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Systematic review

Preoperative radiotherapy for extremity soft tissue sarcoma; past, present and future perspectives on dose fractionation regimens and combined modality strategies

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ABSTRACT

Introduction: This critical review aims to summarize published data on limb sparing surgery for extremity soft tissue sarcoma in combination with pre-operative radiotherapy (RT). *Methods:* This review is based on peer-reviewed publications using a PubMed search on the MeSH headings "soft tissue sarcoma" AND "preoperative radiotherapy". Titles and abstracts screened for data including "fraction size AND/OR total dose AND/OR overall treatment time", "chemotherapy", "targeted agents AND/OR tyrosine kinase inhibitors", are collated. Reference lists from some articles have been studied to obtain other pertinent articles. Additional abstracts presented at international sarcoma meetings have been included as well as information on relevant clinical trials available at the ClinicalTrials.gov website. *Results:* Data are presented for the conventional regimen of 50–50.4 Gy in 25–28 fractions in 5–6 of weeks preoperative external beam RT with respect to the regimen's local control probability compared to surgery alone, as well as acute and late toxicities. The rationale and outcome data for hypofractionated and/or reduced dose regimens are discussed. Finally, combination schedules with conventional chemotherapy and/or targeted agents are summarized. *Conclusion:* Outside the setting of well-designed prospective clinical trials, the conventional 50 Gy in 5–6 week schedule should be considered as standard. However, current and future studies addressing alternative fraction size, total dose, overall treatment time and/or combination with chemotherapy or targeted agents may reveal regimens of equal or increased efficacy with reduced late morbidities.

Limb sparing surgery combined with preoperative external beam radiotherapy (RT) results in high local control rates of at least 85–90% in patients with extremity soft tissue sarcomas (ESTS) resected with negative margins [1–3] and, in conjunction with limb conservation surgical approaches, has widely replaced the need for amputations [4]. Traditionally, the prescription dose for preoperative RT is 50 Gy delivered in 1.8–2 Gy fractions over five weeks and for post-operative RT is 60–66 Gy delivered in 1.8–2 Gy fractions over six to seven weeks. The surgical community has not yet widely adopted referral of ESTS patients for preoperative RT, basing their reluctance upon the higher rate of wound complications and imposed delay to definitive surgery. This review panel acknowledges these points. However, the (sometimes severe) acute complications are generally of a temporary nature. Conversely, the potential decreased functional morbidity, which is more prevalent and significant following postoperative RT compared to preoperative RT, is, typically permanent and frequently progressive in severity. For this reason, and for the possibility of schedule modification, the remainder of this manuscript will focus on preoperative RT only. Although endpoints for local control and overall survival do not differ for pre- versus postoperative RT, the toxicity parameters differ and these toxicities may be significant for some patients. After postoperative RT, fewer acute wound complications are seen (17% versus 35%) [1]. However, after prolonged follow up, more late toxicities such as fibrosis, arthrosis and edema resulting in diminished functional outcome are reported [5]. Anatomic site also plays an important part in the toxicity profile, since patients with upper extremity lesions are unlikely to suffer

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from the same rate of wound complications following preoperative RT compared to those with lower extremity lesions [1,6].

In patients with negative margins after preoperative RT, an excellent local control outcome can be anticipated. However, local control rates may drop to as low as 62% at 5 years when positive resection margins after preoperative RT are achieved [7–9]. Unfortunately, the addition of a postoperative boost in this setting has not been shown to improve local control outcomes [9–11]. Furthermore, not all clinical settings of positive surgical margins are the same. They should be clearly defined and analyzed separately. O'Donnell et al. [8], were able to retrieve 169 patients, from their prospective sarcoma database, all with positive resection margins, treated between 1986 and 2009. These cases were stratified into 3 groups, each representing a specific clinical scenario: those with a critical structure positive margin (e.g. major nerve, blood vessel, or bone), those with a tumor bed resection positive margin, and those with an unexpected positive margin during primary resection. The 5-year local recurrence-free survival rates were 85.4%, 78.9%, and 63.4% respectively, suggesting, that sparing of adjacent critical structures in this setting is relatively safe and contributes to improved functional outcomes. Therefore, especially when positive margins are planned or expected, these patients could be considered for innovative strategies, such as dose painting (i.e. focal dose escalation) and/or radiosensitization with novel agents. Furthermore, it should be acknowledged, that for those cases that do occur, the site of local recurrence is usually within the high dose irradiated volume [12–15].

Novel treatment strategies to improve outcome of patients presenting with localized ESTS, aiming to maintain or increase local control probability while diminishing early and late toxicity, are warranted. Furthermore, ESTS consists of a group of diseases which includes many histological subtypes with specific characteristics reflective of underlying differences in biology, genetics, clinical behavior and/or sensitivity to both chemotherapy and radiotherapy. Accordingly, it is improbable that all these entities will benefit from a single uniform regimen.

Several additional issues merit consideration: (1) the radiation fractionation including fraction size, total dose and overall treatment time, as well as (2) the opportunity to combine radiotherapy with conventional chemotherapy and/or targeted agents in addition to (3) the possibility that different treatment schedules may be appropriate for different histological subtypes. A consensus statement for sarcoma brachytherapy has been recently published [16]. The role of brachytherapy is beyond the scope of this review article.

Methodology

This review is based on peer-reviewed publications using a PubMed search on the MeSH headings "soft tissue sarcoma" AND "preoperative radiotherapy". Titles and abstracts screened for data including "fraction size AND/OR total dose AND/OR overall treatment time", "chemotherapy", "targeted agents AND/OR tyrosine kinase inhibitors", were collated. Reference lists from some articles were studied to obtain other pertinent articles. Additional abstracts presented at international sarcoma meetings were included. Information on relevant clinical trials was obtained from the ClinicalTrials.gov website.

Current knowledge on fraction size, total dose and overall treatment time

For preoperative RT, the prescription of 50 Gy in 1.8–2 Gy once-daily fractions over 5–6 weeks, is the current standard schedule [2]. Both the NCCN [17] and ESMO guidelines [18] suggest combining conservative surgery and RT for most cases of intermediate or high grade ESTS.

However, in selected patients, omission of RT could be considered [19–21]. In particular, cases where the closest resection margin is more than 1 cm are likely associated with high local control rates even without RT. Pisters et al. [19] analyzed a carefully selected population of 88 patients with T1 sarcomas. The 10 year estimated cumulative local recurrence rate without RT was 16.2% for the entire group and 10.6% for the subgroup after R0 surgery. Baldini and co-workers [20] have reported on 74 patients, with sarcomas of a median size of 4 cm (range 0.5–31 cm) treated by surgery only. They found a 10-year local failure rate of 13% when the surgical margins were <1.0 cm but no local failures when the margins were $\geqslant$1 cm. The Memorial Sloan Kettering Cancer Center (MSKCC) sarcoma database was used to develop a nomogram based on clinicopathologic factors of 684 patients to quantify the risk of local recurrence after limb sparing surgery without adjuvant RT [22]. The prediction tool is available on their website. Since this nomogram was developed from a retrospective series assessing a group of patients who were selected by their clinician not to receive radiation, it may harbor unrecognized selection biases. It may well be that the true risk of local recurrence in an unselected group of ESTS patients treated with surgery alone is underestimated by the nomogram. Conversely, in experienced multidisciplinary sarcoma team management, the most unfavorable subgroup (age above 50 years, sarcomas larger than 5 cm, resected with close or positive margins, and unfavorable histological subtypes) exhibits a local control rate without RT of 53% at 5 years (see also Fig. 1). Local recurrence after 5 years is rare, so this percentage can be considered a true reflection of clinical practice. For these 53% of patients with durable local control following surgery alone, any form of RT would have been overtreatment. This rate of local control after surgery alone should be considered alongside the "no-RT" arms of the 2 available randomized studies reported by Pisters et al. [23] (69% at 5 years) and Yang and

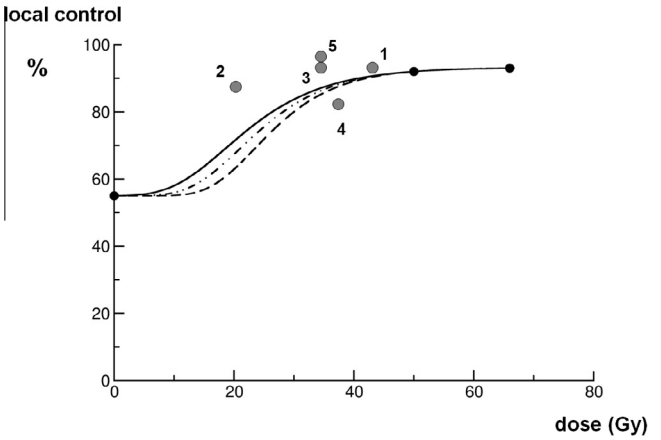

Fig. 1. A hypothetical local control probability curve, for simplification, calculated by: $S = \exp(-[\alpha D + \beta D^2])$. In this graph, at 0 Gy the most unfavorable subgroup of patients (age above 50 years, sarcomas larger than 5 cm, resected with close or positive margins, and unfavorable histological subtypes as outlined in the text) in the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram [22] is chosen and at 50 Gy (preoperative) and at 66 Gy (postoperative) the outcomes of the NCIC SR-2 trial [1]. The three lines come forth from low to high α/β ratio calculations. The gray dot numbers 1, 2 and 3 represent the three consecutive Eilber's studies [26,27], number 4 comes from the Kosela's study [31], and number 5 represents Temple's data [28]. The biological equivalent dose (BED) of these dots are calculated assuming an α/β ratio of 4 Gy (5×3.5 Gy equals BED of 21,875 Gy, 8×3.5 Gy equals a BED of 35 Gy, 10×3.5 Gy equals a BED of 43, 75 Gy, 5×5 Gy equals a BED of 37, 5 Gy, and 10×3 Gy equals a BED of 35 Gy). All points must be skewed to the left if these α/β ratios are higher than 4 Gy. All data derived from clinical studies and observations fairly match the calculated curves.

colleagues [3,24] (68–78% at 10–20 years dependent upon histological grade). Furthermore, 10–15% of patients recur locally despite the use of combined surgery and RT [1,2]. This leaves a potential subgroup of approximately 30–40% of patients who appear to truly benefit from the addition of RT to limb sparing surgery. This percentage is clinically significant and similar to that seen after breast conserving surgery, especially in younger women [25].

It is important to note, that randomized data do not support treatment with surgery alone and the omission of RT for most patients remains investigational. Also, criteria for RT omission need further definition and may include factors such as: tumor of T1 size, superficially located, resected with wide (>1 cm) negative margins, specific histological subtypes (like atypical lipomatous tumors), and location such that a local recurrence would be amenable to salvage surgery.

An alternative dose fractionation approach, employed 3–4 decades ago in the early period of limb preservation, is represented by the studies of Eilber and colleagues [26,27]. In three consecutive time periods, three different preoperative regimens all containing intra-arterial or intravenous adriamycin were tested. From 1974–1981, 77 patients received 10×3.5 Gy, from 1981–1984, 137 patients received 5×3.5 Gy and from 1984–1987, 112 patients received 8×3.5 Gy. In all studies after 1987, either cisplatin or ifosfamide was added, but the RT prescription remained unchanged at 8×3.5 Gy. The local failure rate in the first era was 5% at 8 years, in the second era 12% at 4 years, and in the last era 5% at 2 years. However, no long-term follow up data on late functional sequelae are available from these 3 studies. Temple and colleagues have also combined intra-arterial or intravenous adriamycin with preoperative RT; their regimen was 10×3 Gy [28]. By further reducing the fraction size from 3.5 Gy to 3 Gy, they were able to reduce the wound complication rate to 15%, while maintaining local control at 97% at 5 years of follow up.

Although the α/β ratio for the different sarcoma subtypes is unknown, it is possible that the value is below 10 Gy [29]. Fig. 1 shows a hypothetical local control probability curve as a function of biological equivalent doses (BED) in conventional 2 Gy fractionation assuming an α/β ratio of 4 Gy. In a more conventional calculation with a ratio of 10 Gy, the data points represented by gray dots would be skewed to the left. Thus, the BED of all Eilber's regimens are below the reference schedule of 50 Gy in 2 Gy fractions. It should be noted, that decreasing the RT dose as low as 5×3.5 Gy was unacceptable because it resulted in a higher local recurrence rate.

An alternative approach, explored in the RTOG 9514 study, was to reduce the total radiotherapy dose intensity while combining RT with chemotherapy [30]. Here the investigators reduced the dose of RT from 50 Gy to 44 Gy in 2 split series of 11×2 Gy sequenced with chemotherapy (see further details below). R0 resections were achieved in 91% of cases. At 3 years, the local control rate was 90%, but the toxicity profile for this combined chemotherapy and RT approach was significant as discussed below. Late functional outcome data from this study have not been reported.

Another novel approach to decrease radiotherapy dose is represented by a report from the Polish Sarcoma Study Group. Kosela-Paterczyk and colleagues performed a prospective phase II clinical trial which accrued 272 patients and investigated a dose of 5×5 Gy followed by surgery three to seven days after completion of RT. After a median follow-up of 35 months, the estimated 5 year local failure rate was 19% [31], which may be on the lower level of acceptable local control.

Finally, reports for myxoid liposarcomas (MLS) have consistently shown exquisite radiation sensitivity, characterized by a marked tumor volume reduction during radiotherapy and excellent local control rates [32–34]. After surgery, the resection specimens frequently show a fibrotic myxoid stroma containing, nonlipogenic, hyalinized structures. Gross evidence of tumor necrosis is uncommon, but often only a few (if any) visible tumor cells remain on microscopic examination. Furthermore, the specimens show a substantial effect on medium-sized arterioles with intimal hypertrophy and parietal thrombus formation. The classic delicate crow's feet capillary vasculature can still be identified [35]. A dose reduction to 18×2 Gy for MLS is now being investigated in an international multi-center prospective phase II clinical trial (ClinicalTrials.Gov Identifier: NCT02106312). If excellent local control can be maintained with this reduced dose, and both wound complications and long-term toxicities are also reduced, this would result in a significant advantage for patients, albeit potentially singularly applicable to this sarcoma subtype with unusually high response and sensitivity to radiotherapy.

In order to compare the published data, recalculating the Eilber schedules to a 2 Gy per fraction regimen is necessary. The regimen of 8×3.5 Gy = 28 Gy would result in a BED of 31.5 Gy with a conventional α/β ratio of 10 Gy, a BED of 35 Gy with a reasonable α/β ratio of 4 Gy or a BED of 38.5 Gy with an extremely low α/β ratio of 2 Gy. Reviewing all data on radiation dose, it is reasonable to assume that a dose response relationship exists for local control below 28 Gy [27] in 8 fractions of 3.5 Gy. In the preoperative setting, this dose response relationship between 28 Gy and 50 Gy is uncertain and may well be marginal (see also Figs. 1 and 2). On the other hand, it is also reasonable to assume that acute wound complications are related to RT dose and volume [6,26,27,36–38]. The impact of fractionation on late functional outcome has yet to be fully explored. The mature results of the relatively extreme hypofractionated Polish strategy will provide valuable insight in the relationship between hypofractionation in combination with a dose reduction on late radiation effects.

The data on the fractionation characteristics of all the radiotherapy regimens mentioned above are summarized (see Figs. 1 and 2 and Table 1), including both non-randomized and randomized trial results to appreciate the diverse fractionation schedules evaluated over the last 30 years. Fig. 1 depicts a hypothetical local control probability as a function of dose calculated by: $S = \exp(-[\alpha D + \beta D^2])$. In this graph, at 0 Gy the most unfavorable subgroup of

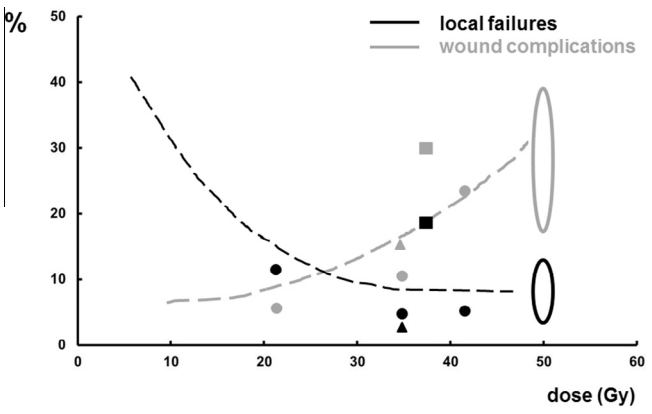

Fig. 2. The two data sets on local control (shapes in black) and wound complications (shapes in gray) are combined. The black dots represent the local failures in the Eilber's studies [26,27] (see also Fig. 1). The black oval summarizes the projected 5 years of local failure probability from Table 2. The black striped line connects these outcome data and intends to intersect the y-axis at a local control achieved by surgery only as described in Table 2. The gray line, dots and oval represents the wound complication rate as a function of BED from the same references. The black and gray squares represent, respectively, the local failure- and wound complication probability as published by Kosela et al. [31]. Finally, the black and gray triangles represent, respectively, the local failure- and wound complication probability as reported by Temple et al. [28].

Table 1
Retrospective and Randomized data on surgery alone and (neo-) adjuvant RT in ESTS. This table summarizes published data on radiotherapy only with respect to the radical resectability R0, wound complications and local control. The – mark means no data are available on this issue in the full paper. In the nomogram by Cahlon [22], the most unfavorable patient characteristics (for details see text) were chosen. In the study by Yang [24] 141 patients were randomized; 91 with high grade sarcomas and 50 with low grade histologies, 70 received radiotherapy and 71 did not.

Author/ reference	*n*	RT regimen	CT regimen	R0 resections	Wound complications	Local control (@ X years)
Cahlon [22]	684	0 Gy (surgery only)	None	–	_	53% @ 5 yrs
Pisters [19]	88	0 Gy (surgery only)	None	84%	_	84% @ 10 yrs
Baldini [20]	74	0 Gy (surgery only)	None	92%	_	93% @ 10 yrs
Rosenberg [4]	Randomized trial *n* = 16 versus 27	0 Gy (amputation) 50 + 10–20 Gy	ACM (all cases)	100% 85%	_	100% @ 4.7 yrs 85% @ 4.7 yrs
Pisters [23]	Randomized trial *n* = 78 versus 86	0 Gy (surgery only) 42–46 Gy brachytherapy	None None	82%	10% 48% (direct afterloading) 14% (delayed afterloading)	69% @ 5 yrs 82% @ 5 yrs
Yang [24]	Randomized trial *n* = 141 (for details see Legend)	0 Gy (surgery only)	Adjuvant 5 times AC for all high grade STS	–	Trial randomized postoperative RT only	In high grade STS 78% versus 100% @ 10 yrs
		45 + 18 Gy postoperative		–		In low grade STS 68% versus 95% @ 10 yrs
O'Sullivan [1]	Randomized trial *n* = 94 versus 96	50 Gy preoperative 50 + 16 Gy postoperative	None None	84% 86%	35% 17%	92% @ 3.3 yrs 93% @ 3.3 yrs

Abbreviations: RT = radiotherapy, ESTS = extremity soft tissue sarcoma, *n* = number of cases, CT = chemotherapy, AC = doxorubicin and cyclophosphamide, ACM = doxorubicin, cyclophosphamide and methotrexate.

patients from the MSKCC nomogram [22] is chosen and at 50 Gy and 66 Gy the data points represent the outcomes of the NCIC SR-2 trial [1]. The clinical trial data between 0 and 50 Gy match the calculated curves. Fig. 2 suggests that there may be a threshold dose for local control not at, but below 50 Gy. The extrapolated curve for wound complications, however, seems to exhibit a more linear to exponential dose response relationship without a threshold value. Obviously, the quality of surgery also has to be considered in the interpretation of local control and toxicity date.

Current knowledge pertaining to the combination of RT and conventional chemotherapy and/or targeted agents for STS

For many epithelial tumors (e.g. rectal-, head and neck-, lung and esophageal cancer), concurrent treatment with systemic agents and external beam RT frequently results in an increased local control probability, which sometimes translates into increased overall survival benefit, and has thus become part of the standard of care. The disadvantage of such approaches is that they are generally associated with an increased, usually temporary, though sometimes severe acute toxicity profile. These toxicities vary based on the tumor site and the specific systemic agents delivered.

This combined modality treatment toxicity may be severe in certain patients. Nonetheless, these data suggest that it may be worthwhile to explore combinations of RT plus systemic agents, including radiosensitizers in ESTS especially in patient subgroups at high risk for local and/or distant failure such as those planned to have positive surgical margins. Obviously, careful long-term observation of late functional outcome is required in the design of such new combinations. It is presently unclear how to best measure the clinical benefit of induction treatment for localized ESTS. Late outcomes such as local control, quality of life and overall survival can be considered as robust endpoints, but they take years to observe. Surrogate early end-points provide an alternative assessment strategy, represented by outcomes such as the pathological evaluation of the resection specimen, wound complications, and potential signals from sophisticated imaging techniques [39–41]. All need to be incorporated into prospective clinical studies to be validated. For this section, the combined modality regimens will be compared to radiotherapy only, especially with respect to the induction of necrosis in the resection specimens, local control and wound healing problems. In the literature, a generally accepted definition of a pathological complete remission (pCR) is represented by greater than or equal to 99–100% necrosis (or less than or equal to 1% residual visible tumor cells), whereas a near pCR can be defined as greater than or equal to 95% necrosis. Canter [42] and Shah [43] demonstrated, that a (near) pCR can be appreciated in only 8–10% of cases following RT alone to 50 Gy in 2 Gy fractions. Nevertheless, the true prognostic significance of treatment-induced pathologic necrosis in ESTS after neoadjuvant therapy has yet to be determined [44].

In the following sections, research focusing on combinations of RT with conventional chemotherapy as well as combinations with more modern targeted agents is summarized (see Table 2).

Conventional chemotherapy combined with RT in preoperative STS management

The previously mentioned RTOG 9514 trial (discussed in the context of its RT dose reduction) investigated the so called "MAID" regimen [30]: mesna, doxorubicin, ifosfamide, and dacarbazine chemotherapy, interdigitated with preoperative split course RT and three cycles of postoperative chemotherapy. While not a true concurrent radiosensitization approach, it merits comments in this section. The regimen was toxic with 83% grade IV and 5% grade V toxicities; in part, this was because the RT fields extended 9 cm above and below gross disease, as well as the fact that the ifosfamide dose was 2500 mg/m^2 which was higher than that explored in a prior pilot study [45]. Nonetheless, this combination appeared to achieve a pCR in 27% of the evaluable patients. Of course, it is difficult to determine if the pCR comes as a consequence of radiotherapy, chemotherapy or the interdigitated combination of both. Reports with longer follow-up of this study have shown a significant survival benefit for those treated with chemotherapy [46]. However, the entire study population also experienced a relatively high local failure rate of 22.2% at 5 years, a relatively high amputation rate of 9.4% (including all amputation for any cause including unsuitability for limb-sparing surgery at the time of assessment after induction chemoradiation) and 2 cases of acute myelogenous leukemia [47].

Table 2
Preoperative RT in ESTS either with or without sensitizers. This table summarizes published data on radiotherapy only or in combination with conventional chemotherapy or targeted agents with respect to the percentage of induced necrosis, the radical resectability, wound complications and local control. The – mark means no data are available on this issue in the full paper.

Setting	Author (Reference)	*n*	RT regimen	CT regimen	(near) pCR	R0 resections	Wound complications	Local control (@ X years)
RT only	Canter [42]	25	25 × 2 Gy	_	8%	84%	28%	100% @ 3 yrs
	Shah [43]	30	25 × 2 Gy	_	10%	_	23%	100% @ 5 yrs
	Kosela [31]	272	5 × 5 Gy	_	_	79%	32%	81% @ 3 yrs
RT + conventional chemotherapy	Eilber '74-'81 [26,27]	77	10 × 3.5 Gy	Adria	12%	_	23%	95% @ 8 yrs
	Eilber '81-'84 [26,27]	137	5 × 3.5 Gy	Adria	4%	_	5%	88% @ 4 yrs
	Eilber '84-'87 [26,27]	112	8 × 3.5 Gy	Adria	6%	_	10%	95% @ 2 yrs
	Temple [28]	42	10 × 3 Gy	Adria	_	_	15% [@]	97% @ 5 yrs
	Kraybill [30]	59	Split course 2 times 11 × 2 Gy	MAID	27%	91%	11%	91% @ 3 yrs
	Ryan [50]	25	8 × 3.5 Gy	Adria/Ifos	40%	88%	20%	88% @ 2 yrs
	MacDermed [49]	34	8 × 3.5 Gy	Ifos	11.8%	100%	17%	89% @ 5 yrs
RT + targeted agents	Yoon [58]	20	28 × 1.8 Gy	Avastin	20%	_	20%	95% @ 2 yrs
	Canter [59]	8	25 × 2 Gy	Sorafenib	38%	75%	38%	100% @ 3 yrs
	Meyer [41]	16	8 × 3.5 Gy	Sorafenib [*]	44%	94%	38%	100% @ 2 yrs
	Lewin [60]	9	28 × 1.8 Gy	Sunitinib	[#]	_	_	[#]
	Haas [61]	11	25 × 2 Gy	Pazopanib	40%	_	20%	91% @ 2 yrs
RT + intratumoral nanoparticles	Bonvalot [65]	20	25 × 2 Gy	Hafnium oxide nanoparticles	18%	_	5%	_

Abbreviations: RT = radiotherapy, ESTS = extremity soft tissue sarcoma, CT = chemotherapy, pCR = pathological complete remission, *n* = number of cases, Adria = doxorubicin, Ifos = ifosfamide, MAID = mesna, doxorubicin, ifosfamide, and dacarbazine. ASCO = the American Society of Clinical Oncology, CTOS = the Connective Tissue Oncology Society.
[*] In this study, Sorafenib was combined with epirubicin and ifosfamide.
[#] In this study, the pathological response was described as the median percentage of necrosis (see text), the 2-years progression-free survival was 44%.
[@] In this study, wound complications were scored as either "major" (wound necrosis secondary to thrombosis of reconstructed artery) in 2.5% of cases or "minor" in 12.5%.

Ifosfamide-based regimens have been investigated in retroperitoneal sarcomas [48] and in ESTS [49]. MacDermed et al. combined the 8 × 3.5 Gy schedule with concurrent ifosfamide (2.5 g/m^2 per day for 5 days) albeit with higher than conventional doses per fraction. They reported a pCR in 11.8% of cases, with R0 resections performed in all cases, and a 5 year local control rate of 89% [49].

Ryan et al. [50] combined the same regimen of 8 × 3.5 Gy regimen with epirubicin 30 mg/m^2 per day and ifosfamide at a dose of 2.5 g/m^2 per day, both on days 1–4, in ESTS and body wall sarcoma patients. These agents are among the more effective drugs in sarcoma. Though this regimen was toxic, a (near) pCR was found in 40% of all resection specimens.

Drugs that possibly deserve additional attention in the setting of STS are gemcitabine and temozolomide due to their proven radiation sensitization, but data for these agents are scarce [51]. Furthermore, apart from the use of gemcitabine as treatment for metastatic leiomyosarcomas, data showing single agent efficacy are lacking [52].

Reviewing (neo-)adjuvant chemotherapy trials (e.g. the Italian/Spanish [53], the EORTC 62931 [54] and the RTOG 9514 [30] studies), it can be concluded that, delaying RT in these trials had no adverse effect on the observed local control rate, but delivery of chemotherapy did not negate the necessity for RT.

Targeted agents combined with RT in preoperative STS management

From a biological point of view, studies combining targeted agents with RT are very appealing. Neovascularization and angiogenesis are fundamental mechanisms in tumor initiation, promotion, and the acquisition of a metastatic phenotype [55]. Overexpression of vascular endothelial growth factor (VEGF) and its receptors have been observed as neoplastic phenomena. Also STS have been shown to overexpress angiogenic factors in both tumor tissue and serum, thereby underpinning the exploration of anti-angiogenic compounds in the treatment of STS [56]. In addition, early stage clinical trials suggest that the combination of RT and antiangiogenic agents may exhibit a synergistic effect [57]. Radiosensitization could be both clinically and biologically significant in STS since complete and near-complete pathologic responses have been associated with improved oncologic outcomes in some series of STS patients treated with neoadjuvant therapy [42] although the relationship is less clear in other series [44]. It should be expected, that combining RT with targeted agents may result both in increased toxicity within the radiation volumes as well as the known systemic side effects of the compounds by themselves (i.e. alterations in thyroid- and liver function tests, blood pressure etc.). Research in this area is outlined below and summarized in Table 2.

Yoon and colleagues [58] combined 28 × 1.8 Gy with bevacizumab in a preoperative setting. This regimen resulted in ⩾80% necrosis in 45% of tumors, 20% grade III systemic toxicities (hypertension and altered liver function tests), 75% R0 resections and 20% major wound complications. At a median follow up of 24 months, there were no local recurrences among the 13 ESTS patients (while only 1 out of 6 patients with a retroperitoneal/pelvic sarcoma had a local recurrence, which is of interest, because this site is known for its high local failure rate).

Canter et al. [59] investigated sorafenib combined with 25 × 2 Gy in a phase I trial where three dose levels were planned. The maximal tolerated dose was reached at the second level (200 mg + 400 mg daily). At this second dose level, grade 3 toxicities in 80% of cases were observed including skin rash that prevented drug re-introduction in 2 of 5 patients, anemia and supraventricular tachycardia in 1 of 5 cases, and a perirectal abscess in one patient. Major wound complications (grade 3) were observed in 3 of 8 cases while 6 of 8 cases underwent R0 resections. All patients exhibited local control at a median follow up

of 3 years. The authors suggest that further investigation of the first dose level that employed twice daily 200 mg Sorafenib is warranted.

Meyer and colleagues [41] combined sorafenib with 8 × 3.5 Gy of preoperative epirubicin and ifosfamide-based chemoradiation for high risk extremity soft-tissue sarcomas. A parallel correlative study with dynamic contrast enhanced (DCE) MRI was performed to assess response to treatment. Patients received 3 cycles of epirubicin and ifosfamide pre-operatively and 3 cycles post-operatively. Epirubicin was omitted during radiotherapy. Sixteen of eighteen patients were evaluable with a maximum tolerated dose of sorafenib at 400 mg once daily. A high incidence of febrile neutropenia (~50%) was reported. Forty-four percent of patients demonstrated ⩾95% necrosis. DCE-MRI after 2 weeks of sorafenib correlated with histologic response.

A note of caution was presented by Lewin and colleagues [60] on the combination of 28 × 1.8 Gy with sunitinib. Here, even after dose de-escalation of sunitinib, they observed an unexpected 44% grade 3+ hepatotoxicity rate and an overall grade 3+ toxicity rate of 78%. Furthermore, a higher local failure rate (HR: 8.1; $p = 0.004$) was apparent in patients receiving sunitinib. However, the combination of sunitinib plus RT led to an almost doubling of the median tumor necrosis percentage (40%, range 5–100%, versus 75%, range 1–95%) as compared to RT alone.

Finally, it has been suggested, that a combination of 25 × 2 Gy plus dose-escalated pazopanib seems safe up to the highest pazopanib dose level of once daily 800 mg [61]. However, in this study the grade 3+ hepatotoxicity rate was unexpectedly high at 27%. In 40% of the resection specimens a pathological (near) complete remission could be appreciated.

These receptor tyrosine kinase inhibitor (RTKI) based studies are encouraging but they need to be confirmed in larger cohorts with longer follow up. Warnings have come forth from animal experiments showing a more invasive and metastatic potential after administration of RTKIs. To date, in humans, there are no available data concerning rapid metastatic disease after RTKI application in the adjuvant setting. There are also no available data in humans, on rapid disease progression after RTKI withdrawal in metastatic patients [62,63].

Preliminary results of other phase I trials have been presented in abstract form: sunitinib in combination with 28 × 1.8 Gy [64], and hafniumoxide nanoparticles (NBTXR3, intended to enhance the RT effect by local electron deposits) in combination with 25 × 2 Gy [65]. Because of the promising results observed with intra-tumoral injection of NBTXR3 nanoparticles just prior to preoperative RT followed by surgery in a phase I trial (showing a median percentage of residual malignant visible cells of 25%), a phase II/III trial has just started comparing preoperative radiotherapy to 50 Gy to the same RT schedule combined with intratumoral NBTXR3 (Trial Identifier NCT02379845). Longer follow up and full manuscripts of these regimens are awaited. Furthermore, the use of the pathological response as a surrogate point of local control or outcome needs to be evaluated in future studies.

Discussion

The sarcoma scientific community should engage in a re-evaluation and optimization of the conventionally fractionated preoperative RT schedule of 25 × 2 Gy. Modifications to this regimen may be challenging because of some systematic barriers faced by sarcoma researchers. Specifically as an "orphan disease", sarcoma research to address translational questions and/or conduct studies has always been more challenging to fund at the grant competition level as well as through industry when compared to common cancers. However, with clear scientific methodology, opportunities for treatment adjustment would exist through investigations addressing both the schedule itself and possible combination with radiation sensitizers. In addition to potential improvement in oncologic outcome (especially after R1 resections and/or in histological subtypes more prone to local relapse such as myxofibrosarcoma and malignant peripheral nerve sheath tumor; [66–69]), these combinations may also offer opportunities to decrease the RT dose for patients where local control would be anticipated to be high but there is concern about the potential toxicity of radiation. Although 25 × 2 Gy remains standard for preoperative management of ESTS [1,2], this regimen is not based upon robust evidence emanating from randomized trials comparing different preoperative RT dose levels. Although, the Polish 5 × 5 Gy schedule and the MLS reduced dose study are examples of completed or ongoing investigations respectively, they remain phase II experiences that need appropriate validation while also recognizing, as mentioned earlier, that the former study reported a lower than expected local control while the control rate for the latter study is not yet reported. In the treatment of breast cancer, conventional 2 Gy fractionation regimens have largely been replaced by hypofractionated schedules with adequate total dose for the fractionation chosen. This may be a reasonable approach for the treatment of many types of STS as well [70].

Delayed wound healing is a serious adverse event after preoperative RT. This risk is probably partly related to patient and tumor characteristics (e.g. obesity, diabetes, smoking habits and the location of the sarcoma especially those in proximity to major neurovascular structures in the lower extremities), as well as radiotherapy parameters such as total dose, fraction size, treatment volume, skin flap sparing and sophisticated RT techniques [6,13,36–38,71]. The approach of a reduced preoperative RT dose in combination with sensitizing agents could be a great step forward if such combinations could maintain or improve local control in association with a reduction in perioperative and long-term morbidity (see Fig. 2), ideally improving late functional outcome and quality of life for these patients. The toxicity profile and costs of such agents should be balanced against the desired gain in oncological outcome parameters. Well-designed randomized phase III clinical trials are the best tools to evaluate proposed new regimens. Unfortunately, in the setting of rare diseases like sarcomas, this may be problematic. New approaches to address this challenge should be explored. For example, trials based upon modern Bayesian principles [72], such as the reduced dose MLS trial, may provide alternative means to acquire reasonable evidence to guide future local management in this rare malignancy.

Conflicts of interest

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