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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Contra:

R.B. Keus

Department of Radiotherapy, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

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

trunk wall from the southern health care region of Sweden during the study period. In addition, in a group of 30 patients from the same region, treated by local surgery for previously untouched intramuscular tumours without invasion of the deep fascia, only 2 patients developed a local recurrence, while only 4 patients received postoperative radiotherapy for marginal excision [3]. The authors argue that there is no place for routine combination surgery and radiotherapy for these specific sites.

Despite these favourable results, showing that in selected cases wide excision alone can be adequate treatment, for many patients sufficient surgical margins cannot be obtained at all points on the periphery of the tumour mass, due to the location of the tumour in relation to vital anatomic structures. In this situation, the use of combined modality treatment strategies is required for an adequate clinical outcome. In particular, the combination of surgery and some form of radiotherapy has proven to be extremely effective in obtaining local control with acceptable function.

Two randomised studies on the value of radiotherapy in the treatment of soft tissue sarcomas have been conducted. Rosenberg and colleagues at the NCI performed a randomised study comparing limb-sparing surgery plus irradiation versus amputation in extremity lesions [4]. At 5 years' follow-up, the overall survival was 88% and 89%, disease-free survival was 78% and 81% for patients receiving limb-sparing treatment and amputation, respectively. Local recurrence was 4/27 in the limb-sparing group and 0/17 in the amputation group. Although the number of patients in this study was small, it clearly demonstrated the validity of the combined therapy strategy.

The second randomised clinical trial on the value of radiotherapy in the treatment of soft tissue sarcomas was carried out at the Memorial Sloan-Kettering Cancer Center. Wide resection with intra-operative brachytherapy (BRT) was compared with surgery alone. For high-grade lesions, local control was significantly improved in patients treated with surgery and BRT with 90% and 65% local control at 5 years for the BRT and surgery alone groups, respectively [5]. However, in a recent follow-up study, the authors showed that for patients with positive resection margins, the additional use of postoperative external radiation (EBRT) was essential to obtain acceptable local control rates (90% after both BRT + EBRT versus 59% after BRT alone) [6].

These two important prospective studies, plus a number of retrospective series from large oncology centres, have provided ample data to adopt the combined therapy option as the preferred strategy in standard practice for most sarcomas [7, 8]. It is now recognised that local control can be achieved in 80–90% of patients with combined therapy. This has, therefore, abolished the need for more radical surgical procedures, as can be illustrated by the steady decrease in amputation rates for extremity sarcomas in some large centres [9, 10].

However, despite these facts, considerable debate remains as to the optimal sequence of the local treatment modalities. As the use of BRT is limited to sites with sufficient facilities and expertise and to high grade sarcomas only, most centres have to make a choice between pre-operative and post-operative external radiotherapy. In the following sections, the arguments for each approach will be reviewed.

PRE- VERSUS POSTOPERATIVE RADIOTHERAPY

Local control

The general acceptance of the combined treatment approach in soft tissue sarcomas can be credited to a great extent to the work of Herman Suit. In a classic paper from 1975, he and his colleagues from the Massachusetts General Hospital (MGH) elegantly described the rationale for the combination of surgery and radiotherapy and the different ways for sequencing these treatment modalities. It was pointed out in this paper, and confirmed when more patients were later treated, that pre-operative radiotherapy seemed superior in terms of local control, especially for the larger tumours (Table 1) [11, 12].

Although the numbers in each subgroup in this table are small, it appears that for lesions larger than 10 cm the use of pre-operative radiotherapy is to be preferred over post-operative treatment. However, whether this difference will hold in a formal comparison is unknown. The analysis of prognostic factors from retrospective series is often confusing. While large tumour size is seen as an adverse prognostic factor for local control after postoperative radiotherapy, in the MGH and in other series this could not be confirmed [13]. In a recent study of Pisters and colleagues of the Memorial Sloan-Kettering Cancer Center, an important analysis of prognostic factors for local control in extremity soft tissue sarcomas was performed [14]. This database consists of prospectively collected data from more than 1000 extremity sarcoma patients. In the Cox regression analysis, the significant adverse prognostic factors for local control were age greater than 50 years, local recurrence at presentation, histological subtype (fibrosarcoma and malignant peripheral nerve tumour) and positive surgical margins. Surprisingly, tumour size, depth and histological grade were not important

Table 1. *Five-year actuarial local control results according to size of primary soft tissue sarcomas (Massachusetts General Hospital series)*

	Postoperative		Pre-operative	
Size (mm)	No. of patients	Local control (%)	No. of patients	Local control (%)
25	20	100	11	80
26–49	45	95	16	100
50–100	64	83	63	93
101–150	12	91	34	100
151–200	6	50	25	79
>200	3	67	11	100
Total	150	87	160	92

predictive factors for local control, although they were important for predicting distant recurrence.

Even if pre-operative radiotherapy seems favourable compared with postoperative, when reported from within the same institution, this has to be interpreted carefully. Many of the postoperative radiotherapy series include patients with suboptimal surgery often performed at some referral hospital. In the Amsterdam series, 87% of the patients had previous surgery elsewhere [13]. These patients already had recurrent disease or had been operated with inadequate margins needing re-excision. Of course, this is far different from the ideal situation when a patient with a suspected soft tissue sarcoma is seen by a multidisciplinary team and the optimal sequence of treatment steps can be chosen. Keeping this in mind, it is not surprising that centres using pre-operative radiotherapy show better results.

The claim for superior results after pre-operative radiotherapy focuses on patients with large primary tumours. However, it is especially for these larger tumours that several new treatment policies have been recently proposed. Isolated limb perfusion with tumour necrosis factor in combination with γ-interferon and melphalan as induction therapy for locally advanced sarcomas is an example of this [15]. This procedure seems to be extremely potent in achieving complete responses in advanced lesions that would have been otherwise treated with mutilating surgery and wide field radiation. Long-term results are awaited and the late toxicity of this treatment, especially when subsequent oncological procedures are needed, is not fully explored. Other approaches, such as hyperthermia and high linear-energy transfer radiation, are other options that are being pursued at this moment, and it will remain unclear which strategy will become standard for these larger lesions at least for the next few years [16, 17].

Complications and functional outcome

The purpose of the combination of limited surgery and radiotherapy is to achieve adequate local control with preservation of function. Although there is a clear reduction in surgical morbidity when radical surgical procedures such as compartmental resections or even amputations can be avoided, the use of radiotherapy will adversely influence the functional outcome. Late effects, such as limb oedema, soft tissue fibrosis, vascular and nerve injury and bone fractures, have been reported after all forms of combined therapy [6, 13, 18, 19].

It is generally believed that pre-operative radiotherapy can lead to increased wound healing problems after surgery. A wound complication rate of 25–30% was seen in several large centres [18–20]. Considering that major wound complication, such as delayed healing, wound infection, necrosis and dehiscence, are associated with poor functional outcome [21], it is conceivable that the alleged advantage of pre-operative radiotherapy in reducing the irradiated volume compared with postoperative radiotherapy [22] is at least partly nullified by an increased complication rate with potential inferior functional results.

A review of the literature on complications after combined therapy is hampered by the heterogeneity among sarcoma patients with respect to site, histology, prior surgery, age and medical status. Additionally, surgical and radiation techniques and supportive therapies will influence the functional results and have to be taken into account in any formal comparison between pre- and postoperative radiotherapy.

Actual situation

A remarkable observation is that although some theoretical arguments in favour of pre-operative radiotherapy exist, it appears from the literature that the actual situation in many institutions is that postoperative treatment is used for the treatment of soft tissue sarcomas. In a recent Dutch consensus text, postoperative radiotherapy is also recommended as the most practical method [8]. Several reasons for this have been mentioned.

An advantage of postoperative radiotherapy is the possibility of adjusting the radiation technique to the tumour extent as demonstrated during surgery or documented by the pathologist. During surgery, clips can be placed at specific areas of residual disease or doubtful surgical margins where a boost dose can be applied. In some situations, radiotherapy is difficult to apply due to the specific site of the tumour. For example, in the retroperitoneal space, high doses of radiation will lead to unacceptable normal tissue complications. Intraoperative measures, such as the insertion of a spacer between the target area and critical organs, can enable adjuvant radiation treatment, making postoperative radiotherapy for these situations the treatment of choice.

Another explanation why postoperative radiotherapy is more widely used, is the fact that in many countries, such as the Netherlands, many patients have their tumours surgically removed in local hospitals, often without knowledge of its malignant character. Only after the diagnosis of soft tissue sarcoma is made are these patients referred to an oncology centre for postoperative radiotherapy. One of the strongest arguments in favour of pre-operative radiotherapy might, therefore, be that by following this policy more patients are treated by experienced sarcoma surgeons.

CONCLUSIONS

It is clear that like most controversies in clinical oncology the question of the optimal sequence of combined therapy can only be solved in properly conducted randomised trials. Even then, the results merely reflect the effect of treatment in a well defined setting and are not necessarily transferable to a different situation. At least one (probably the only) study is presently being carried out by the Clinical Trials Group of the National Cancer Institute of Canada/Canadian Sarcoma Group. While the outcome of this study will be awaited eagerly, all that can be done for the moment is to consider all the arguments for each policy, since it appears that different situations require different strategies. Pre-operative radiotherapy seems attractive in larger lesions where surgical margins are expected to be narrow and combined treatment is recommended at the outset. These lesions will mainly be large, deep seated, high-grade and surgery will be extensive often requiring reconstructive procedures.

Postoperative radiotherapy should be chosen when pre-operative measures are needed to enable safe irradiation or when the extent of the tumour is not completely known or when surgery is presumed to be wide and the possibility exists that radiotherapy can be omitted. In this fast case, the typical lesion is small, superficial, low-grade and at a favourable site so that wide margins can be obtained. Between these situations, a third group of patients exists for which the optimal treatment remains questionable. Although the theoretical advantages make the pre-operative approach attractive, the feasibility of its wide use in many parts of the world is questionable. Until a prospective randomised study, such as the

one being carried out in Canada, demonstrates the validity of one of these concepts, postoperative radiotherapy will remain widely used in many centres as the treatment that is both feasible and yields satisfying results.

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Arbiter:

D. Shasha and L.B. Harrison

Department of Radiation Oncology, Beth Israel Medical Centre, 1st Ave. At 16th Street New York, New York 10003, U.S.A.

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-