Radiotherapy and Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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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ARTICLE INFO

Article history:
Received 8 September 2015
Received in revised form 7 December 2015
Accepted 13 December 2015
Available online xxxx

Keywords:
Limb Soft Tissue Sarcoma
Surgery
Preoperative radiotherapy
Combined modality treatment
Targeted agents
Chemotherapy

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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http://dx.doi.org/10.1016/j.radonc.2015.12.002
0167-8140/

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

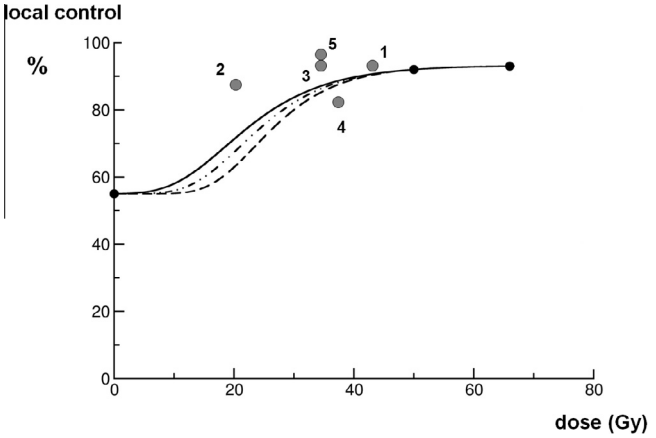

Fig. 1. A hypothetical local control probability curve, for simplification, calculated by: $S = \exp(-[\alpha D + \beta D^2])$. In this graph, at 0 Gy the most unfavorable subgroup of patients (age above 50 years, sarcomas larger than 5 cm, resected with close or positive margins, and unfavorable histological 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.

Please cite this article in press as: Haas RLM et al. Preoperative radiotherapy for extremity soft tissue sarcoma; past, present and future perspectives on dose fractionation regimens and combined modality strategies. Radiother Oncol (2015), http://dx.doi.org/10.1016/j.radonc.2015.12.002