Radiotherapy in soft tissue sacoma of the extremities

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Local control rates of about 80% are achievable with wide resection and radiotherapy. Attention should now focus on reduction of acute toxicities and improvement in long term functional result. Pre-operative radiotherapy has theoretical advantages over post-operative radiotherapy. The issue of whether local recurrence compromises survival is not entirely clear.

While limited resection alone is associated with high failure rates, radical resection offers good local control in soft tissue sarcoma. It involves removal of the tumour and includes one uninvolved anatomical structure in both longitudinal and the transverse planes. The resected tissue includes the origins and insertions of the musculo-aponeurotic structures, any neurovascular structures within the resection compartment, and any adjacent bone and joint if it is contained within the tissue encompassed by the surrounding plane of resection. The recurrence rate after 'adequate' surgical procedure, either radical local resection or ablation at an appropriate level, was only 2% in the Simon and Enneking series (1976). All patients with 'inadequate' surgical procedures recurred. The overall rate of local recurrence rate was 17%. In the same series, amputation was performed in 29 out of 54 patients. Local control is achieved at a cost of significant functional deficit and a high amputation rate.

Limited excision is associated with unacceptable rates of local recurrence, as microscopic residual disease frequently remains. Radiotherapy alone also has unsatisfactory results, especially for large tumours. It is unable to control tumours of moderate size without causing significant morbidity. Combining the two modalities, with surgery for the macroscopic tumour and radiotherapy for its microscopic extensions, combines the advantages of both modalities. A moderate dose of radiotherapy of about 60 Gy will inactivate the subclinical disease, usually without significant toxicity. The advantage of this approach over compartmentectomy is that it can be applied in most situations. It can be applied equally to both compartmental and non-compartmental sites, eliminating the need for amputation in many situations. Better functional and cosmetic outcome is the result of lesser amounts of macroscopically normal tissue being removed.

Radiosensitivity

The impression that soft tissue sarcoma was resistant to radiotherapy was based on early experience when large unresectable tumours were treated with now obsolete equipment. The radiation response was judged in terms of rapidity of reduction in tumour size rather than long term control. In terms of radiosensitivity, soft tissue sarcoma may not be very different from epithelial tumours. Weichselbaum et al. (1990) studied 33 tumour cell lines from biopsy samples obtained from patients prior to radiotherapy. The epithelial tumour cells derived from head and neck cancer patients were found to be more radioresistant than tumour cell lines derived from patients with sarcoma regardless of method of analysis.

There is evidence that radiotherapy alone can control a proportion of small soft tissue sarcomas. With dose equal to or greater than 64 Gy, Tepper and Suit (1985) reported 5-year actuarial local control of 44% in a group of 36 patients treated with radiation alone. For tumours less than 5 cm treated to 64 Gy or greater, the control rate was a respectable 88%. However, local failure was the rule in patients receiving less than 65 Gy, especially for the larger tumours, which is not surprising given that radiotherapy alone, using doses within the tolerance of surrounding tissues, has a similarly poor result in most epithelial tumours of more than 5 cm.

Preoperative or post-operative radiotherapy

Magnetic resonance imaging (MRI) has replaced the necessity of direct visualisation and palpation of the tumour to define the tumour volume accurately. Postoperative radiotherapy can sometimes be a disadvantage. Wound complications may delay radiotherapy thus allowing residual microscopic disease to proliferate.

The treatment volume for preoperative radiotherapy is significantly smaller than that required for post-

operative radiotherapy. The preoperative volume is planned according to the clinically and radiologically demonstrated tumour mass and the pattern of its microscopic extension. In contrast, the postoperative volume has to include all tissue handled at operation, including surgical scar, drain sites and any haematoma. Reduction of radiation treatment volume improves long term functional result.

An advantage for pre-operative radiotherapy is seen in treating sarcomas of more than 15 cm in size. It offers better local control than post-operative radiotherapy (Suit et al. 1985). Size of the sarcoma does not seem to affect the probability of local control (Sadoski et al. 1993). Most tumour cells will be inactivated by the time of surgery reducing the chance of autoimplantation of tumour into the surgical bed and establishment of distant metastasis.

For patients with fixed or large sarcomas who otherwise require amputation, radiotherapy improves the likelihood of complete resection. Robinson et al. (1992) reported the experience at the Royal Marsden Hospital, where 70 patients with large or fixed extremity soft tissue sarcomas were treated with pre-operative radiotherapy. 60% of patients responded, with 4 cases of complete tumour resolution. Pre-operative radiotherapy for initially inoperable tumours offers an alternative to amputation.

Brachytherapy

Brachytherapy gives excellent local control with the advantage of a short overall treatment time. Its effectiveness is demonstrated in the Memorial Sloan-Kettering Cancer Centre (MSKCC) experience. 126 patients with soft tissue sarcomas of extremity or superficial trunk underwent grossly complete resection with limb-sparing surgery and were randomised to adjuvant brachytherapy or no adjuvant treatment. At 5 years, local control was 82% in the brachytherapy group of receiving 45 Gy versus 67% in the no radiotherapy group. When analysed by grade, high grade tumours had local control of 90%. Total length of stay in hospital for the whole treatment was 10–14 days (Harrison et al. 1993).

In the above study, a 2 cm margin was used with satisfactory results. However, the marginal failure rate, i.e. adjacent to the area implanted initially, was high (31%) in the Institut Gustave Roussy series treated with brachytherapy (Habrand et al. 1991). Only 4% of patients failed centrally. The difference in experience may be related to the extent of excision.

Irradiation using brachytherapy techniques deviates substantially from the general principles of treatment with external beam irradiation (Lindberg et al. 1981). The target area used in the MSKCC study was defined by adding a 2 cm margin in the superior and inferior dimensions, and a 1.5-2.0 cm margin in the medial and lateral dimensions. No effort was made to cover surgical scars, or drain sites, and the irradiated volume was in general substantially less than that treated using external beam techniques.

Size and location of tumour

Selected small soft tissue sarcomas can be managed by wide excision alone. Geer et al. (1992) reported a series of 174 adult patients with small soft tissue sarcoma (< 5 cm) of the extremity treated with wide local excision. The local recurrence and survival rates of the 53 patients treated with post-operative radiotherapy were no different from those patients managed without radiotherapy. However, 15 patients in this series had amputation for tumours in areas where wide resection margins could not be achieved. The locations of those tumours were at the knee or elbow (one each) or distal location of the tumours (hand 5, foot 8).

In formulating the treatment plan for an individual patient with a small soft tissue sarcoma, the location of the tumour is a critical consideration. While adequate resection margins can often be achieved for a small lesions of the lower limb, the resection margin is usually more limited for a lesion of the upper limb or trunk. Lesions around the elbow and knee are invariably difficult to excise with adequate margins. Radiotherapy is an essential component of limb-sparing approach to such tumours.

Soft tissue sarcomas of hand and foot are often treated with amputation. Radiotherapy was believed to cause unacceptable morbidity leading to a functionless hand or a painful foot. In a functional study, Kinsella et al. (1983) reported 7 patients with Ewing's sarcoma treated to 50 Gy and 3 patients with soft tissue sarcomas treated to 60 Gy, and local control was achieved in 9 with all 3 patients with soft tissue sarcomas achieving local control. 6 out of the 9 patients with local control had essentially normal function and were able to tolerate prolonged activity with the treated hand or foot. Even with higher radiation dose, function can still be preserved with attention to radiation technique. Okunieff et al. (1986) reported 17 patients with sarcoma of hand and wrist treated at the Massachusetts General Hospital. 10 out of 12 patients with local and distant control had less than 25% decrement in limb function and had no pain or oedema associated with normal use of their hand. Talbert et al. (1990) at MD Anderson Cancer Centre reported actuarial local control rates of 80% and 74% at 5 and 10 years, respectively for a group of patients with soft tissue sarcoma of the wrist, hand, ankle and foot. 68% of patients retained a normal or fairly normal extremity.

Low grade sarcoma

Low grade soft tissue sarcomas are locally aggressive malignancies, associated with a low likelihood of metastatic disease and an excellent overall survival rate. In a National Cancer Institute (NCI) series of 80 patients with low grade sarcomas, 5 patients developed distant metastasis (Marcus et al. 1993). In the MSKCC series, 1 in a group of 45 patients developed distant recurrence (Pisters et al. 1994).

Low grade sarcomas are not radioresistant. In a retrospective review (Slater et al. 1986) of 72 patients treated with radiotherapy for unresectable sarcoma, 12 patients with low grade sarcomas (Malignancy group 1) consisting of desmoid fibromatosis, well differentiated liposarcoma and dermatofibrosarcoma protuberans, local control was achieved in 58% at 5 years. This compares favourably with the local control rates of higher grade sarcomas (33% for group II and 17% for group III). Sherman et al. (1990) reported results for desmoid tumours treated with radiotherapy alone. Local control was achieved in 10 of 14 patients with inoperable and gross residual tumours.

Local failure after conservative resection is a problem in at least 20-30% of patients with low grade soft tissue sarcomas. Further surgery results in further reduction in limb function. Amputation may be required in some recurrent tumours. Radiotherapy together with excision is recommended for larger tumours, less than ideal excision margins, residual unresectable disease, local recurrences, and in situations where amputation will be required in the event of tumour recurrence.

Brachytherapy, however, does not seem to be effective for low grade sarcomas. In a randomised study of limb-sparing surgery alone versus limb-sparing surgery with interstitial iridium brachytherapy of 45 Gy for low grade sarcoma, there was no difference in local control (Pisters et al. 1994). It is possible that for low grade sarcomas which proliferate only slowly, the short overall treatment time may be inadequate to allow redistribution of cells to the radiosensitive M and G2 phases of the cell cycle to effect measurable local control. External beam radiotherapy with extended overall treatment time is preferred for such tumours.

Management

Patients with soft tissue sarcomas are best managed in a combined consultative clinic consisting of surgical, radiation and medical oncologists specialised in the field. Being a rare tumour, experience should be concentrated in order to develop technical skills and clinical studies. The treatment results of pre-operative and post-operative external beam irradiation, and brachytherapy are quite similar, except in a few special circumstances. The cumulative experience in the treatment centre is important as extent of resection, radiation volume and radiation dose are interlinked. Communication among different specialties is crucial in achieving the best possible outcome in the management of each patient.

Surgical scars are best placed directly over the tumour, and parallel to the long axis of the intended radiation field. Accurate tumour localisation is assisted by insertion of surgical clips at time of operation to outline the surgical bed and areas of concern. Meticulous haemostasis is necessary to avoid haematoma formation.

Attention to details of radiation technique is essential in order to treat a large volume of tissue to a radical dose with a good functional result. Correct positioning of the patient simplifies the treatment technique (Tepper et al. 1982). Immobilisation device should be used routinely to improve accuracy.

CT planning is used for accurate localisation of tumour volume. Tissue compensators or wedges are usually necessary to ensure dose homogeneity. Conformal planning techniques require further development, but may offer treatment volume reductions of up to 30% (Robinson et al. 1992). Customised blocks maximise the normal tissue excluded from unnecessary radiation. A strip of skin of at least 5 cm should be spared if possible to minimised the risk of lymphoedema. Pressure areas and major tendons should be spared if possible. Treating whole joints should be avoided to prevent contracture. Tissue equivalent build up material is placed over the scar if it is not tangential to the radiation field to ensure adequate dose to the scar. As the number of clonogenic cells decreases with distance from the macroscopic disease, the radiation dose required to sterilise microscopic disease diminishes accordingly. As such, a "shrinking field" technique, consisting two to three treatment volume reductions during the radiotherapy course, is used routinely. Small fraction sizes (1.8–2.0 Gy) should be used to minimise long term morbidity. For post-operative radiotherapy, the initial volume is treated to 45–50 Gy with a 5–10 cm margin with 60–66 Gy delivered to a smaller volume. For pre-operative radiotherapy, 50 Gy is used. Weekly port films, to ensure accuracy of treatment set-up, are performed for quality control.

The patient is also monitored by a physiotherapist and a clinical nurse during the course of treatment. For suspected recurrence, MRI, nuclear scan and fine needle aspiration cytology can often provide a diagnosis. Incisional biopsy in an heavily irradiated area should be avoided.

Treatment related morbidity

Bujko et al. (1993) studied the wound complications in a series of 202 patients treated with pre-operative radiotherapy and conservative surgery between 1971 and 1989 at the Massachusetts General Hospital. A radiation boost was also given in 71% of patients. The overall wound complication rate was 37%. Secondary operation was necessary in 17%, including 6 patients who required amputation. The wound complications in the remaining 20% were treated conservatively without operation. Surgery alone can be associated with wound healing problems. Although pre-operative radiotherapy is associated with a higher wound complication rate, it has the potential advantage of reduced late toxicity and improved function.

Stinson et al. (1991) reviewed the case records of 145 patients treated with combined modalities at NCI in between 1975 and 1986. A higher complication rate was associated with inclusion of more than 50% of a joint in the radiation field, treatment to more than 63 Gy at 1.8 Gy per fraction, and radiation fields of greater than 35 cm. Overall, the percentage of patients ambulating without assisting devices and with mild or no pain was 84%.

Mundt et al. (1995) reviewed the outcome of 64 adult patients with soft tissue sarcoma of the extremities who underwent conservative surgery and radiotherapy. With an initial margin for the radiation field of less than 5 cm, the local control rates were inferior. There was however no difference in local control between 5 to 9.9 cm and more than 10 cm margin. Patients who received less 60 Gy had lower local control rates, but there was no difference between 60–63 Gy and 64–67 Gy.

Local control can now be achieved in more than 80% of patients with soft tissue sarcoma. Our focus should be on reducing acute and chronic toxicity, and improving long-term function. Attention to radiation technique, and a less aggressive approach will improve long term function. Overly generous margins and doses more than 60 Gy may not be necessary in patients after wide excision with clear margins. As excision margin, radiation margin and dose are interlinked, a combined consultative effort is necessary to reduce toxicity.

Local recurrence and survival

A number of studies have suggested that improved local control does not necessarily translate into improved survival. In the NCI randomised study (Rosenberg et al. 1982) of amputation compared with conservative surgery plus radiotherapy, there was no difference in overall survival. In a randomised study of brachytherapy versus no radiotherapy after wide excision, there was a significant improvement in local control in favour of the brachytherapy group but it did not translate into improvement in survival (Harrison et al. 1992).

In studying of the influence of surgical margins on outcome in patients with pre-operative radiotherapy for intermediate and high grade extremity sarcoma at MD Anderson Cancer Centre, patients with positive margins had increased risk of local failure. However, neither the presence of a positive surgical margin nor the occurrence of a local failure adversely affected overall survival (Tanabe et al. 1994). The authors suggested that these data should be factored into patient management decisions in cases where the goal of achieving clear surgical margins requires amputation or the significant functional compromise of the extremity.

Suit and Willet (1991) stressed the importance of local control in long term survival. Experimental animal studies demonstrated that local failure was associated with significant increase in distant metastasis. A number of studies (Collin et al. 1988, Emrich et al. 1989, Habrand et al. 1991) concluded that distant metastasis was significantly more likely in patients with local recurrence. Stotter et al. (1990) at St Mary's Hospital, London analysed their results and found that local recurrence was significantly associated with reduced survival, but only when considered as a time-dependent variable in multivarivate analysis. They found that patients with local recurrence were five times as likely to die as those with local control. Barr et al. (1991) reviewed the literature and concluded that a survival deficit due to local tumour recurrence cannot be excluded on present data. Studies that appear to indicate that local recurrence does not jeopardise survival are shown to be inappropriately analysed, to have inadequate patient numbers, or both.

However, local recurrence could be an indicator of more aggressive disease which will cause earlier death independently of local recurrence. Patients with local recurrence often have unfavourable features such as high grade and large initial tumour size. There is also a difference in the natural history of such recurrent tumours. The time from initial presentation and subsequent local recurrence may allow the subclinical disease to manifest itself. Further studies are necessary to determine whether local recurrence will lead to dissemination of disease and death (see also page 152).

Summary

The local treatment of soft tissue sarcoma is evolving.

Limb-sparing compartmentectomy offers local control but at the expense of function and a high amputation rate. The functional outcome is improved with combined wide excision and radiotherapy, at the same time achieving a similar local control rate. Future directions should include attempts to reduce toxicity and maximise the functional result. As the limb function is ultimately related to the aggressiveness of the local treatment, the optimum surgical margin, radiation volume and dose, require further investigation. The pursuit of local control should not be compromised in the quest for reducing morbidity, as the relationship between local control and survival remains unclear.

References

Barr LC, Stotter AT, A'Hern RP (1991). Influence of local recurrence on survival. A controversy reviewed from the perspective of soft tissue sarcoma. Brit J Surg 78: 648-50.

Bujko K, Suit HD, Springfield DS, Convery K (1993). Wound healing after preoperative radiation for sarcoma of soft tissue. Surg Gynecol Obstet 176: 124-34.

Collin CF, Friedrich C, Godbold J, et al. (1988). Prognostic factors for local recurrence and survival in patients with localised extremity soft tissue sarcoma. Seminars Oncol 4: 30-7.

Emrich LJ, Ruka W, Driscoll DL, Karakousis CP (1989). The effect of local recurrence on survival time in adult high-grade soft tissue sarcomas. J Clin Epidemiol 42: 105-10.

Geer RJ, Woodruff J, Casper ES, Brennan MF (1992). Management of small soft-tissue sarcoma of the extremity in adults. Arch Surg 127: 1285-9.

Harrison LB, Franzese F, Gaynor, Brennan MF (1993). Long term results of a prospective randomised trial of adjuvant brachytherapy in the management if completely resected soft tissue sarcomas of the extremity and superficial trunk. Int J Radiat Oncol Biol Phys 27: 259-65.

Habrand JL, Gerbaulet A, Pejovic MH, et al. (1991). Twenty years experience of interstitial iridium brachytherapy in the management of soft tissue sarcomas. Int J Radiat Oncol Biol Phys 20: 405-11.

Kinsella TJ, Loeffler JS, Fraass BA, Tepper J (1983). Extremity preservation by combined modality therapy in sarcoma of hand and foot. Int J Radiat Oncol Biol Phys 9: 1115-9.

Lindberg RD, Martin RG, Romsdahl MM, Barkley HT (1981). Conservative surgery and post-operative radiotherapy in 300 adults with soft tissue sarcoma. Cancer 47: 2391-7.

Marcus SG, Merino MJ, Glatstein E, et al. (1993). Long term outcome in 87 patients with low grade soft tissue sarcoma. Arch Surg 128: 1336-43.

Mundt AJ, Awan A, Sibley GS, et al. (1995). Conservative surgery and adjuvant radiation therapy in the management of adult soft tissue sarcoma of the extremities: clinical and radiobiological results. Int J Radiat Oncol Biol Phys 32: 977-85.

Okunieff P, Suit HD, Proppe KH (1986). Extremity preservation by combined modality treatment of sarcoma of hand and wrist. Int J Radiat Oncol Biol Phys 12: 1923-9.

Pisters PW, Harrison LB, Woodruff JM, et al. (1994). A prospective randomised trial of adjuvant brachytherapy in the management of low grade soft tissue sarcomas of the extremity and superficial trunk. J Clin Oncol 12: 1150-5.

Robinson MH, Ball AB, Schofield J, et al. (1992). Preoperative radiotherapy for initially inoperable extremity soft tissue sarcomas. Clin Oncol 4: 36-43.

Robinson MH, Bidmead AM, Harmer CL (1992). Value of conformal planning in the radiotherapy of soft tissue sarcoma. Clin Oncol 4: 290-3.

Rosenberg SA, Tepper J, Glatstein E, et al. (1982). The treatment of soft tissue sarcomas of the extremities: prospective randomised evaluations of (1) limb-saving surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 196: 305-15.

Sadoski C, Suit HD, Rosenberg A, et al. (1993). Preoperative radiation, surgical margins, and local control of extremity sarcomas of soft tissues. J Surg Oncol 52: 223-30.

Sherman NE, Romsdahl M, Harvey E, et al. (1990). Desmoid tumours: a 20-year radiotherapy experience. Int J Radiat Oncol Biol Phys 19: 37-40.

Simon MA, Enneking WF (1976). The management of soft tissue sarcomas of the extremities. J Bone Joint Surg 58-A: 317-30.

Slater JD, McNeese MD, Peters LJ (1986). Radiation therapy for unresectable soft tissue sarcomas. Int J Radiat Oncol Biol Phys 12: 1729-34.

Stinson SF, DeLaney TF, Greenberg J, et al. (1991). Acute and Long Term Effects on Limb Function of Combined Modality Limb Sparing Therapy for Extremity soft Tissue Sarcoma. Int J Radiat Oncol Biol Phys 21: 1493-9.

Stotter AT, A'Hern RP, Fisher C, et al. (1990). The influence of local recurrence of extremity soft tissue sarcoma on metastasis and survival. Cancer 65: 1119-29.

Suit HD, Mankin JH, Wood WC, Proppe KH (1985). Preoperative, intra-operative and post-operative radiation in treatment of soft tissue sarcoma. Cancer 55: 2659-67.

Suit HD, Willett CG (1991). Radiation therapy of sarcomas of the soft tissues. In: Soft tissue sarcomas: new developments in the multidisciplinary approach to treatment. Pinedo HM, Verweij J, Suit HD (Eds.). Kluwer Academic Publishers. Boston: 61-74.

Talbert ML, Zagars GK, Sherman NE, Romsdahl MM (1990). Conservative surgery and radiation therapy for soft tissue sarcoma of the wrist, hand, ankle, and foot. Cancer 66: 2482-91.

Tanabe KK, Pollock RE, Ellis LM, et al. (1994). Influence of surgical margins on outcome In patients with preoperatively irradiated extremity soft tissue sarcomas. Cancer 73: 1652-9.

Tepper JE, Suit HD (1985). Radiation therapy alone for sarcoma of soft tissue. Cancer 56: 475-9.

Tepper JE, Rosenberg SA, Glatstein E (1982). Radiation therapy technique in soft tissue sarcoma of extremity. Int J Radiat Oncol Biol Phys 8: 263-73.

Weichselbaum RR, Beckett MA, et al. (1990). Radiobiological characterisation of head and neck and sarcoma cells derived from patients prior to radiotherapy. Int J Radiat Oncol Biol Phys 19: 313-9.