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Managing Extremity Soft Tissue Sarcomas Before Definitive Surgery; Preoperative Radiotherapy Alone or Combined Modality Strategies?

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Abstract

Introduction: This critical review aims to summarize published data on pre-operative radiotherapy (RT) with or without concurrent systemic therapy followed by limb sparing surgery for extremity soft tissue sarcoma.

Methods: This review is based on peer-reviewed publications using a PubMed search on the MeSH headings "soft tissue sarcoma" AND "preoperative radiotherapy" AND "chemotherapy" AND/OR "targeted agents AND/OR tyrosine kinase inhibitors", are collated. Reference lists from some articles have been studied to obtain other pertinent articles. Additional information on relevant clinical trials available at the ClinicalTrials.gov website was also added.

Results: Data are presented for the conventional regimen of 50-50.4 Gy in 25-28 fractions in 5-6 weeks preoperative external beam RT alone or in combination with conventional chemotherapy and/or targeted agents.

Conclusion: Outside the setting of well-designed prospective clinical trials, the conventional 50 Gy in 5-6 weeks schedule should be considered as standard. However, current and future studies addressing combinations with chemotherapy and/or targeted agents may reveal regimens of equal or increased efficacy with reduced late morbidities.

Keywords: Limb soft tissue sarcoma; Surgery; Preoperative radiotherapy; Combined modality treatment; Targeted agents; Chemotherapy

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Introduction

For most extremity soft tissue sarcomas (ESTS), a combination of limb sparing surgery and radiotherapy (RT) results in high local control rates of at least 85% especially when resection margins are negative [1-3]. This combined modality approach, as described by both NCCN [4] and ESMO guidelines [5] has widely and significantly reduced the rates of amputations [6]. Conventionally, for preoperative RT 50 Gy is to be delivered in 1.8-2 Gy fractions over five to six weeks and for postoperative RT 60-66 Gy in the same fraction sizes over six to seven weeks. Surgeons may be reluctant to refer ESTS patients for preoperative RT, because of fear for a higher rate of wound complications and delay to definitive surgery. However, these (sometimes severe) acute complications are generally of a temporary nature. The potentially decreased functional morbidity, significantly more prevalent following postoperative RT, are typically permanent and frequently progressive in nature and severity. Especially after prolonged follow up, more late toxicities can be observed such as fibrosis, arthrosis and edema resulting in diminished functional outcome [7]. Patients with upper extremity lesions are less likely to suffer from the same rate of wound complications following preoperative RT as compared to those with lower extremity lesions [1,8]. 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 including many histological subtypes each with specific characteristics reflecting 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. The question can be raised whether these future strategies should focus on RT by itself (issues like fraction size, total dose and overall treatment time) or on combination regimens with systemic agents. Recently an overview focused on several RT fractionation and dose characteristics [9]. Based upon all these considerations and

Table 1: Preoperative RT in ESTS alone or in combination with systemic therapy.

Reference	n	RT schedule	Systemic therapy	Wound complications	R0 resections	(near) pCR	Local control (at X years)
Shah [17]	30	25 x 2 Gy	_	23%	_	10%	100% at 5 years
Canter [16]	25	25 x 2 Gy	_	28%	84%	8%	100% at 3 years
Kraybill (RTOG 9514) [19]	59	split course 2 times 11 x 2 Gy	MAID	11%	91%	27%	91% at 3 years
Mac Dermed [21]	34	8 x 3.5 Gy	Ifos	17%	100%	11.8%	89% at 5 years
Ryan [22]	25	8 x 3.5 Gy	Adria / Ifos	20%	88%	40%	88% at 2 years
Temple [23]	42	10 x 3 Gy	Adria	15% @	_	_	97% at 5 years
Eilber [24, 25]	77	10 x 3.5 Gy	Adria	23%	_	12%	95% at 8 years
Eilber [24, 25]	137	5 x 3.5 Gy	Adria	5%	_	4%	88% at 4 years
Eilber [24, 25]	112	8 x 3.5 Gy	Adria	10%	_	6%	95% at 2 years
Meyer [12]	16	8 x 3.5 Gy	Sorafenib $	38%	94%	44%	100% at 2 years
Canter [29]	8	25 x 2 Gy	Sorafenib	38%	75%	38%	100% at 3 years
Haas [30]	11	25 x 2 Gy	Pazopanib	20%	_	40%	91% at 2 years
Jakob [32]	16	25-28 x 1.8 Gy *	Sunitinib	29%	93%	36% **	86% at 3 years ***
Lewin [33]	9	28 x 1.8 Gy	Sunitinib	_	_	#	#
Yoon [34]	20	28 x 1.8 Gy	Avastin	20%	_	20%	95% at 2 years

The table summarizes published data on radiotherapy alone or in combination with conventional chemotherapy or targeted agents with respect to wound complications, the radical resectability, the percentage of induced necrosis, and local control. The - mark means no data are available on this issue in the full paper.
Abbreviations: RT = radiotherapy, ESTS = extremity soft tissue sarcoma, n = number of cases, pCR = pathological complete remission, MAID = mesna, doxorubicin, ifosfamide, and dacarbazine, Ifos = ifosfamide, Adria = doxorubicine.
@ 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%. $ in this study Sorafenib was combined with epiribucin and ifosfamide. * 6 ESTS and 10 RPS, 14 out 16 cases went on to undergo surgery (1 refusal and 1 intercurrent metastatic disease), ** defined as >90% necrosis, *** 2/14 local recurrences after a median FU of 38 months. # in this study, the pathological response was described as the median percentage of necrosis (see text), the 2-years progression-free survival was 44%.

because of the possibility to combine RT with systemic agents in patients with the sarcoma still *in situ,* enabling for instance imaging-, biological- and pathological investigations, the remainder of this manuscript will focus on preoperative RT only.

Not only for epithelial malignancies (like head and neck-, lung-, rectal-, and esophageal cancer, to name a few), but also for brain tumors (like glioblastoma) concurrent regimens of external beam RT with systemic agents are designed aiming to increase the local control probability, sometimes even translating into an increased overall survival benefit. These approaches have thus become part of the standard of care. Although these combinations come with the disadvantage of an increased acute toxicity profile (indeed sometimes severe based on the tumor site and the specific systemic agents prescribed), these toxicities are usually temporary. The experience in epithelial malignancies and glioblastoma raise the suggestion that it might be worthwhile to explore combinations of RT plus systemic agents, including radio sensitizers, in ESTS as well. Hypothetically speaking, either these combinations could be explored especially in patient subgroups at high risk for local failure, or they may offer the opportunity to lower the RT dose. Presently, it is not clear how to best evaluate the clinical benefit of preoperative RT for localized ESTS. Obviously, late outcomes such as local control, quality of life and overall survival can be considered as robust endpoints, but they take years to observe. Evaluation of the additional (both additive and synergistic) benefit of systemic compounds to RT is even more difficult. The pathological evaluation of the resection specimen, wound complication rates, and potential signals from sophisticated imaging techniques, both CT and MRI, could be used as surrogate endpoint [10-15]. Without doubt, prospective clinical studies are needed for validation.

Methods

This review is based on peer-reviewed publications using a PubMed search on the MeSH headings "soft tissue sarcoma" AND "preoperative radiotherapy" AND "chemotherapy" AND/OR "targeted agents AND/OR tyrosine kinase inhibitors". Reference lists from some articles have been studied to obtain other pertinent articles. Additional information on relevant clinical trials available at the ClinicalTrials.gov website was also added.

Results

Here onwards, the combination regimens will be compared to RT only, focusing on local control, wound healing and the induction of necrosis in the resection specimens. 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. In the upper 2 rows of the Table 1, Canter et al. [16] and Shah et al. [17] 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 [18]. In the middle section of the Table, studies on RT and conventional chemotherapeutic agents are summarized. The RTOG 9514 trial investigated the so called "MAID" regimen [19] consisting of mesna, doxorubicin, ifosfamide, and dacarbazine chemotherapy, interdigitated with preoperative split course RT and three cycles of postoperative chemotherapy. In itself, this design does not really reflect radiosensitization because the two therapies are applied sequentially and not concurrent. This regimen illustrates perfectly, that indeed combination regimens, also in the setting of ESTS management can be quite toxic: 83% grade IV and 5% grade V toxicities. This may be explained in part because of the RT field sizes extending 9 cm above and below gross disease, as well as the relatively

high ifosfamide dose at 2500 mg/m^2, higher than that explored in a prior pilot study [20]. Nonetheless, in this trial a pCR rate of 27% could be observed. MacDermed et al combined a relatively low dosed RT schedule of 28 Gy in 8 fractions with concurrent ifosfamide 2500 mg/m^2 per day for 5 days). 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% [21]. Ryan et al. [22], combined the same regimen of 8 x 3.5 Gy low dose schedule with epirubicin 30 mg/m^2 per day and ifosfamide 2500 mg/m^2 per day, both on days 1 to 4. Again, this regimen turned out to be toxic, but a (near) pCR was found in 40% of all resection specimens Intra-arterial or intravenous adriamycin in combination with 10 x 3 Gy preoperative RT, was investigated by Temple et al. [23]. They observed a relatively low wound complication rate of 15%, while maintaining local control at 97% at 5 years follow up. Historically and scientifically interesting are the three consecutive phase II studies by Eilber and colleagues [24,25]. Like in Temple's study [23], in all schedules intra-arterial or intravenous adriamycin was applied. From 1974-1981, 77 patients received 10 x 3.5 Gy, from 1981-1984, 137 patients received 5 x 3.5 Gy and from 1984-1987, 112 patients received 8 x 3.5 Gy. The local failure rate in the three era's was 5% at 8 years, 12% at 4 years, and 5% at 2 years respectively. Unfortunately, no long-term follow up data on late functional sequelae are available from these 3 studies. In the lower section of the Table, modern targeted agents in combination with preoperative RT are described. Indeed, from a biological point of view, studies combining these targeted agents with RT are very appealing because neovascularization and angiogenesis are fundamental mechanisms in tumor initiation, promotion, and the acquisition of a metastatic phenotype [26]. Over expression of vascular endothelial growth factor (VEGF) and its receptors have been observed as promoting phenomena in neoplastic development. Angiogenic factors in both tumor tissue and serum are frequently overexpressed in STS [27]. In addition, early stage clinical trials suggest that the combination of RT and antiangiogenic agents may exhibit a synergistic effect [28]. Meyer et al. [12] combined sorafenib with 8 x 3.5 Gy of preoperative RT. 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 400mg once daily. Toxicity was substantial with febrile neutropenia observed in 50% of patients. Forty four percent of patients demonstrated ≥ 95% necrosis. Canter et al. [29] investigated sorafenib combined with 25 x 2 Gy in a phase I trial where three dose levels were planned. The maximal tolerated dose was reached at the second level (200mg + 400mg 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 200mg Sorafenib is warranted. Haas and co-workers have suggested, by performing a dose finding phase I study, that a combination of 25 x 2 Gy plus dose-escalated pazopanib seems safe up to the highest pazopanib dose level of once daily 800 mg [30]. However, the grade 3+ hepatotoxicity rate was unexpectedly high at 27%. In 40% of the resection specimens a pathological (near) CR could be appreciated. This experience led to the design of a currently accruing phase II study (PASART-2, Identifier NCT 02575066) with the aim to conform the feasibility and efficacy of the 800 mg pazopanib dose level. The German Interdisciplinary Sarcoma Group is currently investigating preoperative pazopanib in the GISG-04/NOPASS study, but here no preoperative RT is prescribed (Identifier NCT 01543802) [31]. Although current data on sunitinib combinations are also limited, published series do present a note of caution. Jakob et al. [32] reported a sunitinib dose reduction in 9/16 patients leading to an interruption in 4/16 patients, mainly due to hematologic, skin and gastrointestinal side effects. In total, an overall grade 3+ toxicity rate of 81% was observed. Lewin et al. [33] also observed an unexpected toxicity profile of 44% grade 3+ hepatotoxicity rate and an overall grade 3+ toxicity rate of 78%, even after dose de-escalation of sunitinib. Furthermore, a higher local failure rate (HR: 8.1; p = 0.004) was apparent in patients receiving sunitinib. Finally, bevacizumab in combination with 28 x 1.8 Gy was investigated by Yoon et al. [34]. 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. All these receptor tyrosine kinase inhibitor based studies are encouraging but they need to be confirmed in larger cohorts with longer follow up.

Discussion

The principles of Personalized Medicine and Individualized Patient Care should also apply to extremity soft tissue sarcoma (ESTS) patients, but, due to the rarity of this disease, is difficult to implement. For now, in case the multidisciplinary tumor board has decided upon prescribing preoperative RT, a conventionally fractionated schedule of 50-50.4 Gy in 1.8-2 Gy fractions is the internationally suggested regimen [2,4,5]. When looking at RT schedules alone, it is remarkable to conclude that both historically (e.g. the Eilber schedules form 1974 until 1987; [24,25], but also more recently, sarcoma investigators worldwide are attempting to lower this dose level. For all histological ESTS subtypes, the Polish sarcoma group has investigated an ultra-short regimen of 5 x 5 Gy followed by surgery after 3-7 days of RT completion [35]. Myxoid liposarcomas (MLS) studies have consistently shown exquisite radiation sensitivity, characterized by a marked tumor volume reduction during radiotherapy and excellent local control rates [36-38]. After surgery, the resection specimens frequently show a fibrotic myxoid stroma with hyalinization. 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 [39]. A dose reduction to 18 x 2 Gy for MLS is now being investigated in an international multi-center prospective phase II clinical trial (Identifier: NCT02106312). To the best of my knowledge, only for retroperitoneal sarcomas (not the scope of this review), where achieving local control is much more difficult than for ESTS, attempts are being made to apply additional doses by "dose painting" high risk areas [40,41]. Delayed wound healing is a serious complication after preoperative RT. Both 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 [8,42-46] may contribute to this risk. Attempts to reduce the 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, thereby improving late functional outcome and quality of life for these patients. Obviously, all toxicities and costs of such agents should be balanced against the desired gain in oncological outcome parameters. Although well-designed randomized phase III clinical trials are the best tool to evaluate proposed new regimens, in the setting of rare diseases like sarcomas, this may be a challenge.

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