

Preoperative radiotherapy in soft tissue sarcoma: from general guidelines to personalized medicine

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Abstract: This critical review aims to generate hypotheses when to adhere to guidelines and when it could be considered to individualize management of extremity soft tissue sarcomas. Based upon peer-reviewed publications using a PubMed search on the MeSH headings “soft tissue sarcoma” AND “preoperative radiotherapy”, data were compiled. 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 screened as well as their respective reference. Furthermore, new data presented in abstract form at international sarcoma meetings have been included as well as relevant clinical trial information available at the ClinicalTrials.gov website. Generally accepted guidelines suggest applying preoperative external beam radiotherapy (RT), conventionally fractionated in 25–28 fractions of 1.8–2 Gy to a total dose of 50–50.4 Gy in 5–6 weeks. This regimen aims to increase the local control probability as compared to surgery alone. This regimen inflicts both acute and late toxicities. The reasons for and results of hypofractionated and/or reduced dose regimens are summarized and discussed. Finally, RT could be combined with conventional chemotherapy as well as targeted agents and data are summarized. Outside the setting of well-designed prospective clinical trials, the conventional 50 Gy in 5–6 weeks schedule should be considered as standard. However, in individual cases and based upon current and future studies alternative fraction size, total dose, overall treatment time and/or combination with chemotherapy or targeted agents may be considered in order to increase efficacy with reduced late morbidities.

Keywords: Limb soft tissue sarcoma; surgery; preoperative radiotherapy; combined modality treatment; targeted agents; chemotherapy

Submitted Jan 25, 2018. Accepted for publication Apr 19, 2018.

doi: 10.21037/cco.2018.05.02

View this article at: <http://dx.doi.org/10.21037/cco.2018.05.02>

Introduction

Both the NCCN (1) and ESMO guidelines (2) suggest combining limb sparing surgery (LSS) and external beam radiotherapy (RT) for patients affected with intermediate or high-grade ESTS. LSS and RT result in high local control rates exceeding 85% in patients with extremity soft tissue sarcomas (ESTS) after surgery with negative margins (3-5). This combination regimen has widely replaced the need for

amputations (6). Both guidelines (1,2) offer the opportunity to select individual patients for both pre- and postoperative RT. 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 6 to 7 weeks (4). Surgeons may still be reluctant to refer ESTS patients for preoperative RT, basing their hesitation upon a higher wound complication rate and delayed definitive surgery. Although these arguments can

be acknowledged, it should be noted that the (sometimes severe) acute complications are generally of a temporary nature. Conversely, long-term functional scores, may be significantly more impaired following postoperative RT compared to preoperative RT, and typically this morbidity profile is permanent and frequently progressive in nature. Local control and overall survival do not differ after pre- versus postoperative RT (3), but the toxicity parameters differ and these toxicities may be significant for some patients. After postoperative RT, the rate of wound complications is lower (17% versus 35%) (3). However, more late toxicities such as fibrosis, arthrosis and edema resulting in diminished functional outcome are reported after prolonged follow-up (7). Furthermore, patients with sarcomas in arms are unlikely to suffer from the same rate of wound complications following preoperative RT compared to those with sarcomas located in legs (3,8). For this reason, and for the possibility of schedule modification with the sarcoma still in situ, the remainder of this manuscript will focus entirely on preoperative RT.

An excellent local control outcome can be anticipated in patients with negative margins after preoperative RT. However, local control rates may decrease 62% or below at 5 years when resection margins after preoperative RT are tumor-positive (9-11). The addition of a postoperative boost as such has not been shown to improve local control outcomes, unfortunately (11,12). Furthermore, not all clinical settings of R1 and/or R2 surgical margins are the same. They should be clearly defined and analyzed separately. O'Donnell *et al.* (10), analyzed the outcome of 169 patients selected on having positive resection margins, and 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 deliberately sparing of adjacent critical structures and causing R1 resection margins after preoperative RT is relatively safe and contributes to improved functional outcomes. It is specifically here that multimodality management could be considered with a personalized approach, when positive margins are planned or expected. For these patients, innovative strategies, such as dose painting (i.e., focal dose escalation) and/or radiosensitization with novel agents could be discussed. An interesting observation is, that for those cases that do recur, the site of local recurrence is usually

within the field of high RT dose and much less frequently as a marginal radiation miss (13-16).

Novel treatment strategies, individually deviating from general guidelines, should aim to improve outcome of non-metastatic ESTS patients, maintaining or increasing local control probability while diminishing early and late toxicity. Obviously, ESTS consists of a group of diseases including many histological subtypes with specific features, differences in biology, genetics, clinical behavior and/or sensitivity to both chemotherapy and RT. Accordingly, it is improbable that all these entities will benefit from a single uniform regimen which is an inevitable shortcoming of generalized guidelines.

Several questions could be raised at the multidisciplinary tumor board prior to any therapeutic intervention: (I) what would be the optimal radiation fractionation including fraction size, total dose and overall treatment time, as well as (II) should RT be combined with conventional chemotherapy and/or targeted agents, and (III) should different histological subtypes be treated by different treatment schedules?

Methodology

This overview is based on a systematic analysis of 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 collected. Other relevant articles were obtained by studying reference lists from these articles. Additional abstracts presented at international sarcoma meetings were included. Information on relevant clinical trials was obtained from the ClinicalTrials.gov website.

Evidence-based medicine on fraction size, total dose and overall treatment time

Outside the setting of well-designed prospective clinical trials, the combination of LSS and conventionally fractionated RT is the current standard approach, as proposed by the National Comprehensive Cancer Network (NCCN) (1) and European Society for Medical Oncology (ESMO) guidelines (2). However, in selected patients, in an attempt to adapt management in an individualized manner, omission of RT could be considered (17-19).

If the closest resection margin is more than 1 cm the likelihood of an additional gain in local control rates even without RT is probably small. Pisters *et al.* (17) 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 *et al.* (18) have reported on 74 patients, treated by surgery only with sarcomas of a relatively small size (median, 4 cm; range, 0.5–31 cm). At 10 years, the local failure rate was 13% when the surgical margins were <1.0 cm. They observed no local failures when the margins were ≥ 1 cm. Data on 684 sarcoma patients from the Memorial Sloan Kettering Cancer Center (MSKCC) were used to develop a nomogram based on clinicopathologic factors to quantify the risk of local recurrence after LSS without adjuvant RT (20). 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, leading to an underestimation of the actual risk. Conversely, 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. Since local recurrences (if they occur) are more frequently observed within the first few years after surgery, local control rates reported at 5 years, with very few beyond, may be considered as realistic. These data suggest that in half of all patients durable local control following surgery without RT may be anticipated. Another source of local control rates after surgery alone are the “no-RT” arms of the two available randomized studies as reported by Pisters *et al.* (21) and Yang and colleagues (5,22). Dependent upon histological grade, local control rates ranging from 68% to 78% at 10–20 years have been reported. As ubiquitous in oncology, even with adjuvant RT local relapses do occur. In sarcoma literature, up to 10–15% of patients may recur locally despite the use of combined LSS and RT (3,4). This leaves a potential subgroup of approximately 30–40% of patients who appear to truly benefit from the addition of RT to LSS. This percentage is clinically significant and at least similar to or even much larger than the benefit rates observed after breast conserving surgery, especially in younger women (23).

Obviously and very important to note, is the fact that there is no support forthcoming from randomized trials to treat ESTS patients with surgery alone. Refraining from RT for most patients remains an investigational and

personalized decision. This statement holds true specifically for the most prevalent clinical manifestation of patients with large and/or deep seated and/or intermediate to high grade sarcomas and to a much lesser extend (if any) for small, low grade superficial tumors. For personalized care, 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. Furthermore, factors like age, co-morbidities, smoking habits, travel distances to not the nearest but sarcoma specialized RT department and patient preference need to be taken into account when counselling an individual patient on the pros and cons of RT in combination with LSS.

In the early period of limb preservation, 3–4 decades ago, Eilber and colleagues (24,25) investigated alternative dose fractionation approaches all containing intra-arterial or intravenous adriamycin. From 1974–1981, 77 patients received 10 \times 3.5 Gy, from 1981–1984, 137 patients received 5 \times 3.5 Gy and from 1984–1987, 112 patients received 8 \times 3.5 Gy. After 1987, schedules with either cisplatin or ifosfamide were tested, but the RT prescription remained unchanged at 8 \times 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. Temple *et al.* have also combined intra-arterial or intravenous adriamycin with 10 \times 3 Gy preoperative RT (26). This reduction of the fraction size from 3.5 to 3 Gy, was correlated with a reduced wound complication rate of 15%, while maintaining local control at 97% at 5-year follow-up. Unfortunately, no long-term follow up data on late functional sequelae are available from these four studies. From a radiobiological point of view, however, it can be estimated that the normal tissue complication probabilities after these regimens may be lower than after schedules with biological equivalent doses of 50 Gy conventionally fractionated. Although the α/β ratio for the different sarcoma subtypes is unknown, it is possible that the value is below 10 Gy (27). On the other hand, the α/β ratio for surrounding normal tissues are known and estimated around 3 Gy.

The RTOG 9514 study tested an alternative approach, reducing the total RT dose to 44 Gy in combination with chemotherapy (28). In 93% of all participating patients R0 resections were achieved and at 3 years, the local control rate was 90%. Of note, the toxicity profile for this combined chemotherapy and RT approach was significant.

Late functional outcome data from this study have not been reported.

Another opportunity to decrease RT dose is by hypofractionation as reported by the Polish Sarcoma Study Group, reporting on 272 patients in their phase II study. A dose of 5×5 Gy followed by surgery three to seven days later was investigated. After a median follow-up of 35 months, the estimated 5-year local failure rate was 19% (29). Another hypofractionation study on 5×6 Gy is currently accruing patients (NCT02701153).

Studies on myxoid liposarcomas (MLS) are consist in their observation of exquisite radiation sensitivity. Marked tumor volume reductions during RT and excellent local control rates (30–32) have been reported. After surgery, the resection specimens frequently show a fibrotic myxoid stroma containing, non-lipogenic, hyalinized structures. Gross evidence of tumor necrosis is uncommon, but often only a few (if any) visible tumor cells remain on microscopic examination (33). 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). The study, accruing MLS patients only, aims to maintain local control after this reduced dose, hopefully reducing both wound complications and long-term toxicities.

To compare all published data, radiobiological Linear-Quadratic Model calculations have been performed by Haas *et al.* (34). It has been suggested, that in the preoperative setting a dose response relationship for local control above 28 Gy (25) in 8 fractions of 3.5 Gy could be questionable and if it exists it might be marginal. Biologically it could be assumed that wound complications are related to RT dose and volume (8,24,25,35–37). The impact of fractionation on late functional outcome has yet to be fully explored. Mature results of both these strategies may provide clinical insight in the relationship between hypofractionation in combination with a dose reduction on late radiation effects.

Evidence based medicine on the combination of RT and conventional chemotherapy and/or targeted agents for soft tissue sarcomas (STS)

For many carcinomas, concurrent chemoradiotherapy frequently results in increased local control rates sometimes translating into increased overall survival. Therefore, it may be worthwhile to explore concurrent systemic agents with RT, including radiosensitizers in ESTS especially among patient subgroups at high risk for local and/or distant failure

such as those expected to have positive surgical margins. Without exceptions, reporting on short-term parameters like toxicity and long-term characteristics like local control, late functional outcome, quality of life and survival are mandatory in the design of such new combinations. It is presently not clear how to best estimate the clinical benefit of induction treatment for localized ESTS. Although the above mentioned late outcomes measures 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 (38–41). There is a need for prospective clinical studies incorporating these aspects with the purpose of validation. In the next paragraph, combination regimens will be compared to RT only, focusing on the induction of a pathological response such as necrosis in the operation specimens, local control and wound healing problems. A frequently accepted definition of a pathological complete remission (pCR) is the induction of greater than or equal to 99–100% necrosis (or less than or equal to 1% residual visible tumor cells). A near pCR can be defined as greater than or equal to 95% necrosis. Canter (42) and Shah (43) have suggested, that a (near) pCR can be anticipated in only 8–10% of cases following RT alone to 50 Gy in 2 Gy fractions. Nevertheless, the true prognostic significance of a treatment-induced pathologic response in ESTS after neoadjuvant therapy has yet to be determined (44,45).

Studies on conventional chemotherapy combined with RT in preoperative STS management

The already discussed RTOG 9514 trial (because of its RT dose reduction) investigated the so called “MAID” regimen (28): mesna, doxorubicin, ifosfamide, and dacarbazine chemotherapy, interdigitated with preoperative split course RT and three cycles of postoperative chemotherapy. This schedule merits caution because it was highly toxic with 83% grade IV and 5% grade V toxicities possibly due to the fact that the RT fields extended 9 cm above and below gross disease, as well as to the fact that the ifosfamide dose was 2,500 mg/m² which was higher than that explored in a prior pilot study (46). Nonetheless, in 27% of the evaluable patients this combination appeared to induce a pCR. At longer follow-up, a significant survival benefit for those treated with chemotherapy has been

reported (47). Unfortunately, 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 LSS at the time of assessment after induction chemoradiation) and 2 cases of acute myelogenous leukemia have been observed (48).

Ifosfamide-based regimens have been investigated in retroperitoneal sarcomas (49) and in ESTS (50). MacDermid and coworkers combined 8×3.5 Gy with concurrent ifosfamide (2.5 g/m² per day for 5 days) and reported a pCR rate of 11.8%, R0 resections in all cases, and a 5-year local control rate of 89% (50).

Ryan *et al.* (51) applied epirubicin 30 mg/m² per day and ifosfamide at a dose of 2.5 g/m² per day, both on days 1 to 4, in combination with the same regimen of 8×3.5 Gy regimen in ESTS and body wall sarcoma patients. This though toxic regimen induced a (near) pCR rate of 40%.

Gemcitabine and temozolomide have been shown to act as radiation sensitizers, but data for these agents in the setting of STS are scarce (52). Furthermore, apart from the use of gemcitabine as treatment for metastatic leiomyosarcomas, data showing single agent efficacy are lacking (53).

Studying (neo-)adjuvant chemotherapy trials such as the Italian/Spanish (54), the EORTC 62931 (55) and the RTOG 9514 (28) studies, it can be concluded that a delay of the start of RT in these trials did not correlate with an adverse effect on local control but delivery of chemotherapy did not negate the necessity for RT.

Studies on targeted agents combined with RT in preoperative STS management

From a biological rationale, combinations of RT with targeted agents are very appealing. Neovascularization and angiogenesis are fundamental mechanisms in tumor initiation, promotion, and the acquisition of a metastatic phenotype (56). It has been shown, that STS may overexpress angiogenic factors in both tumor tissue and serum (57) and that the combination of RT and antiangiogenic agents potentially exhibits synergistic effects (58). Radiosensitization could be both clinically and biologically significant in STS because pCR and near-pCR have been associated with improved oncologic outcomes in some but not all series of STS patients treated with neoadjuvant therapy (42,44). It should be anticipated, that a combination of RT with targeted agents may result both in increased toxicity profiles (within the radiation volumes as well as the known systemic side effects of the compounds by

themselves, research in this area is summarized below.

Yoon and colleagues (59) combined 28×1.8 Gy with bevacizumab and observed an induction of ≥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 and only 1 out of 6 patients with a retroperitoneal/pelvic sarcoma had a local recurrence.

Canter *et al.* (60) 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 were observed in 80% of cases. Major (grade 3) wound complications were reported in 3 of 8 cases while R0 resections could be performed in 6 of 8 cases. No local failures have been observed after a median follow-up of 3 years.

Meyer and colleagues (40) combined sorafenib with 8×3.5 Gy and epirubicin and ifosfamide-based for high risk extremity soft-tissue sarcomas. Patients received 3 cycles of epirubicin and ifosfamide pre-operatively and 3 cycles post-operatively. Epirubicin was omitted during RT. 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.

Jakob and colleagues (61) have investigated sunitinib in combination with 28×1.8 Gy. Although all patients completed the RT schedule, in 5 out of 9 patients sunitinib dose had to be adjusted. Pathological examination revealed ≥95% tumor necrosis in 3/9 resected specimens. Lewin and colleagues (62) also cautioned on the combination of 28×1.8 Gy with sunitinib. Irrespective of dose de-escalation of sunitinib, a 44% grade 3+ hepatotoxicity rate and an overall grade 3+ toxicity rate of 78% have been observed. Remarkably, a substantial higher local failure rate (HR, 8.1; P=0.004) was apparent in patients receiving sunitinib. However, after this combination an almost doubling of the median tumor necrosis percentage (40%, range 5–100%, versus 75%, range 1–95%) as compared to RT alone was observed.

Finally, Haas *et al.* have 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 (63). They also observed an unexpectedly high rate of grade 3+ hepatotoxicity of 27%. In 40% of the resection specimens a

pathological (near) complete remission could be appreciated.

Obviously, receptor tyrosine kinase inhibitor (RTKI) based studies are encouraging but they need to be confirmed in larger cohorts with longer follow-up.

Hafnium oxide nanoparticles (NBTXR3, intended to enhance the RT effect by intratumoral injection) have been shown to induce relatively few side effects in a 22-patient phase I study (64). A pathological near complete remission has been observed in two patients, at the highest NBTXR3 dose of 20%. This dose level, however, was not recommended for further studies due to unacceptable injection-related pain and postoperative wound complication. The subsequent phase II/III trial is currently accruing patients comparing RT to 50 Gy alone to the same RT schedule combined with intra-tumoral NBTXR3 (Trial Identifier NCT02379845).

Prolonged follow-up of all these studies are awaited and finally, the use of the pathological response as a surrogate marker for local control or other oncological outcome parameters needs to be evaluated in future studies.

Discussion

This overview of available literature should be concluded with repeating the evidence-based statement that the current standard on preoperative RT is a conventionally fractionated schedule of 50–50.4 Gy in 1.8–2 Gy fractions. It is our medical and legal obligation to provide the best care available based upon peer reviewed treatment guidelines. However, it is also our duty to deviate from these general guidelines, to be clearly documented by arguments in respective medical files, when characteristics of an individual patient so dictate. In a shared decision-making process, on an individualized approach, treatment burden together with its efficacy and toxicity should be discussed. A major challenge as sarcomas represent an “orphan disease”, is to perform research addressing translational issues and the conduct of studies. However, with transparent scientific methodologies, opportunities still exist for treatment adjustment modifying both the RT schedule itself and addressing possible combination with systemic compounds. Specifically, after R1 resections and/or in sarcoma subtypes more at risk for to locally relapse [e.g., myxofibrosarcoma and malignant peripheral nerve sheath tumor (65–68)], such combination regimens may possibly provide improvement in oncologic outcome. Conversely, these combinations may enable a reduced RT dose in the setting where local control rates are already anticipated to be high, especially

in the concern of potential radiation induced toxicities like wound complications. Although the 50 Gy regimen remains standard for preoperative management of ESTS (3,4), 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 RT dose reduction study are examples of completed or ongoing investigations respectively, they remain phase II experiences that need appropriate validation.

Delayed wound healing is a serious side effect after preoperative RT. In part, this risk might be related to patient and tumor characteristics (e.g., obesity, diabetes, smoking habits and the location of the sarcoma), as well as RT parameters such as total dose, fraction size, treatment volume, skin flap sparing and modern RT techniques (8,14,35–37,69).

The approach of a reducing the preoperative RT, enabled by the combination with sensitizing agents could be a major step forward, provided such combinations maintain or improve local control in association with a reduction in perioperative and long-term morbidity, ideally improving late functional outcome and quality of life for these patients. The side effects and costs of the studied agents should be carefully balanced against the desired gain in oncological outcome parameters. Of course, well-designed randomized phase III clinical trials should be regarded as the golden standard to test new regimens, but in the setting of rare malignancies like sarcomas, this may be extremely problematic. New models to overcome this challenge should be explored. Trials based upon modern Bayesian principles (70), like the MLS “DOREMY” trial (NCT02106312), may provide alternative means to acquire reasonable evidence to guide future local management in this rare malignancy.

Acknowledgements

None.

Footnote

Conflicts of Interest: RL Haas received research grants to the institution, though these grants and the supplying sponsors are unrelated to the topic of this manuscript.

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Cite this article as: Haas RL. Preoperative radiotherapy in soft tissue sarcoma: from general guidelines to personalized medicine. *Chin Clin Oncol* 2018;7(4):41. doi: 10.21037/cco.2018.05.02