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THE TWO papers by Drs Keus and Robinson present a comprehensive overview of the issue of pre-operative versus postoperative radiation therapy in the management of soft tissue sarcomas. Historically, the standard local therapy of localised soft tissue sarcomas of the extremities was amputation. However, the realisation that many patients ultimately die of metastatic disease, coupled with the absence of any randomised data to support the hypothesis that improved local control renders an improvement in disease specific survival for soft tissue sarcomas [1, 2], provided the impetus to define therapies which offer equivalent local control without amputation. Thus, in an attempt to optimise functional outcome and quality of life, treatment strategies have rapidly evolved over the past three decades to limb sparing surgery in conjunction with radiation therapy.

Both authors have identified this combined modality, limb sparing approach as appropriate management for many soft tissue sarcomas. As demonstrated in a randomised trial at the National Cancer Institute, this limb sparing approach has resulted in local control and survival rates which are equivalent to those achieved with amputation alone [1]. Radiation can be administered prior to, following and during the surgical procedures, with expected local recurrence rates of 5–20%. Each option is associated with practical and theore-

tical advantages and disadvantages, with the goal of therapy being limb preservation with maximal functional and quality of life outcome, with minimal risk of local recurrence and treatment related morbidity. Both authors have identified several of the issues central to this discussion of the timing of radiation therapy which are used in the selection of the most appropriate treatment for any individual.

PRE-OPERATIVE RADIATION THERAPY

Several theoretical advantages alluded to by Dr Robinson are associated with the use of pre-operative radiation therapy.

(1) Pre-operative radiation portals are defined on the basis of extent and location of disease defined by clinical radiographic assessment. On the contrary, postoperative fields generally encompass the entire operative bed, including the drain site. Thus, pre-operative fields are usually smaller [3] and doses are generally lower [4, 5]. In a prospective study evaluating radiation field size, Nielson and colleagues [3] reported results on 26 patients who were planned for pre-operative radiation and then were replanned for postoperative radiation following surgery: field sizes were 241 cm^2 and 391 cm^2, respectively. Smaller portals and lower doses as used pre-operatively may lower the treatment related morbidity.
(2) Pre-operative radiation therapy avoids tumour hypoxia and potential decreased radiosensitivity which may occur in a violated tumour bed.
(3) Resectability may be improved with tumour shrinkage with a potential to convert unresectable lesions and may enable the surgeon to perform a limb sparing procedure. Microscopic tumour cell sterilisation may reduce the risk of iatrogenic tumour seeding at the operative bed. This in turn may enable the surgeon to reduce the extent of resection without compromising margin status, thereby enhancing the possibility of improved functional outcome.
(4) The early multidisciplinary involvement necessary in the implementation of pre-operative radiation therapy fosters a higher level of care that is otherwise often compromised.

The disadvantages are that a course of pre-operative radiation therapy may delay resection, or result in artifactual interference with accurate pathological evaluation and consequently alter prognostic information, or may compromise surgical wound healing.

POSTOPERATIVE RADIATION THERAPY

Theoretical advantages associated with the use of post-operative radiation therapy include the following:

(1) Resection without delay, which provides a more accurate assessment of histology and grade than an incisional biopsy, and may also relieve some patients' trepidation.
(2) Avoid the increased risk of surgical wound complications associated with pre-operative therapy.
(3) As alluded to by Dr Keus, a wide excision alone, obtaining negative margins may suffice for treatment of some sarcomas, without the need for adjuvant radiation therapy. The effectiveness of treating high grade soft tissue sarcomas measuring less than 5 cm with wide excision alone was demonstrated by Geer and colleagues [6], who reported a recurrence rate of 11%, and an overall 5-year survival of 94%. Neither adjuvant chemotherapy nor radiation therapy will substantially improve the outcome. Similar results were reported by two additional studies [7, 8]. Clearly, not all patients with soft tissue sarcoma require adjuvant radiation therapy. Surgery alone may be sufficient for completely resected, less than 5 cm lesions resected with clearly negative margins. Similarly, for smaller, more superficially compartmentalised tumours in which resection would likely yield widely negative margins, pre-operative therapy would not likely be of benefit.

Unfortunately, no prospective randomised trial comparing pre-operative radiation therapy with postoperative radiation therapy has been completed. The authors allude to the seminal work reported by Suit and Spiro [9], which demonstrated improved local control in larger (> 15 cm) lesions in patients treated with pre-operative radiation therapy compared with postoperative radiation. This result is echoed by Barkley and colleagues who reported 90% local control, 100% limb salvage and 14% complication rate in 114 patients with lesions larger than 5 cm who were treated with 50 Gy pre-operative radiation therapy. The value of these studies is limited by their retrospective non-randomised trials and by invariably including patients with soft tissue sarcomas of other sites (e.g. head and neck, retroperitoneum and truncal) and occasional patients with recurrent disease. Data from these trials also suffer due to the inclusion of a variety of other therapies (i.e. amputation, chemotherapy). Nevertheless, for the reasons alluded to above, strong consideration for pre-operative radiation therapy should be given to those patients who present with large tumours, especially when the ability to achieve clear surgical margins is in doubt. The bottom line is that the combination of radiation therapy in some form with conservative surgery will achieve adequate local control in the majority of cases. As pointed out by the authors, the importance of the size and grade of the tumour are not to be underestimated in predicting risk for disseminated disease [10].

BRACHYTHERAPY BY AFTERLOADED INTERSTITIAL IMPLANTATION

It is noteworthy that in a prospective, randomised trial reported by Harrison and colleagues from Memorial Sloan-Kettering Cancer Center evaluating adjuvant brachytherapy with or without external beam boost, local control was achieved in 90% of implant alone-treated patients with completely resected high grade soft tissue sarcomas. It is interesting that these results were achieved despite the implantation of no more than a 2–3 cm margin around the tumour bed in this study [11]. For patients with positive resection margins, the use of combined implant and external beam therapy produced better local control than brachytherapy alone (90% versus 59%, respectively). This treatment approach offers the advantages of resection of the primary without delay, while tailoring and limiting the radiation field and volume to reflect the operative and pathological findings. In this manner, when positive margins are identified postoperatively, the dose of postoperative radiation therapy is reduced by being combined

with an implant. Furthermore, when pathologically negative margins were obtained, postoperative external beam radiation therapy could be avoided altogether. In either circumstance, the goals of optimising quality of life and functional outcome are achieved. This form of therapy also reduces the overall treatment time, and may, thereby, reduce the cost of treatment.

MARGINS

The issue of appropriate margins is well discussed by Dr Robinson. Of note, data from the Massachusetts General Hospital [13] indicate that the extent of margin negativity (i.e. greater or less than 1 mm) does not impact on local control, which was reported at 96% or better in these patients. Furthermore, tumour size did not impact on local failure in negative-margin patients. As pointed out by Dr Robinson, the clinical importance of negative margins for patients who receive postoperative radiation therapy is also important, as reported by Tanabe and others [14–16].

WOUND HEALING AFTER RADIATION AND SURGERY

As mentioned by both authors, a number of large centres have reported increased wound healing complications associated with pre-operative radiation therapy, as compared with postoperative treatment. However, it should be noted that the pre-operatively treated patients generally have larger, more deep-seated tumours and are, therefore, more likely to require more extensive resections. The extent of resection was identified as a factor associated with wound morbidity in the Massachusetts General Hospital study [17]. Furthermore, two series reporting patients managed surgically only describe a wound complication rate of 27.5% (8/29 patients) and 33% (21/64 patients), which is similar to the 37% reported in the Massachusetts General Hospital study [17]. No doubt, the heterogeneity in anatomical site, histological type, age, medical status, and extent of surgery all play a role in predicting treatment complications.

CONCLUSION

As apparent in the two author's discussions, there is no consensus on the optimal sequencing of radiation and surgery. A multidisciplinary team approach at the time of presentation would undoubtedly advance the level of patient care and outcome. Although the precise relationship between local control and disease specific survival remains controversial in the literature, the impact of minimising the extent of surgical resection on functional outcome is obvious. For patients with stage IA, IIA, and IIIA disease, reported local control and disease-free survival rates remain high, regardless of the timing of radiation therapy. However, local control for patients with larger and high grade lesions is slightly less favourable, and disease-free survival is also lower, especially for stage IIIB patients, mainly due to the development of distant metastases. For patients with large, high grade lesions and in patients with deep seated lesions where negative margins may otherwise be difficult to attain, preoperative radiation therapy may be better suited to facilitate the reduction in extent of resection with negative margins and to optimise local control. Brachytherapy offers an excellent compromise between pre-operative and postoperative radiation by immediately addressing the primary site surgically, and tailoring and limiting the postoperative external beam radiation therapy doses and portals. Enrolment of patients into the Canadian study comparing pre-operative and postoperative treatment is strongly encouraged to best attempt to answer this question.

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