The primary management of localised soft tissue sarcomas is surgical resection to achieve a negative margin. Historically, local excision of soft tissue sarcoma resulted in local failure of 50-70%. Generally adjuvant radiation therapy is recommended for all intermediate to high grade sarcomas, with the exception of small (<5 cm) superficial tumours which have been widely excised. For low grade sarcomas, adjuvant radiation therapy is not recommended in the setting of a clear margin. In case of close/positive margins, further surgical excision is the preferred option to adjuvant radiation therapy.

A landmark study by Rosenberg et al established the role of limb conservation in extremity soft tissue sarcoma. Forty three patients were randomised to amputation or limb sparing surgery and postoperative radiation therapy. There was no significant difference in local recurrence, disease free survival and overall survival in the two treatment groups. The role of postoperative radiation therapy after limb sparing surgery is supported by two randomised studies. The National Cancer Institute randomised 91 patients with high grade extremity tumours to limb sparing surgery followed by chemotherapy alone or chemotherapy plus radiation therapy. A second group of 50 patients with low grade tumours was treated with resection alone versus resection with radiation therapy. With a median follow-up of 9.6 years, the 10 year local control rate for all patients with high grade sarcoma treated with radiation therapy was 98%, compared with 70% for those not treated with radiation therapy, but no overall survival benefit was shown. Of 50 patients with low grade lesions, there was also a significantly lower probability of local recurrence in patients receiving XRT, again, without a difference in overall survival.

A second randomised study by the Memorial Sloan Kettering Cancer Center also confirmed the role of post-operative radiation therapy in local control. In this study of 164 patients, patients were randomised to observation or post-operative brachytherapy after limb sparing surgery. For patients with high grade sarcoma, the five year local control rate was significantly better for those who were randomised to post-operative brachytherapy (89%) than those who were observed (66%). There was no difference in the five year disease specific survival in the two groups. For those with low grade sarcoma, there was no significant difference between the two groups of patients. However, these two randomised trials may not have been large enough to detect a small difference in survival, and the issue between local control and overall survival remains controversial.

In the setting of positive resection margins, the risk of local recurrence remains high despite the addition of postoperative radiation therapy. Further re-excision to achieve a clear margin should be considered. Several studies have shown that local recurrence is significantly associated with reduced survival on multivariate analysis, suggesting that wide surgical margins are necessary. However, an analysis by Heslin et al demonstrated a statistically significant association between a positive surgical margin and the development of distant metastases. Therefore, the positive margin was believed to be simply an indicator of a biologically aggressive tumour. This data suggests that patients who require an extensive surgical resection to obtain negative microscopic margins have a poor prognosis, related to the development of distant metastasis, and that further debilitating surgery or amputation to obtain a clear margin may not be appropriate.

Pre-operative v post-operative radiation therapy

The sequencing of surgery and radiation therapy is often determined by institution preference. The advantages of pre-operative radiation therapy include smaller field size and lower radiation dose, facilitating surgical resection by tumour shrinkage and reducing the risk of seeding at the time of surgery. In the post-operative setting, there is no delay in definitive surgery, less wound complication and no interference with pathological analysis of the resection specimen.
There is only one randomised study comparing pre-operative radiation therapy with post-operative radiation therapy in extremity soft tissue sarcoma. This multicentre trial performed by the National Cancer Institute of Canada compared 50 Gy in 25 fractions of pre-operative radiation therapy with 66 Gy in 33 fractions of post-operative radiation therapy. The primary end point of this study was the rate of major wound complication. The trial was closed early by the data monitoring committee because of a significant difference in the primary endpoint. The rate of major wound complication within 120 days of surgery was 35% in the pre-operative group and was significantly lower in the post-operative group (17%, p=0.01). There was no difference in local recurrence rate, or regional and distant failure rate. This study also examined the functional outcome and quality of life using three different instruments in the first year after treatment. The timing of radiation therapy had minimal impact, but there was a detrimental effect on the functional outcome in patients with a major wound complication. As expected, with longer follow-up, patients treated with post-operative radiation had more fibrosis because of the higher radiation dose and larger field size used in the post-operative setting. Pre-operative radiation therapy should only be given to tumours suitable for limb conservation. For extensive tumours where limb conservation surgery is not feasible, pre-operative radiation has no role in limb salvage.

**Advances in external beam radiation therapy**

Traditional 3D conformal radiation therapy in extremity soft tissue sarcoma uses parallel-opposed field or 3-field arrangement covering a large volume of the limb. Sparing of normal surrounding tissue is technically difficult. Large areas of irradiated normal soft tissue increase the risk of severe late morbidity such as fibrosis, decreased range of movement, osteonecrosis, nerve injury and oedema.

In the last decade, advances in radiation therapy delivery have allowed better sparing of normal tissue outside the treatment target volume. Reduction of the normal tissue exposed to higher doses can be expected to yield significant benefits in terms of decreasing the severity and frequency of radiotherapy related toxicities. Intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) have both been shown to provide better target coverage and tissue sparing than traditional 3-D conformal radiation therapy.

Figure 1a shows the dose distribution of a VMAT plan (left panel) and a 3D conformal plan (right panel) for chest wall soft tissue tumour. The VMAT plan has a more homogenous cover and better sparing of the heart, lungs and breasts. Figure 1b shows the better conformity and sparing of the femur and normal structures outside the target volume with VMAT (right panel) than traditional 3D conformal plan (left panel).

In the pre-operative setting, Griffin et al assessed the potential of IMRT to spare future surgical skin flaps in extremity sarcoma IMRT. This was achievable without compromising target coverage and at the same time provided better target volume conformity. The ability of sparing the femur, neurovascular bundle and soft tissue using IMRT in soft tissue sarcoma of the thigh has also been demonstrated.

VMAT can sculpt 3D dose distribution with 360 degree rotation of the linear accelerator, while simultaneously varying the rotation speed of the gantry, dose rate and the treatment aperture. It has been shown to be superior to IMRT in terms of target coverage conformity, better sparing of normal structures and significant reduction in treatment time, with the potential of minimising intra-fraction variation for different clinical scenarios. The demonstrated technical superiority of VMAT and IMRT approaches does not automatically imply that this will be associated with a patient derived clinical benefit, however the data presented make this highly suggestive.

**Figure 1:** Comparison of VMAT (left panel) and traditional 3D conformal radiation therapy. (a) 33 year-old female with a soft tissue tumour of the chest wall. VMAT provides more homogenous target coverage and better sparing of normal structures (heart, lung and breasts). (b) 57 year-old female undergoing post-operative radiation therapy for a soft tissue sarcoma of the thigh. VMAT (right panel) provides much better sparing of the femur.
Retropertioneal soft tissue sarcoma

Retropertioneal soft tissue sarcoma account for about 10% of all soft tissue sarcomas. In most series, complete resection is achieved in less than 70% of cases and local recurrence occurs in more than 50% of patients who have macroscopic complete resection. The use of combination surgery with radiation therapy is based on phase III data from soft tissue sarcoma of the extremity. The delivery of adjuvant radiation therapy is complex because of the proximity of radiosensitive normal surrounding structures. Pre-operative radiation therapy is the preferred because of the lower dose required and the displacement of the small bowel away from the radiation field by tumour mass. A prospective study of 72 patients on pre-operative radiation therapy in retropertioneal soft tissue sarcoma showed 52% local recurrence despite a macroscopic complete resection. The five year local recurrence free survival and overall survival were 60% and 61%.

Conclusion

Radiation therapy has an important role in the management of soft tissue sarcoma. Patients with soft tissue sarcoma should be referred to a multidisciplinary clinic attended by surgeon, radiation oncologist and medical oncologist - where the relative merit of each treatment modality and sequencing of treatment can be discussed. Advances in radiation therapy have the potential of lessening long-term toxicities.

References

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