Pergamon

European Journal of Cancer Vol. 30A, No. 10, pp. 1459–1463, 1994

0959–8049/94 $7.00+0.00

0959-8049(94)00302-5

Limb-sparing Therapy of Extremity Soft Tissue Sarcomas: Treatment Outcome and Long-term Functional Results

R.B. Keus, E.J.Th Rutgers, G.H. Ho, E. Gortzak, C.E. Albus-Lutter and A.A.M. Hart

The purpose of this study is to assess the long-term success rate and functional results of limb-sparing therapy in a group of 156 patients with soft tissue sarcomas of the extremities in the Netherlands Cancer Institute, treated according to a standard protocol of surgery and radiotherapy, if indicated. The patients (79 females and 77 males) were treated between 1977 and 1983 by an intended wide local excision with a margin of at least 2 cm. Postoperative radiotherapy was applied in 117 patients; 26 patients had surgery only, including 13 patients who had to be treated by amputation. The total dose was 60 Gy, with 40 Gy to a large volume and a boost of 20 Gy to the tumour bed at 2 Gy per fraction, five fractions per week. Most sarcomas were located in the proximal part of the lower extremity (51%). The group comprised 50 liposarcomas, 47 malignant fibrous hystiocystoma (MFH) and 59 other histologies; 69 (44%) had high-grade tumours. Three treatment groups with limb-sparing treatment were defined: group I (n = 26) patients who had a complete excision receiving no further treatment, group II (n = 64) with narrow surgical margins and radiotherapy and group III (n = 53) with incomplete resection and radiotherapy. The 10-year actuarial overall survival and local control rate for all patients was 63 and 81%, respectively. Multivariate analysis showed that histological grade ($P < 0.0001$), age ($P = 0.0005$) and location deep to the fascia ($P = 0.0008$) were independent prognostic factors for survival, while local control was predicted by grade ($P = 0.0014$) and treatment group ($p = 0.028$). Patients with surgery only (group I) had 81% 5-year local control as compared to 92% with radiotherapy after narrow surgery (group II) and 74% with incomplete surgery and radiotherapy (group III). Limb preservation when attempted was achieved in 90% of the patients. After limb-sparing treatment, 7% had severe impairment of mobility, 3% had lymph oedema and 16% marked fibrosis. Fractures in the irradiated bone occurred in 6% of the patients. The combination of limited surgery followed by radiotherapy resulted in a high local control rate with good functional results. Ultimately limb sparing treatment was successful in 83% of all patients with extremity sarcomas.

Key words: soft tissue sarcoma, combined therapy, radiotherapy, limb-sparing therapy
Eur J Cancer, Vol. 30A, No. 10, pp. 1459–1463, 1994

INTRODUCTION

SOFT TISSUE sarcomas are relatively uncommon in the adult population. They constitute 0.5 to 1% of all malignancies. Sixty per cent of all sarcomas occur in the extremities, predominantly in the lower extremity, and for these particularly, treatment strategy has changed in recent years. Whereas historically, radical surgery often by amputation was the treatment of choice, during the last two decades, combined modality therapy has become an accepted alternative for these patients. Moderate to high dose pre- or postoperative radiotherapy as well as brachytherapy, when used as an adjunctive to a limited excision, could reproduce the results of radical resection alone [1–4]. Despite these results, there remains controversy as to the optimal approach in these tumours. Further studies are needed to identify the protocol that gives the highest local control rate with acceptable normal tissue complications and functional outcome.

In the Netherlands Cancer Institute since the 1960s, ablative surgery has been reserved only for very extensive tumours. A consistent policy of conservative resection followed by radiation therapy, in most cases, has been followed during the entire study period. The purpose of this study was to identify prognostic indicators for the treatment outcome, and to assess the success rate and the long-term functional results of limb-sparing therapy in patients with extremity soft tissue sarcomas, according to a standard protocol of surgery and radiotherapy in case of narrow margins or incomplete excision.

Correspondence to R.B. Keus.
The authors are at The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands.
Revised 24 June 1994; accepted 5 July 1994.

PATIENTS AND METHODS

Patient population

The records of all patients treated for soft tissue sarcomas between 1977 to 1983 at the Netherlands Cancer Institute were reviewed. The criteria for inclusion in the present study were site of origin of the primary tumour in an extremity including shoulder girdle, groin and gluteal region, local treatment with curative intent and no known distant metastases. Excluded from the study were patients with desmoid tumours and rhabdomyosarcomas in children. There were 156 patients matching these criteria, 79 females and 77 males, with a median age at the time of diagnosis of 46 years (range 4–89). The histology was reviewed by one pathologist in all cases. The histological classification of Enzinger and Weiss, with malignancy grading on a three-grade scale was used. The most common histological subtypes were liposarcoma 50 (32%) and malignant fibrous histiocytoma 47 (30%). For 12 patients, there was insufficient material for accurate grading. Almost half of the patients had high-grade tumours (Table 1). The primary tumour was localised in the lower extremity in 115 patients, 48 (42%) of whom had tumours larger than 10 cm, as taken from the pathological description. In the 41 patients with upper limb tumours, there were 8 (20%) with tumours exceeding 10 cm.

Treatment

Previous surgical treatment at an outside institution had been given to 136 patients. In 34 patients, this excision was judged to be adequate and they received only radiotherapy from our centre. Subsequent surgery at our institution took place in 102 patients for a recurrent tumour or for re-excision of an incompletely removed sarcoma. Of these 102 patients, 71 were given radiotherapy. Only 20 of the 156 patients received primary surgery at our centre and 12 of these received postoperative radiotherapy. Thus, a total of 117 of 156 patients (75%) received combined treatment with surgery and radiotherapy, and 39 patients were treated with surgery only. The surgical treatment of choice was wide local excision with a margin of 2 cm of healthy tissue around the macroscopic tumour. If this could not be achieved, a marginal excision was performed in most cases. Ablative surgery was performed in 13 patients in advanced cases where a complete macroscopic excision was not possible. These 13 patients were excluded from the analysis of the results of limb-sparing treatment.

Table 1. Pathological findings

Histological subtype	Number of patients				
	Grade 1	Grade 2	Grade 3	Unknown	Total
MFH	8	6	30	3	47
Fibrosarcoma	6	3	5	0	14
Liposarcoma	32	7	7	4	50
Rhabdomyosarcoma	0	0	1	0	1
Leiomyosarcoma	1	1	5	1	8
Neurofibrosarcoma	4	0	2	0	6
Synoviosarcoma	0	3	7	1	11
Angiosarcoma	0	0	1	0	1
Other sarcomas	0	3	5	1	9
NOS	1	0	6	2	9
Total	52	23	69	12	156

MFH, malignant fibrous histiocystoma; NOS, not otherwise specified.

Table 2. Treatment results

Variable	No.	5-year actuarial local control (%)	5-year actuarial overall survival (%)
Treatment group			
I Surgery only	26	81	65
II Narrow surgery and radiotherapy	64	92*	78
III Incomplete surgery and radiotherapy	53	74†	60
Histological grade			
Grade 1	49	93	88
Grade 2	22	95	82
Grade 3	61	68	49

*Local control in treatment group II for patients with reexcision after incomplete surgery was 30/31 (98%), and for patients with narrow margins or spill this was 29/33 (88%). †Local control in treatment group III for patients with microscopic residual disease was 22/31 (71%) and with macroscopic residual disease this was 18/22 (82%).

The indications for postoperative radiotherapy in the combined treatment group of 117 patients were macroscopic residual tumour in 22 patients, microscopic residual tumour in 31, margins less than 1 cm in the pathological specimen in 33 and re-excision after incomplete surgery in 31 patients. For the analysis of the results of limbsparing treatment, the patients were grouped into three categories: group I consists of 26 patients with wide surgical margins without radiotherapy, group II consisted of 64 patients with re-excision or narrow surgical margins followed by radiotherapy, and group III consisted of 53 patients with incomplete surgery either microscopically or macroscopically followed by radiotherapy (Table 2). In general the size of the macroscopic tumour volume at the time of radiation did not exceed 2 cm.

Radiation was delivered with megavoltage equipment in all cases. Treatments were delivered in daily fractions of 2 Gy, five times a week. The initial target volume was the entire operative field with generous margins. For intramuscular tumours, the entire compartment was usually irradiated. This volume received a dose of 40 Gy in 4 weeks. A subsequent boost of 20 Gy in 2 weeks was given with reduced portals to the original tumour bed including areas of suspected residual disease. The technique most commonly used were opposed parallel fields, the prescribed dose delivered to the midplane. A strip of normal tissue was spared to avoid circumferential irradiation to allow for lymphatic drainage.

All irradiated patients were seen by a revalidation physician at the beginning of treatment who prescribed and monitored the results of physical therapy for 1 or 2 years, aiming at maximal preservation of limb function by preventing muscle and joint capsule contracture.

Only 9 patients in this series were treated with adjuvant chemotherapy according to the CYVADIC protocol of the Soft Tissue and Bone Sarcoma Group of the EORTC [5].

Analysis

The results of limb-sparing treatment in 143 patients were analysed as follows. Overall survival was calculated on a actuarial basis from the date of first treatment at our centre until death, and for the local control analysis to the date of a local recurrence. Univariate and multivariate analysis using the Cox proportional

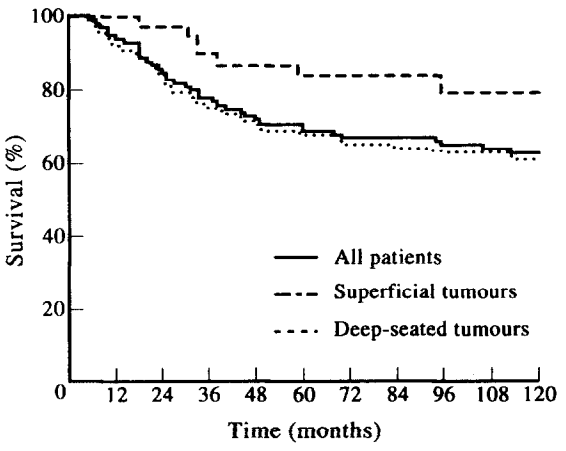

Figure 1. Actuarial overall survival of all patients, grouped by tumour depth.

hazards model was performed to identify prognostic factors for survival and local recurrence. The median and mean follow up times were 89 and 91 months, respectively, for all patients.

The functional outcome was assessed at the time of analysis by scoring the limb preservation rate and incidence of bone fractures in the treated limb. Fibrosis, lymph oedema, vascular impairment and decreased range of motion were scored as either normal, mild or severe. All data on complications and limb function was acquired from the patients files.

RESULTS

At the time of analysis, 84 patients were alive with a median follow-up of 114 months (range 30–251). 59 patients had died with a median survival of 31 months (range 1–170).

Survival

The overall 5- and 10-year overall survival rates for all patients were 69 and 63%, respectively (Figure 1). In univariant analysis, the survival decreased with higher age at the time of diagnosis and with higher histological grade (Table 3). A favourable prognosis was seen in smaller tumours and in superficially located tumours. Multivariant analysis resulted in three independent prognostic factors for survival: tumour grade ($P < 0.0001$), age at diagnosis ($P = 0.0005$) and superficial location ($P = 0.0008$; Table 3). Patients with superficial lesions had 83% 5-year survival as compared to 67% for deep-seated tumours (Figure 1).

Table 3. Multivariate analysis of prognostic factors for local control and survival (P values in different steps)

Variable	Local control step 0	Local control step 2	Survival step 0	Survival step 4
Gender	0.13	0.20	0.28	0.14
Age	0.11	0.11	0.015	0.0005*
Previous treatment	0.73	0.89	0.12	0.13
Site (upper/lower extremity)	0.97	0.74	0.17	0.62
Proximal/distal	0.76	0.16	0.094	0.31
Tumour size	0.24	0.82	0.0035	0.12
Tumour depth	0.088	0.059	0.0082	0.0008†
Invasion	0.92	0.74	0.97	0.31
Grade	0.003	0.0014	<0.0001	0.0001
Histological type	0.98	0.70	0.50	0.63
Treatment group	0.024	0.028	0.36	0.73
Total dose of radiotherapy	0.66	0.83	n.t.	n.t.
Margin radiation fields	0.81	0.66	n.t.	n.t.
Whole muscle irradiation	0.45	0.87	n.t.	n.t.

*Age: survival decreasing with higher age. †Tumour depth: deep-seated versus superfically located tumors. n.t., not tested.

Local control

A total of 24 local recurrences were seen, with 71% of these failures occurring within 3 years. In the surgery only group, 6 patients (23%) had a local recurrence. From the 18 patients with local failure after combined treatment, 5 (8%) occurred in the narrow surgery and radiotherapy group and 13 (25%) after incomplete surgery and radiotherapy (Table 2). No local recurrences were seen outside the irradiated volume. 6 patients had a marginal recurrence with respect to the radiation fields. All six local failures in the boost-dose region occurred in the group of patients with incomplete resection, while local recurrence in the initial large field region occurred in 3 patients in both groups. The 5- and 10-year local control rates for the whole group were 83 and 81%, respectively (Figure 2). Univariant factors for local control were grade and treatment group (Table 3). The 5-year local control rate by grade was 93% for grade 1 tumours, 95% in grade 2 and 68% in grade 3 tumours (Figure 2). By treatment group, the actuarial local control rates were 81, 92 and 74% for group I, II and III (Figure 3), respectively. In the multivariant analysis, these two factors remained significant for local tumour control, with $P = 0.0014$ for histological grade and $P = 0.028$ for treatment group (Table 3).

Complications and functional results

Amputations were performed in 3/26 patients (12%) treated with limited surgery only: 2 because of a local recurrence and 1 as a result of treatment-related complications. Following combined treatment by limited surgery and radiotherapy, 11/117 patients (9%) required an amputation: 8 patients had ablative surgery for a local relapse and in 3 patients an amputation was performed because of complications. These complications were intolerable pain following treatment of a lesion of the foot-sole in 1 patient, in the 2 other patients, amputation was eventually performed because of recurrent fracture of the femur and soft-tissue necrosis with ulceration, respectively. In 143 patients who received limb-sparing treatment, an ultimate limb preservation rate of 90% was achieved.

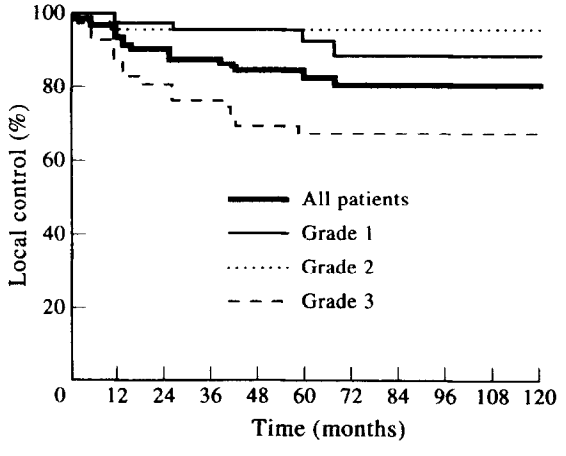

Figure 2. Actuarial local control of all patients, grouped by malignancy grade.

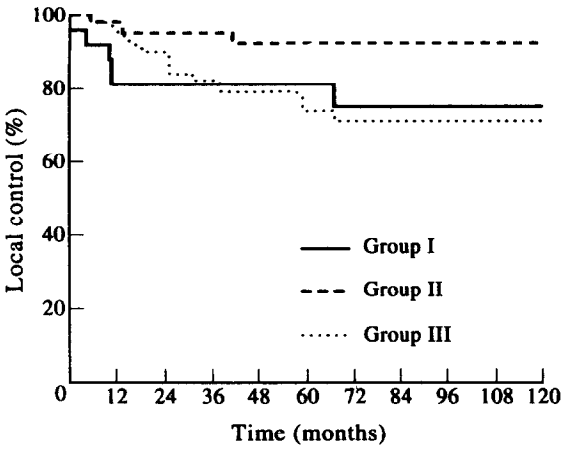

Figure 3. Actuarial local control curves by treatment group. Group I, 26 patients with surgery only; group II, 64 patients with narrow surgery and radiotherapy; and group III, 53 patients with incomplete surgery and radiotherapy.

The complications and functional results after combined therapy could be assessed in a group of 104 patients, after excluding 11 patients who had an amputation and 2 patients with missing data. The most frequently scored complication was mild fibrosis (40%). Severe fibrosis with marked induration or contracture occurred in 16%. In 7%, ulceration or a fistula in the treated area developed. Other severe complications were lymph oedema in 4% and vascular complications in 2% of the patients. In this group of 104 patients, 72 (69%) had a normal functioning limb, in 24 (23%) there was mild loss of motion, while in 8 (7%) severe impairment of function developed.

Fractures in the irradiated bone occurred in 7 patients (7%) (Table 4). In 1 patient, the fracture occurred in an area of bone where a higher absorbed radiation dose was applied due to overlap of fields. In another patient, the fracture arose at the site of a partial bone resection because of suspected tumour invasion of the bone. In the other 5 patients, no predisposing factor could be found.

DISCUSSION

Limb preservation with acceptable morbidity has proven to be feasible in the large majority of patients with soft tissue sarcomas of the extremities by combining conservative surgery with radiotherapy.

Postoperative radiotherapy has been the most widely utilised approach in these tumours, although recently favourable results have been reported with pre-operative radiotherapy [4, 6] or brachytherapy [1]. Using postoperative radiotherapy, Lindberg and colleagues from the M.D. Anderson Hospital observed a local recurrence rate of 20% in extremity tumours, a disease-free survival rate of 61% at 5 years, and in 85% a functional limb was preserved [2]. The Massachusetts General Hospital series showed a local control rate of 84%, and an actuarial survival rate of 73% at 5 years, and 80–85% limb preservation, as reported by Suit and colleagues [4]. The results from these single institution studies are almost identical with this series. In our patients, we achieved a local control rate of 83% at 5 years, the overall survival was 69% at 5 years and limb preservation was attained in 90% of the patients. When including the 13 patients who had an amputation as initial treatment, our overall preservation rate of 83% is very similar to the literature. These findings confirm the validity of the concept of conservative therapy by combining local excision with radiation therapy.

Table 4. Complications and functional results after limited surgery and radiotherapy in 104 patients

	Number of patients	
	Mild	Severe
Fibrosis	42	17
Lymph oedema	17	4
Vascular impairment	4	2
Ulceration of fistula	—	7
Decreased range of motion	24	8
Bone fracture	—	7

Part of the success of these approaches might be related to the benefit of close cooperation between surgeon and radiation oncologist. In our series, 87% of the patients had previous surgery elsewhere, often needing further surgery after incomplete resection. Despite the apparent value of radiotherapy in decreasing the risk for local failure, adequate surgical resection margins remain an important prognostic factor for local control. This is demonstrated by the higher local control rate in the narrow margins group when compared to the incomplete resected patients in this study, as well as data from other reports [7, 8]. General improvement of results in these patients would involve a campaign for earlier referral to a specialised centre.

The combined treatment approach can be carried out in different manners. In series where pre-operative radiotherapy was applied, improved results were reported in larger tumours when compared to postoperative treatment, although until now no randomised study has been performed [6, 9, 10]. Another approach to the management of these tumours is brachytherapy. Shiu and colleagues [1] from the Memorial Sloan-Kettering Cancer Centre showed that tumour-bed brachytherapy after conservative excision of sarcoma involving a major neurovascular bundle is a useful alternative to amputation. The main complication was radiation-induced injury of the treated peripheral nerve in 9% of the patients. Severe wound complications developed in 44% of patients receiving brachytherapy, but this rate was reduced to 14% after altering the treatment schedule. A prospective randomised trial demonstrated improved local control in brachytherapy patients when compared to the surgery only arm, especially in high grade lesions [1].

One argument for the use of postoperative radiotherapy is that a subgroup of patients can be selected who need no further treatment. For small superficial low-grade lesions, surgery with an adequate margin of normal tissue results in high local control not requiring adjuvant local treatment. In these series, radiotherapy has not been applied in patients after first surgery with free surgical margins, resulting in an 81% local control rated. Shiu and associates [1] report on wide excision only for superficial tumours not near a neurovascular or skeletal structure with little functional loss and little risk of local recurrence. Rydholm and colleagues also reported a local recurrence rate of 0 and 7% in, respectively, low- and high-grade superficial lesions after local resection with wide margins without further radiotherapy [11]. However, in patients with marginally resected tumours, the recurrence rate without radiotherapy was 58%.

With respect to the dose of radiotherapy in these series, we feel that in case of an incomplete resected tumour, a higher dose than 60 Gy is needed. In this group, the majority of local failures was seen at the original tumour site that received 60 Gy.

Currently, we apply doses from 66 to 70 Gy for residual disease. Since, in the 40 Gy area, very few recurrences were seen, this dose level can be considered to be sufficient for obtaining local control in electively treated areas, in contrast to the 50 Gy that has been mostly used in other series.

Ajuvant chemotherapy may have a local control benefit as has been reported in some randomised trials. In the EORTC trial, this was limited to truncal and head and neck lesions only [5], where optimal local treatment is often hampered because of neighbouring critical organs, while in the NCI trial, chemotherapy reduced local failures in high-grade extremity lesions only [12]. However, considering adjuvant chemotherapy as a safe replacement for radiotherapy in the local management of these tumours is unwise. It is important to note that patients with high grade tumours that do not receive radiation therapy, a local control rate of only 66% at 4 years is seen despite the administration of doxorubicin-containing adjuvant chemotherapy [1].

No prospective study comparing morbidity after postoperative, pre-operative radiotherapy or brachytherapy has been performed. The complication rate in our series was considered acceptable. The most significant complication was severe fibrosis of subcutaneous tissues in 16% of the patients. Bone fractures were seen in 7%, often with delayed healing. Similar complication rates have been reported in the literature [13, 14]. It is felt that optimisation of radiation techniques will be able to prevent a large part of these complications. The optimal radiation techniques for the postoperative radiation treatment of extremity tumours have elegantly been described by Tepper and associates [15]. Modern treatment techniques comprise the use of fixation methods to obtain reproducibility and accuracy in daily setup, individually shaped fields, and CT-based 3-D treatment planning. While the patients in this series were mostly treated with opposed AP/PA fields, often including the entire bone, we feel that complications can be diminished substantially by these new techniques [16]. In our experience, long-term physical therapy also has immense value in preventing muscle and joint contracture. It has become standard policy to involve a rehabilitation physician in the management of these patients.

The combination of limited surgery followed by radiotherapy results in a high local control rate with good functional results in the large majority of patients with soft tissue sarcomas. Whether radiotherapy should be pre-, intra- or postoperative needs to be established in prospective studies with emphasis on local control and functional results.

1. Shiu MH, Hilaris SH, Harrison LB, Brennan MF. Brachytherapy and function-saving resection of soft tissue sarcoma arising in the limb. *Int J Radiat Oncol Biol Phys* 1991, **21**, 1485–1492.

2. Lindberg RD, Martin RG, Romsdahl MM, Barkley HT. Conservative surgery and and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. *Cancer* 1981, **47**, 2391–2397.
3. Suit HD, Russell WO, Martin RG. Sarcoma of soft tissue: clinical and histological parameters and response to treatment. *Cancer* 1975, **35**, 1478–1483.
4. Suit HD, Mankin HJ, Wood WC, Proppe H. Preoperative, intraoperative and postoperative radiation in the treatment of soft tissue sarcoma. *Cancer* 1985, **55**, 2659–2667.
5. Bramwell V, Rousse J, Steward W, *et al.* European experience of adjuvant chemotherapy for soft tissue sarcoma: interim report of a randomized trial of CYVADIC versus control. In Ryan JR, Baker LH, eds. *Recent Concepts in Sarcoma Treatment.* Dortrecht, The Netherlands, Kluwer Academic, 1988, 156–163.
6. Brant TA, Parsons JT, Marcus RB, *et al.* Irradiation for soft tissue sarcomas of the trunk and extremities in adults. *Int J Radiat Oncol Biol Phys* 1990, **19**, 899–906.
7. Rosenberg SA, Tepper J, Glatstein E, *et al.* The treatment of soft-tissue sarcomas of the extremities. Prospective randomized evaluation of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg*, 1982, **3**, 305–315.
8. Collin C, Godbold J, Hadju S, Brennan M. Localized extremity soft tissue sarcoma: An analysis of factors affecting survival. *J Clin Oncol* 1987, **5**, 601–612.
9. Suit HD, Mankin JH, Wood WC, *et al.* Treatment of the patients with soft tissue sarcomas. *J Clin Oncol* 1988, **61**, 854–862.
10. Barkley HT, Martin RG, Romsdahl MM, Lindberg R, Zagars GK. Treatment of soft tissue sarcomas by preoperative irradiation and conservative surgical resection. *Int J Radiat Oncol Phys* 1988, **14**, 693–699.
11. Rydholm A, Gustafson P, Rööser B, Willén H, Berg NO. Subcutaneous sarcoma. A population-based study of 129 patients. *J Bone Joint Surg [Br]* 1991, **73-B**, 662–667.
12. Chang AE, Kinsella T, Glatstein E, *et al.* Adjuvant chemotherapy for patients with high-grade soft-tissue sarcomas of the extremity. *J Clin Oncol* 1988, **6**, 1491–1500.
13. Stinson SF, DeLaney TF, Greenberg J, *et al.* Acute and long-term effects on limb function of combined modality limbsparing therapy for extremity soft tissue sarcoma. *Int J Radiat Oncol Biol Phys* 1991, **21**, 1493–1499.
14. Bell RS, O'Sullivan B, Nguyen C, *et al.* Fractures following limb-salvage surgery and adjuvant irradiation for soft-tissue sarcoma. *Clin Orthop* 1991, **271**, 265–271.
15. Tepper J, Rosenberg SA, Glatstein E. Radiation therapy technique in soft tissue sarcomas of the extremity—policies of treatment at the National Cancer Institute. *Int J Radiat Oncol Biol Phys* 1982, **8**, 263–273.
16. Keus RB, Noach P, de Boer R, Lebesque J. The effect of customized beam shaping on normal tissue complications in radiation therapy of parotid gland tumours. *Radiat Oncol* 1991, **21**, 211–217.

Acknowledgement—The authors thank Dr Angenot, rehabilitation physician, for his contribution in the management of these patients.