution.

Currently, there are no large series evaluating high dose rate BRT for STS, nor has it been compared to LDR.

Several contraindications to BRT as a sole treatment modality include<sup>16</sup>:

i) the implant geometry does not allow for adequate CTV coverage;

- ii) the close proximity of critical structures, such as neurovascular structures to target structures;
- iii) positive surgical margins;
- iv) skin involvement by tumor.

## Other techniques

Various other modalities are evolving, but a detailed review of each is beyond the scope of this paper. In brief, the use of particle therapy (*i.e.*, hadrons) has theoretical advantages due to their physical and radiobiological properties. Particle therapy is generally restricted to bone tumors, pediatric sarcomas, and skull-base and spinal lesions<sup>17</sup> due to their ability to restrict dose maximally to critical anatomy or vulnerable developing tissues. For example, DeLaney et al.<sup>18</sup> reported good LC (81% at 5 years; 74% at 8 years) with high dose photon/proton RT in the management of spine chordomas, chondrosarcomas and other sarcomas with acceptable late morbidity rates.

IORT or intraoperative electron radiotherapy (IOERT) allows delivery of radiation to a target volume during surgery. IORT/IOERT has typically been combined with fractionated EBRT in the studies evaluating its efficacy, making it difficult to evaluate the true contribution. For example, in a prospective phase 2 trial of high grade extremity lesions conducted by Roeder et al.<sup>19</sup>, excellent LC and overall survival (97% and 79%) was shown in subgroup analysis. However, further studies are required to evaluate its superiority to EBRT since these outcomes seem relatively similar to those of IMRT alone, and patient selection may also be relevant for optimal delivery of IORT due to the need to achieve optimal implant geometry. Additionally, the use of IORT has been applied in the management of RPS. Long-term results of IOERT (10-20 Gy) after preoperative EBRT (median dose 45 Gy) and gross total resection for RPS were reported for a small subgroup ( $n=16$ ). The LC rate was 83% in the IOERT group *vs.* 61% with no IOERT<sup>20</sup>. However, it is also difficult to evaluate the relative efficacy of IORT in this setting due to its usual combination with preoperative RT; randomized trials would be necessary to evaluate the relative contribution of each modality. Furthermore, such findings need to be prospectively validated in larger series if trials are not available. A more detailed discussion of adjuvant RT in retroperitoneal sarcoma is provided below (see “RPS” section).

## Timing and dose considerations for the application of adjuvant RT

The Canadian Sarcoma Group NCIC SR2 trial evaluated the

difference in late toxicities after preoperative *vs.* postoperative RT in extremity STS<sup>21</sup>. Long-term outcomes showed lower rates of late toxicities in the preoperative RT arm than in the postoperative arm. Largely this relates to the lower doses and smaller volumes used in the preoperative RT, with the former predicated on negative resection margins. The lower RT dose (50 Gy) evolved from almost simultaneous observations at 3 institutions (MD Anderson Cancer Centre, PMH and Massachusetts General Hospital)<sup>22-24</sup> that demonstrated that a postoperative boost was unnecessary in the presence of clear resection margins, which was evident in approximately 85% of cases in both arms of the SR-2 trial<sup>12</sup>. Fibrosis (> grade 2) was higher (31.5% *vs.* 48.2% in the postoperative group,  $P=0.07$ ), as well as edema (23.2% *vs.* 15.5%) and joint stiffness (23.2% *vs.* 17.8%) in the postoperative cohort. These late effects were associated with lower limb function ratings based on the Toronto Extremity Salvage Score and the Musculoskeletal Tumor Society Rating Scale. From the SR2 trial<sup>21</sup>, a larger RT field size (treatment volume) was associated with higher fibrosis rates ( $P=0.002$ ), joint stiffness ( $P=0.006$ ), and marginally predicted for edema ( $P=0.06$ ). Although late effects were more apparent in the postoperative RT setting, acute wound healing complications were twice as common in the preoperative RT group, in particular in the lower extremity (43% preoperative RT *vs.* 21% postoperative RT;  $P=0.01$ ). Notably, a potential mitigating strategy to avoid the higher fibrosis and other tissue effects in postoperative RT may also be feasible based on reports of dose reduction in margin negative cases<sup>25,26</sup> and is currently being explored prospectively in a clinical trial, as mentioned later.

In contrast to the prospective SR2 randomized trial, two retrospective studies also inform this topic. Moore et al.<sup>27</sup> also reported higher wound complication rates for the proximal lower extremity location. In particular, the adductor compartment may be the most predisposed site for major wound complications due to surgical disruption of the lymphatic drainage system, heightening the risk of infection. At six weeks after surgery, postoperative RT patients had better functional outcomes, though this difference diminished over time, most likely due to the resolution of wound complications. Diabetes, tumor size >10 cm, tumor proximity to skin surface <3 mm, and use of vascularized flap or split thickness skin graft (STSG) closure were found to be significant independent predictors of major wound complications in a multivariate analysis by Baldini et al.<sup>28</sup>. The authors also found increased wound complications in lower extremity tumors compared with upper extremity

tumors (40% *vs.* 24%, respectively) although this was not a statistically significant finding due to a small number of events.

There was no difference in LC, progression free survival or overall survival between the 2 groups in the NCIC SR2 trial, although the study was not powered to evaluate these end points. Others have suggested a survival benefit for high grade sarcomas may result from preoperative RT using administrative data compiled within the SEER registry<sup>28</sup>. In general, the increase in wound healing complications seen with preoperative RT are transient and manageable, offering potential advantages for this approach over postoperative RT where the risk of late effects and the associated reduction in limb function may persist and be irreparable, *i.e.*, fibrosis and stiffness and risk of bone fracture, if conventional postoperative higher doses are used in all cases. If the preoperative RT approach is chosen, it also appears that potential wound complications may be minimized if definitive surgery is performed four to five weeks after RT completion<sup>30</sup>. See **Table 2** for a summary of the differences between preoperative and postoperative RT.

Another evolution in management to be considered after preoperative RT is whether the additional RT boost is needed in the presence of positive surgical margins, a concept that was introduced previously for negative margin cases (see earlier discussion in this section). Of note, not all positive margins confer equal risks to patients<sup>31</sup>. Nonetheless, the value of adding a RT boost after surgery has been questioned in two retrospective reviews<sup>32,33</sup>, both of which showed high control rates and no significant advantage to a boost in enhancing control. Therefore, a postoperative boost following preoperative RT and surgery with positive margins is controversial, and the benefits should be weighed against the risk of late RT morbidities associated with higher radiation doses, *i.e.*, radiation induced fractures and fibrosis. For these reasons, a PMH/Mount Sinai Hospital (Toronto, Canada) prospective phase 3 trial “Preoperative *vs.* postoperative IMRT for extremity/truncal STS” (NCT02565498) that employs equivalent doses (50 Gy when resection margins are clear) in both arms has commenced accrual, and aims to address controversies surrounding tailoring total RT doses to the quality of the surgical margin<sup>34</sup>.

Preoperative RT may also be appealing for the management of RPS, which will be described in a separate section later in this paper (see “RPS” section).

### Can RT be avoided

There may be a select group where RT can be omitted after

**Table 2** Key differences in preoperative and postoperative RT

Item	Preoperative RT	Postoperative RT
Dose	Lower dose (50 Gy)	Higher dose (60-66 Gy)
Treatment volume	Smaller treatment volume	Larger treatment volume
Rate of wound complications	More acute wound complications (35%)	Wound complications up to 17%
Features	Offers the possibility to perform translational research on the clinicopathological behaviour of individual sarcoma subtypes to RT	Increase late RT toxicities: increased fibrosis increased edema increased joint stiffness  Rarely, may provide the option of omission of RT when adequate margins are achieved. Ideally this should be discussed in a multidisciplinary meeting

complete surgical excision<sup>1,35-38</sup>. Indirectly, this was discussed earlier in considering indications for adjuvant RT (see “The rationale for the use of RT” section). RT omission may be considered in the following settings: i) “contained” and/or superficial lesions, especially those of low-grade malignancy; ii) pathologically assessed surgical margins greater than 1 cm. A recent large retrospective series<sup>39</sup> which included 684 patients with primary, nonmetastatic extremity STS showed in multivariate analysis that the predictors of local recurrence are positive/close margins, high grade, age > 50, size > 5 cm, and unfavourable histology<sup>40</sup>. This retrospective review found that the LC rate without RT was 53% at 5 years when there were unfavorable features described above. The rationale for omitting RT may be most applicable for young patients in order to mitigate potential late RT toxicities. Single modality treatment can also preserve excellent function.

However, the omission of RT must be carefully considered by an expert multidisciplinary team because precise criteria (such as uncontaminated surgical bed, intact fascia, tumor containment, proper principles of biopsy, etc.) for selection may be elusive in individual cases. Further studies are required to evaluate which subgroup may benefit from surgery alone. A prospective randomized trial (trial number: NCT00870701) by the French Sarcoma Group investigating the outcomes following observation versus post-surgery RT after complete excision in soft tissue extremity sarcoma is currently ongoing but results are not anticipated before 2021.

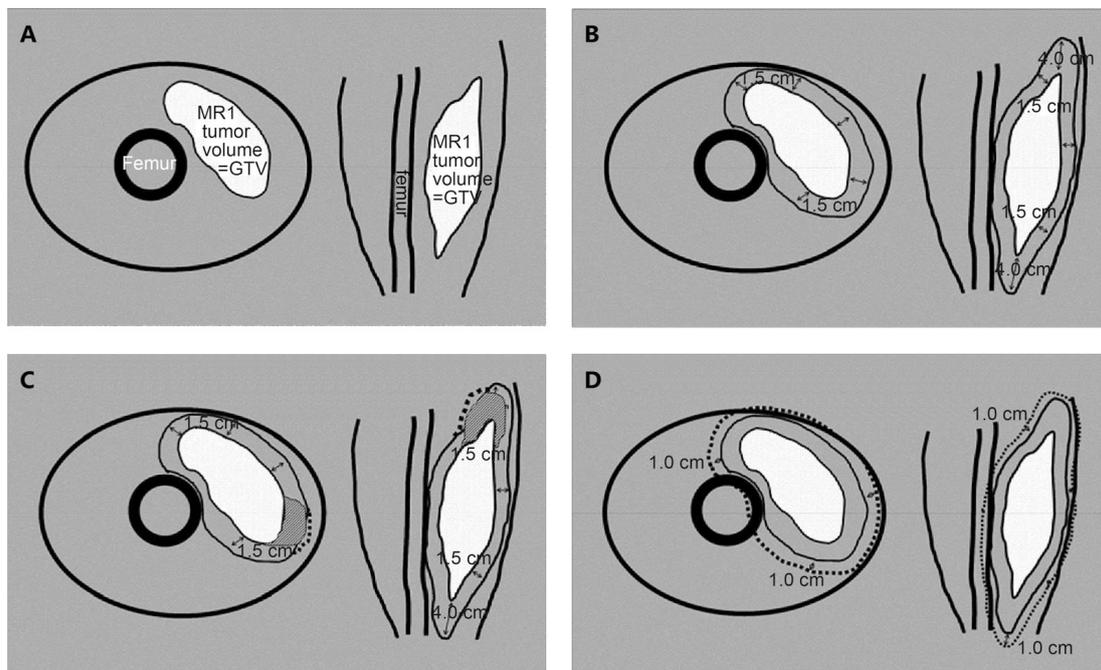
## RT target and dose

In the preoperative setting, the gross tumor volume (GTV) is best visualized with gadolinium-enhanced T1-weighted magnetic resonance imaging<sup>1</sup>. Ideally MRI, registered in the treatment position and in the individual immobilization device, fused with the RT planning CT provides optimal

contouring information. However, cognitive fusion is often practically applied (computer screens side by side), as there are issues with reproducibility of patient setup position and challenging image registration that may negate any benefit of deformable image registration. At the Princess Margaret Cancer Center, Toronto and many other institutions, the CTV encompasses areas at risk of microscopic disease, and is achieved by adding 1.5cm radially and 4cm longitudinally around the GTV, accounting for anatomical boundaries to tumor incursion such as bone, fascia, and joints, unless involved. The CTV should also include peri-tumoral edematous tissues that can harbor satellite tumor cells<sup>41-43</sup> (visualized on T2-weighted images) in all dimensions with a 1-2 cm margin. The planning target volume (PTV) expansion is dependent upon institutional policies and procedures and should take patient positional stability / positioning into account. Typically, a 0.5 cm to 1.5 cm isotropic expansion on CTV is applied (**Figure 1**). The preoperative RT dose is 50 Gy.

In the postoperative setting, traditionally a two-phase technique is employed, treating to a total dose of 60 to 66 Gy. The first phase would receive a dose of 45-50.4 Gy (1.8-2 Gy per daily fraction) to the elective CTV, followed by Phase 2 that would receive 10-16 Gy to a smaller boost volume encompassing the tumor bed and high-risk area for microscopic involvement. Such cases may also be managed with single-phase treatments where both volumes are simultaneously treated over the full duration. As a consequence, the elective region will require a somewhat higher total dose fractionated over the full 6.5-week course due to the smaller dose per fraction employed (e.g., 56 Gy in 33 fractions for elective CTV, and 66 Gy in 33 fractions to the boost volume using a simultaneously integrated boost technique).

Diagnostic MRI may be fused with CT images to assist in the delineation of the high-risk region by “re-constructing”



**Figure 1** Target definitions for preoperative RT in a case without peritumoral edema (A and B) and with peritumoral edema (C and D). T1-weighted, post-gadolinium MRI scan is fused with planning CT scan to delineate tumor. The GTV does not include peritumoral edema, which is generally best visualized on T2-weighted MRI scan. (A) 1.5 cm radial expansion from GTV, but limited to surfaces of fascia and bones, unless invaded. The longitudinal expansion was 4 cm. (B) In sarcoma case with peritumoral edema, the GTV will expand 1.5 cm radially, and limited at surfaces of fascia and bones unless invaded. The longitudinal expansion was 4 cm. The CTV has been manually edited (see dashed line) to include the edema zone in both transverse and coronal planes. The striped zone indicates peritumoral edema. (C) Planning target volume (PTV) is generated by a 1 cm expansion from CTV in all directions, although PTV is dependent on local institutional protocols, as described in text. Reproduced with permission from Ref. 43. Copyright 2012 Elsevier.

the preoperative GTV on the planning CT scan. Other clinical information such as clinical photographs (where applicable), pathology and operative notes should also be reviewed. Image registration, and postoperative anatomical changes need to be taken into account. The CTV should include the preoperative GTV with a margin to account for microscopic disease. Biopsy sites, drain sites and surgical scars should be included, especially in high risk, large and high-grade tumors. CTV can be limited to bone, joints or fasciae, unless these structures are involved. The elective CTV should not include skin (See **Figure 2** for postoperative target volume delineation).

CTV66 should encompass the entire “postoperative” GTV (that was reconstructed based on the clinical information that is available), and immediate area of surgical disruption and 1 to 2 cm margin in the longitudinal plane, and 1.5 cm margin in the transverse section. The PTV expansion is institutional-dependent, typically with a 0.5 cm to 1.5 cm around the CTV (See **Figure 3** for postoperative RT boost

definition).

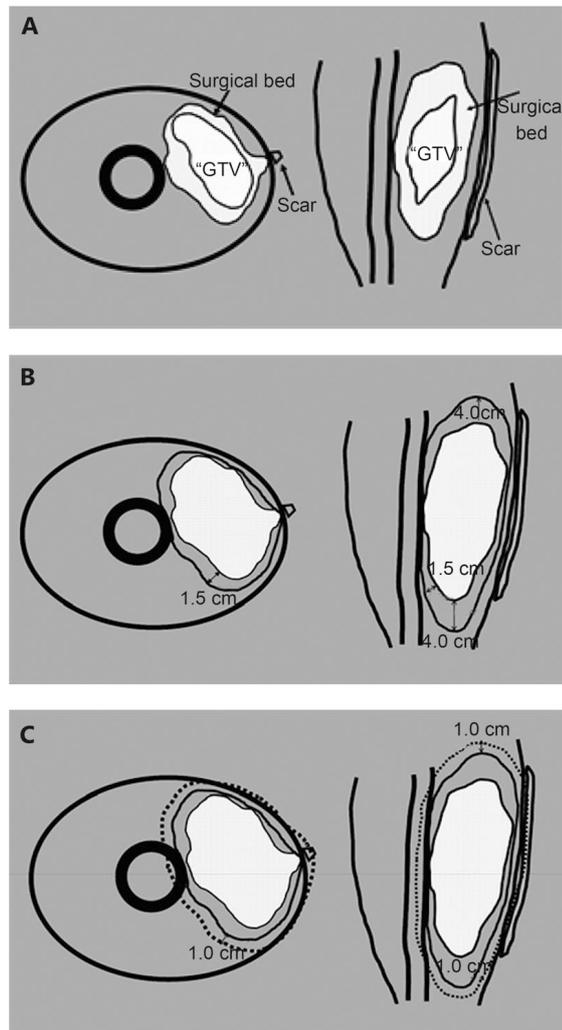
CTV56 should include all areas at risk of microscopic spread. It should include reconstructed GTV with a 4 cm expansion longitudinally, and 1.5 cm radially. Anatomical boundaries should be excluded, such as bone or other anatomic barriers to disease spread (e.g., fasciae). Surgically disturbed tissues and any scars, or drain sites are included with a 1 to 2 cm margin expansion. PTV56 is 0.5 cm to 1.5 cm expansion around CTV56, and is dependent on the institution protocol.

A prospective phase 3, multicenter, randomized controlled trial (VORTEX NCT00423618)<sup>44</sup> evaluated the impact of CTV margin reduction in the postoperative setting comparing conventional margins with 2 cm on GTV, and has completed accrual but results of the trial are not yet available.

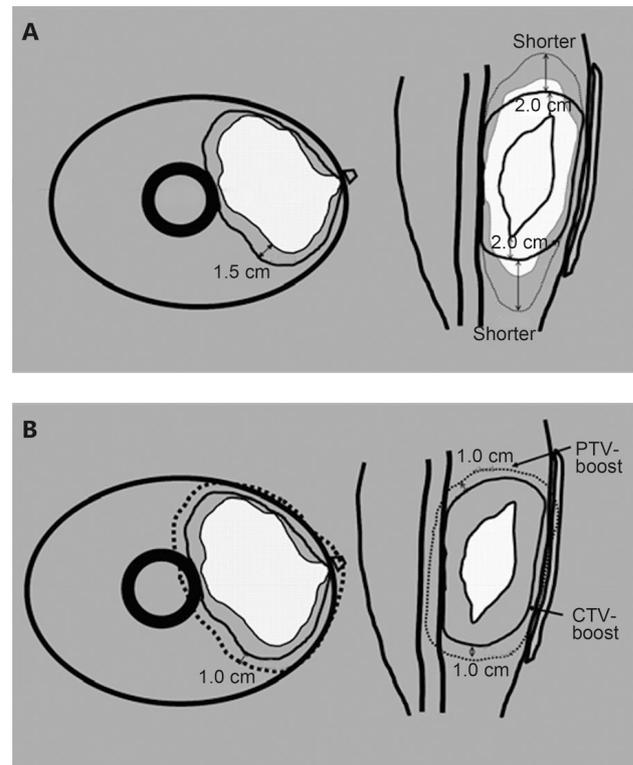
### Risk of RT dose on bone fracture

Bone fracture is a serious late complication of combined

modality treatment. Radiation-induced fractures are those that occur within the previous RT field, with minimal or no trauma<sup>45</sup>. Fractures tend to occur more commonly in the weight bearing bones of the lower extremities (2%-10%), and



**Figure 2** Target definitions for postoperative RT. (A) Both original sarcoma extensions GTV and the surrounding surgical bed is visualized. (B) Margins for postoperative RT elective target (CTV56) are demonstrated; 1.5 cm in transverse plane, accounting for surfaces of bones and fascia, unless there was tumor involvement at surgery. Elective CTV should remain within the skin. Furthermore, the elective CTV is longer than the marker of the skin scar. If 4 cm expansion of reconstructed surgical volume in longitudinal direction is shorter than surgical scar, the elective CTV should be expanded to include the surgical scar. (C) PTV is generated by 1 cm expansion in all directions, but is dependent on local institutional protocols, as described in text. Reproduced with permission from Ref. 43. Copyright 2012 Elsevier.



**Figure 3** Target definitions for postoperative RT boost. (A) In the longitudinal direction, the elective CTV66 is 2 cm longer on both sides than the reconstructed GTV prior to surgery. (B) The boost PTV is generated by a 1 cm expansion from boost CTV, but PTV expansion is dependent on institutional protocols, as described in text. Reproduced with permission from Ref. 43. Copyright 2012 Elsevier.

the risk may be higher (> 20%) for those with known risk factors<sup>45-47</sup>. A retrospective review reported a crude fracture risk of 6.3%, and reported a higher incidence of fracture in females, in the femoral shaft or the femoral neck, and in patients who received higher doses of radiation 60-66 Gy<sup>48</sup>. Dickie et al.<sup>13</sup> reviewed the relationship between dose and risk and fracture, and found that bone fracture risk could be reduced if the volume of irradiated bone to 40 Gy or greater was < 64%, the mean bone dose was < 37 Gy and the maximum dose along the bone length was < 59 Gy.

## RPS

RPS represent a distinct entity of STSs, and account for 15% of all sarcomas<sup>49,50</sup>. The RT planning is often more complex given that the total prescribed dose is limited by the proximity of critical organs, i.e., small bowel, liver and kidneys. Patients often present with large sized tumors and,

finally, diaphragmatic mobility with patient respiration has to be taken into consideration.

There is no level 1 evidence to support the role of RT in RPS, but local control benefit has been suggested by several retrospective and prospective reviews<sup>17,51-55</sup>. In addition a small randomized trial of archival importance suggested enhanced control but also taught us lessons about adjuvant strategies in this disease<sup>56</sup>. This trial used an IORT boost (20 Gy) to the tumor bed followed by postoperative external beam (35 to 40 Gy); this approach was compared with conventional postoperative RT (50 to 55 Gy). In this study of 35 patients, the incidence of loco-regional recurrence was lower in the experimental treatment arm, but no improvement in survival was demonstrated<sup>56</sup>. The authors also reported differences in the types and distributions of complications between the two trial arms because IORT was associated with a high rate of peripheral neuropathy when large, sometimes overlapping, RT portals were used to cover the sacral plexus region<sup>56</sup>. This interpretation is additionally confounded by the fact that a radiosensitizing agent with additional neurotoxic capability, i.e., misonidazole, was used in all patients receiving IORT, and further complicated by the addition of various chemotherapy agents during the early accrual phase of the trial. In contrast, gastrointestinal complications were more common in the control group, since higher bowel doses can potentially cause adhesion of less mobile bowel loops.

More recently interest has emerged in the use of preoperative RT for several reasons and particularly to protect normal tissues from injury as discussed below. Consensus treatment guidelines for preoperative radiation therapy for RPS have now been published to guide management. The combined modality approach is widely practiced clinically<sup>57</sup> to attempt to achieve optimal LC in a disease that traditionally has demonstrated ominous long-term prognosis with risks of late recurrences.

Multidisciplinary management of RPS is crucial. Preoperative RT is preferred in this situation for several reasons. Firstly, the peritoneal barrier remains intact with no contamination from surgery. RT dose used in the preoperative setting is lower, i.e., 50 Gy or 50.4 Gy *vs.* 60-66 Gy in the postoperative case, given the relative ease of defining and visualizing the tumour. Delivery of a postoperative RT dose of 60-66 Gy is limited by the presence of small bowel and other critical organs, e.g., the kidneys and liver. Preoperatively, the tumor mass serves as a tissue-expander, and displaces small bowel and other critical organs from the radiation volume, a feature that is enhanced by their mobility if prior surgery has not been undertaken. The

putative disadvantages of preoperative RT are the lack of histological sampling, potential delay of definitive surgery and management of positive margins following preoperative RT. In practice, these considerations are largely theoretical since, in reality, the alternative approach of postoperative treatment is generally compromised from a delivery and tolerance standpoint. This results from the larger RT volumes and potentially less mobile bowel loops, for the reasons discussed above.

A recent retrospective review showed that combined modality treatment with preoperative RT is associated with a 5-year LC and overall survival rates of 56% and 57%, respectively, with higher rate of RT related complications if postoperative RT was used<sup>58</sup>. Prospective trials have also demonstrated the safety of preoperative external beam RT for RPS, and favourable LC and overall survival in their long-term follow-up<sup>51,59</sup>.

Roeder et al.<sup>60,61</sup> further reported on toxicity outcomes in their trial that combined preoperative RT and IORT. They have thoughtfully distinguished toxicities according to temporal sequence (acute *vs.* late) and treatment modality. Severe acute radiation related toxicity (Grade 3) was present in 15% of patients, mainly involving haematological and gastrointestinal complications. Severe postoperative complication rates such as bowel/anastomotic leakage, pancreatic fistula/leakage, intra-abdominal bleeding, sepsis and left ventricular dysfunction, were reported at 33% including 2 deaths, but this could equally be related to the subsequent IORT phase<sup>61</sup>. This highlights the limitation of interpreting toxicity data as it is difficult to distinguish toxicities from separate treatment modalities at time of occurrence, and especially retrospectively where toxicities are reported remotely in time.

There is currently no consensus on the role of RT in RPS<sup>62</sup>. The European Organization for Research and Treatment (EORTC) is currently conducting a phase 3 randomized trial (STRASS-62092-22092) to address the question of preoperative RT and surgery *vs.* surgery alone with over 200 patients accrued at this time<sup>63</sup>.

## Conclusions

Surgery remains the primary modality of choice in the management of STSs, with local recurrence following limb-sparing surgery alone in the range of 30%-50% depending on the selection characteristics. RT improves local control up to greater than 90% for extremity sarcoma, and maintains function by negating the need for amputation. These results can be reasonably extrapolated to other sites including the

head and neck, and torso. The role of RT is controversial in the management of RPS, and results from an ongoing multi-institutional trial to validate its role are awaited.

## Conflict of interest statement

No potential conflicts of interest are disclosed.

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