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EDITORIAL

Fine Tuning the Radiation Treatment for Extremity Soft Tissue Sarcomas

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In this issue of *Annals of Surgical Oncology*, Roeder et al. present the results of a large European pooled analysis of patients treated with intraoperative electron radiation therapy (IORT) combined with external beam radiation therapy (EBRT) after gross total resection of extremity soft tissue sarcoma.[1] The authors offer compelling, confirmatory evidence that this treatment strategy yields high rates of local tumor control with excellent rates of preserved limb function.

To better understand the results presented by Roeder et al., readers are reminded that traditional postoperative EBRT uses a shrinking field technique, generally consisting of two phases—an initial phase treating the tumor bed, with approximately 3–4 cm proximal/distal margins and approximately 1.5 cm (anatomically constrained) radial margins to 50 Gy/25 fractions, followed by a 'boost' of an additional 10 Gy/5 fractions to the tumor bed and approximately 1 cm margin if surgical margins are negative and 16 Gy/8 fractions if the margins are positive. For those patients receiving preoperative radiation, 50 Gy/25 fractions is delivered to the tumor, with approximately 3–4 cm proximal/distal margins and approximately 1.5 cm radial margins.[2] If the surgical margins are negative after preoperative radiation therapy (RT), no additional postoperative 'boost' RT is administered since local control is very high, i.e. 97% in a series from Massachusetts General Hospital.[3] Even for patients resected with a positive margin after preoperative RT, some centers will not administer any additional postoperative radiation, arguing that the oncologic value of the additional radiation is uncertain, in part because of the very long interval (approximately 2 months) between the end of preoperative radiation and the start of any postoperative boost radiation.[4]

Because late toxicity and functional outcome correlate with the high-dose irradiated volume, several groups have replaced the external beam boost phase with an intraoperative electron (IOERT) or brachytherapy (HDR-IORT) boost.[5,6] Guiding a high single dose directly to the tumor bed under visual control during surgery does not only result in smaller high-dose volumes while maintaining or even increasing local control, but also enables the exclusion of organs at risk, such as major nerves or skin from the radiation field, which may reduce late toxicities and/or improve long-term functional outcome. However, the value of an intraoperative boost has been questioned because most of the available evidence is based on retrospective, single-center analyses with small sample sizes, inhomogeneous patient cohorts, and different inclusion criteria.[7] As randomized, prospective studies on soft tissue sarcomas can be challenging to complete (due to a variety of reasons, including the rarity of the disease and difficulties in funding studies in orphan diseases), their pooled analysis represents a reasonable way to address issues not otherwise assessable in small cohorts.

The results presented by the consortium, as noted above, are relevant for the boost phase of treatment for patients receiving postoperative radiation for either negative or positive margins, and those patients who have received preoperative radiation and resected with a positive margin for whom the effectiveness of the boost RT might be

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augmented by intraoperative radiation that can be administered within a shorter time interval (approximately 1 month) after completion of the preoperative EBRT.

The target area for IORT was defined in conjunction with the surgeon, and usually included the high-risk area for positive margins with a safety margin of 1 cm. Uninvolved radiosensitive tissues (for example, major nerves) were displaced or protected by lead. All patients received additional EBRT either preoperatively (17%) or postoperatively (83%).

The reported rate of local tumor control at 5 years was 86%, which is in the expected range of that achievable with EBRT, especially when one considers that 29% of patients had positive margins.[8] The 10-year local control rate was 85%, confirming multiple series indicating that most local failures occur within 5 years.[8] Only margin status was predictive of local control on multivariate analysis, with a 5-year local control rate of 94% in patients with negative margins versus only 69% when margins were positive. It is worth emphasizing, as the authors have done in their discussion, that the intraoperative radiation boost did not compensate for positive margins; hence, re-excision, if technically feasible, should always be considered for patients with positive margins.

Secondary amputations were necessary in 14 patients (5%), mainly due to recurrences (n = 11). In patients with preserved extremities, only 34 (14%) reported a poor functional outcome (14%).

These data presented by Roeder et al. provide a strong rationale for using IORT for the boost phase of treatment in the appropriate patient groups, as noted earlier. It should be mentioned that this technique is not likely applicable for patients with subcutaneous tumors because of the likely adverse impact on wound healing, unless the boost was only delivered to deeper tissues and spared adjacent skin and underlying subcutaneous tissues. I would also be reluctant to use this technique for myxofibrosarcomas, which can be so infiltrative at multiple margins that the wider coverage afforded by external beam irradiation would seem to be more appropriate.[9] Roeder et al. indicate that they plan to further test their hypothesis that the good functional outcome with this approach might be a direct consequence of the smaller high-dose volume of an IORT-boost compared with an EBRT-boost in a prospective trial using validated assessment tools. While we await the results of that prospective study, the data presented here from their pooled analysis support the use of IORT for appropriately selected patients with extremity soft tissue sarcomas.

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