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Current Controversies in Cancer

Is Pre-operative Radiotherapy Superior to Postoperative Radiotherapy in the Treatment of Soft Tissue Sarcoma?

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INTRODUCTION

In 1930 Leucutia wrote that 'a review of the literature concerning the 5 year cure of sarcoma in general reveals the not altogether surprising fact that the problem of radiation therapy still forms a favoured subject of speculative argumentation' [1]. Many of the issues appertaining to the delivery of adequate radiotherapy in the treatment of soft tissue sarcomas remain undecided nearly 70 years later. Foremost among these is the issue of the timing of radiotherapy in patients who will clearly require radiotherapy as part of their combined treatment. The main issues which need to be addressed are the rationale behind the choice of pre-operative radiotherapy rather than postoperative radiotherapy and case selection. The other issues are the importance of an adequate surgical margin, the radiotherapy margins to be used, the dose fractionation and the response achieved and the concomitant use of chemotherapy and consequent complications.

RATIONALE

The aim of delivering tumoricidal doses of radiotherapy pre-operatively to the patient with an extremity soft tissue sarcoma is either to render the inoperable tumour operable, or to facilitate and improve the results of surgery in otherwise operable tumours. Following pre-operative radiotherapy, the perineoplastic vascular oedema, visible particularly on magnetic resonance imaging scans, almost always resolves, making it easier to define the extent of the tumour radiologically [2]. Experimental work by Gitelis and colleagues has demonstrated thickening of the capsular structure surrounding the sarcoma following irradiation of a rat sarcoma [2].

Theoretically, there should also be a reduced likelihood of seeding of viable tumour cells locally or systemically during surgery following treatment which has killed the majority of tumour cells. However, there are no randomised data to suggest the existence of survival differences between patients receiving pre-operative and postoperative radiotherapy which might result from this.

Radiotherapists have always suggested that a decreased volume of tissue needs to be irradiated when delivering treatment pre-operatively [3]. This is because the tumour bed has not been contaminated and there is no long scar that may require treatment. Nielsen and associates [4] quantitated this by planning patients both before and after surgery and demonstrated that the size of the pre-operative field was less than the postoperative field and the number of joints included was reduced. The impact of this should be that the use of pre-operative radiotherapy is associated with an improved functional result, since other workers [5, 6] have been able to correlate the functional outcome in extremity soft tissue sarcoma patients with radiotherapy dose and the field length treated.

Another important advantage of pre-operative radiotherapy is that it engages the multi-disciplinary team early. This referral of patients prior to inappropriate biopsy or surgery improves the outcome. This has been demonstrated in a number of retrospective studies. For example, Eilber and colleagues have shown that in 18% of cases, patient management is compromised by an inappropriate first operation or procedure [7]. The use of pre-operative radiotherapy permits time to plan the surgery and encourages meticulous attention to detail in all aspects.

CASE SELECTION

Comparison of the results from pre-operative and post-operative radiotherapy is complicated by case selection.

Patients with larger, higher grade, proximal lower extremity lesions tend to be more difficult to operate on and have been selected for pre-operative radiotherapy [8]. Similar selection criteria have been used in other series. The Royal Marsden experience has been reported where pre-operative radiotherapy was given for initially inoperable lesions [9]. Barkely and associates also reported a series of large unresectable tumours or those requiring hemipelvectomy disarticulation or amputation [10]. Tumours which are more readily operable are more likely to receive postoperative radiotherapy.

SURGICAL MARGINS

The data on the importance of surgical margins following pre-operative radiotherapy are conflicting. Tanabe and colleagues found that there was 91% local control in those patients with a negative margin compared with 62% with a positive margin [8]. Intra-operative tumour violation was a highly significant risk factor for local failure. Those patients in whom there was a positive surgical margin had four times the risk of local recurrence compared with those who did not. However, others have found local control to be independent of the extent of clear margin.

RADIOTHERAPY MARGINS

It is rare for authors to detail accurately the normal tissue margins they put around radiologically and clinically evident tumour when treating patients with pre-operative radiotherapy. It is likely that they have been quite variable. However, margins used pre-operatively tend to be smaller than those used postoperatively. Brant and associates obtained 91% local control where generous margins of 7–12 cm were used [11]. Mundt and colleagues found 30% local control where the margins were less than 5 cm and 93% where they were over 5 cm [12]. This extraordinary result has not been reported elsewhere.

DOSE

The dose required pre- and postoperatively may well be different. Conventionally lower doses are used in pre-operative radiotherapy where the tumour has not been violated. Back in 1960, Friedman and Egan reported that 90 Gy was required to eradicate large sarcomas [13]. In our series of pre-operatively treated patients [9], we demonstrated a dose response, with 80% response with doses over 60 Gy. Because of the small number of local failures it was not possible to determine whether there was a correlation between dose response and local control. Tanabe and colleagues found no such correlation [8].

Classical teaching has been that sarcomas are radioresistant. However, recent radiobiological information [12] suggests that sarcomas are in fact radiosensitive. The authors indicated that this might mean that total dose may not be important in achieving tumour control. Conventionally, a dose of 50 Gy in 5 weeks is used pre-operatively, with a boost given where there is tumour present at the surgical margin. However, practice here varies greatly between centres. Some centres will give no boost where there is microscopically clear surgical clearance following pre-operative radiotherapy and others routinely give a postoperative boost which may be intra-operative [3]. Tanabe and colleagues reported a 62% local control in those patients who were surgical margin positive and did not receive a boost [8]. Some evidence that dose may be important was seen in the series reported by Levine and associates [14], where 25 Gy/10 fractions was given with chemotherapy and a postoperative boost where the margin was close. There was a high local recurrence rate for those receiving 25 Gy/10 fractions only.

FRACTIONATION

A number of different fractionation schedules have been evaluated both pre- and postoperatively. Hypofractionated, schedules have been reported by Abbatucci and colleagues using 6.5 Gy×2 [15] and in many patients by Eilber and associates where doses between 17.5 Gy/10 fractions and 35 Gy/10 fractions were used in conjunction with intra-arterial doxorubicin [7]. Interestingly the local recurrence rates rose in the latter studies when the dose was reduced from 35 Gy/10 fractions to 17.5 Gy/10 fractions, suggesting the importance of dose. Hyperfractionated schedules have also been evaluated by Gariss and colleagues using 39.6 Gy/22 fractions twice daily [16] and we used 60 Gy/50 fractions twice daily [17]. No clear evidence for the value of this has yet been demonstrated.

CHEMOTHERAPY

Eilber and colleagues first popularised the use of intra-arterial chemotherapy with rapid hypofractionated pre-operative radiotherapy [7]. The complication rate from combining 35 Gy/10 with intra-arterial doxorubicin was high (37%). This fell when the dose of radiotherapy given pre-operatively was reduced to 17.5 Gy, but with a concomitant increase in local failure. Later work by Eilber and colleagues has also demonstrated no difference between the results from using either intravenous or intra-arterial therapy and recently has suggested that more aggressive chemotherapy may improve the local response [18]. Many others have followed similar schedules [19, 20], but case selection and the lack of randomised data cloud the issue.

COMPLICATIONS

There is some evidence that pre-operative radiotherapy is associated with an increased complication rate compared with postoperative radiotherapy. Frezza and associates [21] reported a 15.4% complication rate versus 6.1% with post-operative radiotherapy. The use of large fractions increases the late morbidity, particularly with intra-arterial doxorubicin [7, 17]. These authors have found a 26–41% major complication rate. Wound complications have been documented in a number of series. Bujko and colleagues in 202 cases found a 37% complication rate with 16.5% re-operation rate [22]. On multi-variate analysis, the important factors appeared to be: a tumour in the lower extremity; increasing age; postoperative boost implant; accelerated twice daily radiotherapy.

We reported a 13% major complication rate with pre-operative radiotherapy compared with postoperative radiotherapy [9, 23]. Age was the only important independent factor associated with this problem. Bell and associates reported the use of vascularised tissue transfer to improve major wound healing [24]. Eilber and colleagues have indicated that the complication rate increases with tumour size, being over 70% for tumours over 20 cm and 18% for those under 5 cm [7].

CONCLUSION

Pre-operative radiotherapy is effective in facilitating limb conservation surgery. In retrospective studies it is as effective

as postoperative radiotherapy. It may be better for larger tumours. The lower dose that is used is associated with an improved functional outcome. In order to answer the question about the difference between pre- and postoperative radiotherapy, institutions should be encouraged to consider entry into the excellent Canadian study comparing these two treatment methods.

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INTRODUCTION

In the last few decades, better understanding of the clinical behaviour of soft tissue sarcomas has considerably changed the local treatment of these tumours. The lesions were often assumed to be well delineated, but are now known to possess an infiltrating growth pattern often well beyond their pseudocapsule. This could explain the poor local control of surgical procedures such as shelling out the macroscopic mass (oops surgery) or excisional biopsies leading to contamination of the surroundings by tumour cells. It is clear that an inadequate surgical approach with incomplete haemostatic control and the wrong choice of skin incisions hampering definitive surgery are predisposing factors for local failure.

The correct surgical procedure aims at complete removal of all tumour tissue. In general, a wide local excision is recommended, consisting of removal of the entire tumour with a margin of 2 cm healthy tissue [1]. It should be realised that wide excision as the only local treatment procedure can be sufficient to control the primary tumour. Unfortunately, however, this is only true for a relatively small number of patients. In a population-based study of 73 patients, Rydholm and colleagues reported a 5% local failure rate after wide local excision without radiotherapy [2]. These patients were from a group of 129 patients with tumours located superficially to the deep fascia, that comprised only 31% of all patients with soft tissue sarcomas of the extremities or the