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Limb Function following Conservation Treatment of Adult Soft Tissue Sarcoma

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Quality of life and limb function were studied in 54 patients who were disease-free 2 or more years after limb-conserving treatment for soft tissue sarcoma of the leg or pelvic girdle. Tumours of the thigh predominated (25 patients) and the mean tumour size was 9.9 cm. 41 patients had been treated with a combination of surgery and radiotherapy (29 with conventional and 12 with high dose), 12 with surgery alone and one with irradiation and intra-arterial doxorubicin. Only 15 patients had a normal range of movement in all lower limb joints and only 12 had normal power in all muscle groups; tumours of the lower leg were particularly unfavourable in this respect. Gait was normal in 42 patients but 8 required a walking aid and 4 a joint support. 16 had detectable lymphoedema but only 2 needed to wear compression hosiery. 35 patients still experienced pain at some time but only 6 required analgesia. However, when assessed by questionnaire for locomotion, grooming and home/leisure/vocational activities, 37 patients (68%) reported excellent function, and only 2 had moderate impairment. Function loss was most marked in leisure (25 patients) and vocational (8) activities, but was mild in 66% of cases. Multivariate analysis was carried out to determine the prognostic factors for poor limb function. The results suggested that overall functional score was predominantly determined by gait ($P < 0.001$), muscle power or range of movement ($P < 0.001$), with increasing age, female sex and the use of radiotherapy poor prognostic factors. Reduced muscle power or range of movement were the major factors determining gait ($P < 0.02$) with the use of radiotherapy the significant prognostic factor for both in the conventionally treated group. Doses in excess of 60 Gy resulted in increased fibrosis and a worse functional outcome. Extent of surgery was not an independent prognostic factor for limb function, although univariate analysis suggested an association with range of movement in the conventionally treated group ($P < 0.025$). Despite significant objective loss of range of movement and muscle power patients retain excellent limb function and quality of life following limb conserving treatment. For optimal function, radiotherapy should be given with small fractions to a dose not exceeding 60 Gy.
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INTRODUCTION

LIMB-CONSERVING TREATMENT has become the standard management of adult extremity soft tissue sarcoma over the last 15–20 years. There have been numerous reports of the success of this approach [1–7]. However, almost all the authors have reported their results in terms of survival and local control without detailing the functional outcome.

In 1982, Sugarbaker *et al.* reported an important study into the quality of life of patients with extremity sarcoma entered into a randomised trial comparing amputation and adjuvant chemotherapy with limb sparing surgery, radiotherapy and chemotherapy [6, 8]. The results were surprising. They concluded that there was no evidence for an improved quality of life in those patients in whom the limb had been spared. However, patient numbers were small. In 1984 Lampert *et al.* reported a study of the limb function and quality of life in 40 patients with soft tissue sarcoma of the head and neck, trunk, or upper and lower extermity [9]. Most of their patients had also received chemotherapy. They concluded that patients with lower limb tumours had the greatest functional impairment.

The Royal Marsden Hospital Sarcoma Unit has treated 384 patients with the extremity soft tissue sarcoma over the last 10 years. The results of treatment have been reported [5, 10]. We decided to carry out a study of limb function and quality of life in patients with pelvic girdle or lower limb sarcoma treated by limb conservation. We selected those who were disease-free at 2 or more years because we considered that all treatment effects on limb function would have become apparent by this time and patients would be fully rehabilitated. We elected to confine our study to this group because Lampert *et al.* had shown that the impact of disease/treatment was greatest on these patients and because these are the commonest sites for this disease in adults.

PATIENTS AND METHODS

Patients and treatment details

This study was performed in the Marie Curie Rehabilitation Centre of the Royal Marsden Hospital. 54 patients (35 males and 19 females) attending the sarcoma clinic were studied. Details of the maximum size, histology and grade of tumour according to site are given in Tables 1 and 2. The median age of the patients was 51.5 years (range 23–82) and the median time since treatment was 50 months (range 24–152). The commonest site for the tumour was the thigh (25 cases) followed by the groin (8), lower leg (7), foot (6), buttock (5) and knee (3). The

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Table 1. Tumour size by site

Size (cm)	Buttock	Groin	Thigh	Knee	Leg	Foot
< 5	1	0	3	3	2	2
5 < 10	0	1	10	0	2	3
10 < 15	2	3	7	0	3	1
15 < 20	0	4	2	0	0	0
> 20	2	0	3	0	0	0
Total	5	8	25	3	7	6

Table 2. Tumour histology and grade by site

	Buttock	Groin	Thigh	Knee	Leg	Foot
Histology						
MFH	1	3	9	0	2	2
Liposarcoma	2	3	8	0	4	0
Synovial sarcoma	0	0	2	2	0	0
Ewings	0	0	0	0	2	0
Fibrosarcoma	0	0	2	0	0	2
Others	2	2	4	1	0	1
Grade						
High	1	3	14	2	2	3
Intermediate	0	0	2	0	0	0
Low	4	5	9	1	5	3

MFH = Malignant fibrous histiocytoma.

mean tumour size of those treated by surgery alone was 10.6 cm (range 1–30) and by surgery plus radiotherapy 9.7 cm (range 2–28).

Our principles of treatment for limb and limb girdle sarcomas have been previously described [5, 10]. Surgery was performed first whenever the tumour was operable at presentation. A wide or radical surgical resection was the aim, but marginal excision was performed when this allowed the preservation of structures important for function (major nerve or artery), providing radical radiotherapy could be given. Enneking's classification was used for documenting surgical clearance [11]. Postoperative radiotherapy was given in two phases, commencing within 6 weeks of surgery, where the resection margins were "inadequate" (intracapsular or marginal resection) and with all high grade tumours. The first phase encompassed all sites of potential microscopic spread irradiating the whole compartment of a limb; where tumour was not situated in a compartment a 6 cm margin was given. Phase 2 treated the tumour bed with a 2 cm margin. Where, at presentation, it was considered that adequate surgical clearance could not be achieved radiotherapy was given pre-operatively, usually to 50 Gy in 5 weeks daily treatment. Ideally, surgery was then performed. If, at this time it was considered that the tumour would still be inoperable, a further 10 Gy was given to a reduced phase II volume. 7 patients in this study were treated with a hypofractionated, once a week schedule [12] and 3 with a twice daily hyperfractionated schedule [13].

Chemotherapy was not routinely employed. The exceptions were 2 cases with extraskeletal Ewing's sarcoma, 4 patients entered into a study of intra-arterial doxorubicin for large initially inoperable tumours [14], and 2 patients with lung metastases which were successfully treated by a combination of chemotherapy and surgical resection or radiotherapy.

Table 3. Timing and 2 Gy equivalent dose of radiotherapy by site of primary tumour

	Timing		Dose (2 Gy) equivalent			
Site	Pre-operative	Post-operative	<50	>50<60	>60<70	>70
Buttock	0	2	0	0	1	1
Groin	2	5	1	1	3	2*
Thigh	5	12	3	2	12	1
Knee	0	3	0	0	2	1
Lower leg	2	4	1	1	3	1
Ankle/foot	0	5	0	0	4†	2
Total	9	31	5	4	25	8

* 1 pre-operative and postoperative radiotherapy.
† 1 no surgery.

41 patients were treated by a combination of limb-sparing surgery and radical radiotherapy, 12 by surgery alone and one by a combination of intra-arterial doxorubicin and radiotherapy (without surgery). 13 of the 42 patients who were given radical radiotherapy were either treated with unconventional regimens (hypofractionation or hyperfractionation) or received very high doses. Table 3 details the timing and 2 Gy equivalent dose of all the patients given radiotherapy. The latter is calculated from the equation $D_{2Gy} = D \times (\text{alpha/beta} + d)/(\text{alpha/beta} + 2)$, where D is the total given dose and d is the fraction size used. The alpha/beta ratio for late tissue damage was assumed to be 3 Gy. This calculation was done in an effort to compensate for the different fractionation schedules [15, 16].

The amount of normal tissue, particularly muscle, which is resected in order to obtain an 'adequate' margin in these patients varies depending on the site, size and extension of the tumour and may effect subsequent limb function. In an effort to quantitate the extent of the surgical resection performed in these patients we have used a 3 point scale: grade 1 for patients where only part of a muscle group was taken, grade 2 where the whole of a muscle group was resected, and grade 3 where part/whole of another muscle was also included. Table 4 details this according to tumour site and treatment. 19 patients underwent grade 1 resections, 23 grade 2 and 11 grade 3. 1 patient required

Table 4. Extent of surgery by site of tumour and use of conventional or high-dose radiotherapy

	Radiotherapy								
	None			Conventional			High-dose		
Site	1*	2	3	1	2	3	1	2	3
Buttock	3	0	0	0	1	0	0	1	0
Groin	0	1	0	3	2	0	1	0	1
Thigh	1	6	0	2	8	5	1	1	1
Knee	0	0	0	2	0	0	1	0	0
Lower leg	1	0	0	0	0	3	0	2	1
Foot	0	0	0	2	1	0	2	0	0
Total	5	7	0	9	12	8	5	4	3

No. of patients.
* Extent.

Table 5. Scoring system by range of movement in degrees

Joint	Restriction None	Mild	Moderate	Severe
Hip				
Abduction	40–45	35–39	20–34	< 20
Adduction	25–30	15–24	5–14	< 5
Flexion	115–120	100–114	75–99	< 75
Extension	0–10	1–5	6–10	> 10
Internal rotation	40–45	35–39	30–34	< 30
External rotation	40–45	35–39	30–34	< 30
Knee				
Flexion	130–135	115–129	90–114	< 90
Extension	0–2	3–10	11–14	> 15
Ankle				
Dorsi-flexion	> 20	10–19	−5–9	< −5
Plantar-flexion	45–50	35–44	6–34	< 5
Inversion	15–20	10–14	5–9	< 5
Eversion	10	7–9	3–6	< 2

a flap for skin closure and in 4 cases a split skin graft was used. There were 12 documented wound complications. 12 patients required two operations: 5 for local recurrence and 7 because the initial surgery was considered to be inadequate. Despite re-excision, recurrence necessitated a third operation in a further patient. Another patient was referred after five operations; he was treated by wide excision with a split skin graft and postoperative radiotherapy.

14 patients reported that they did not receive physiotherapy at any time before, during or after their treatment and 29 patients only received physiotherapy immediately after surgery.

Functional assessment

An assessment of lower limb function and patient quality of life was developed. The first part was a formal evaluation of the range of movement (ROM) and muscle power. ROM of all lower limb joints was measured using goniometry. Standard normal ranges of movement for each joint were used [17] and values outside these ranges were grouped into mild, moderate or severe restrictions (Table 5). The power of individual muscle groups was graded from 0–5 according to the standard Oxford scale, following which an overall evaluation was made by placing each patient in one of four categories: normal or mild/moderate/severe reduction in power (Table 6).

Gait was assessed as normal or abnormal and the need for a walking aid or joint support was evaluated along with their ability to manage a flight of stairs. Any radiation induced skin or subcutaneous fibrosis was graded as mild, moderate or severe.

Table 6. Muscle power—overall evaluation

Level	Evaluation
Normal	All grade 5 or grade 4 in one minor group.
Mild	Grade 4 in one major group or grade 3 or 4 in 2 minor muscle groups.
Moderate	Grade 3 in one/two major groups or grade 0–2 in one/two minor groups or grade 4 in 3 or more groups.
Severe	Grade 0–2 in any major group or grade 3 in more than 2 major groups.

Lymphoedema was assessed by pitting and the skin pinch test (Stemmer's sign). The skin on both sides was pinched simultaneously on the foot (the base of the second digit), calf, thigh, side of buttocks and abdomen (avoiding irradiated areas). Measurement of limb circumference was unreliable because of previous surgery. Lymphoedema was thereby categorised according to how far it extended up the limb.

The second part of the assessment was a questionnaire evaluating the patients' perceived quality of life. The degree of lymphoedema and pain since treatment together with the measures required to overcome them were noted. Those patients experiencing pain at the time of the assessment documented the severity by placing a vertical mark on a visual analogue scale 10 cm long with 'no pain' at the 0 cm end and the 'worst pain ever experienced' at the 10 cm end. A modified Erdman scale using a series of nine questions assessed the patients' locomotion, ability to climb stairs, dress/groom themselves and to manage about the home [18, 19]. Changes in vocational and leisure activities were also documented. The four possible answers to each question were graded from normal to mild, moderate, or severe restriction of that activity. The patients scored 1–4 for each question according to their reply. The best possible score for the nine questions was therefore 9 and the worst 36. An overall score of 9 represented normal function. A score between 10–18 was graded as a mild functional deficit, 19–27 as moderate and over 27 a severe functional deficit. The levels of disability included were less than in the Lampert study as none of our patients are wheelchair bound or immobile.

Statistics

The χ^2 test was used to compare the range of movement, muscle power evaluation, degree of lymphoedema, normality of gait, presence of pain and overall functional score of patients grouped according to different prognostic factors. The following patient, tumour and treatment-related variables were entered into a log-linear model (using the GLM package) in an effort to identify any independent factors determining a poor functional outcome: sex and age, tumour site/size and previous local recurrence, the number and maximal extent of any operations performed, the use of flaps or split skin grafts to close the wounds and any associated wound complications, the use of chemotherapy at any time, and the use and dose (as a 2 Gy equivalent) of radiotherapy and size of fields used. The use of physiotherapy was also included in the analysis although its quality could not be evaluated retrospectively.

RESULTS

Range of movement (ROM)

Table 7 details the severest restriction in range of movement for each joint according to site of the primary tumour and as to whether high-dose radiotherapy (HRT) was given. Only 15 patients had normal range of movement in all evaluated joints. 33 (32 of whom had received radiotherapy) had a moderate or severe restriction in one or more joints. 26 patients had some restriction of movement at the hip (48%), 28 at the knee (52%) and 22 at the ankle/foot (41%). Approximately one third had moderate or severe restriction of movement at the hip and knee and one quarter at the ankle/foot. Tumours of the lower leg were particularly unfavourable in that all these patients had problems in the ankle or foot (6/7 moderate or severe). In

Table 7. Severest restriction of range of movement at hip, knee and ankle/foot joint by site of tumour and treatment

	Hip				Knee				Ankle				
Grade *	0	1	2	3	0	1	2	3	0	1	2	3	
Conventional† treatment													
Buttock	3	0	0	1	3	0	0	1	3	1	0	0	1/4‡
Groin	2	2	1	1	2	0	4	0	5	0	1	0	4/6
Thigh	7	4	5	6	10	2	5	5	17	4	1	0	15/22
Knee	2	0	0	0	2	0	0	0	2	0	0	0	0/2
Lower leg	4	0	0	0	1	3	0	0	0	0	1	3	4/4
Ankle	3	0	0	0	2	1	0	0	1	1	0	1	2/3
High-dose treatment													
Buttock	0	0	1	0	0	0	1	0	1	0	0	0	1/1
Groin	0	0	0	2	0	0	0	2	1	1	0	0	2/2
Thigh	1	0	1	1	0	2	0	1	1	1	1	0	3/3
Knee	0	1	0	0	1	0	0	0	0	1	0	0	1/1
Lower leg	3	0	0	0	2	0	0	1	0	1	2	0	3/3
Ankle	3	0	0	0	3	0	0	0	1	0	0	2	2/3
Total	28	7	8	11	26	8	10	10	32	10	6	6	38/54

* 0 = normal; 1 = mild, 2 = moderate, 3 = severe restriction.
† Conventional = surgery alone or surgery with conventional doses of radiotherapy.
‡ Abnormal/total.

contrast, only 1 of 3 patients with tumours around the knee had problems of a mild nature (almost certainly because all 3 tumours were less than 5 cm in size).

The extent of surgery performed in the 41 patients receiving surgery alone or surgery and conventional doses of radiotherapy is plotted against the reduction in range of joint movement in Fig. 1. 9 of 12 patients with a severe restriction in range of movement had grade 2 or 3 resections.

Muscle power evaluation

Table 8 details the muscle power evaluation according to tumour site and treatment group. Only 12 patients had normal power in all muscle groups (6 patients treated by surgery alone and 6 given radiotherapy as well). 32 patients (30 of whom had received radiotherapy) had moderate or severe reduction in power. Once again there was a difference between those patients with tumours of the lower leg, all of whom had moderate or

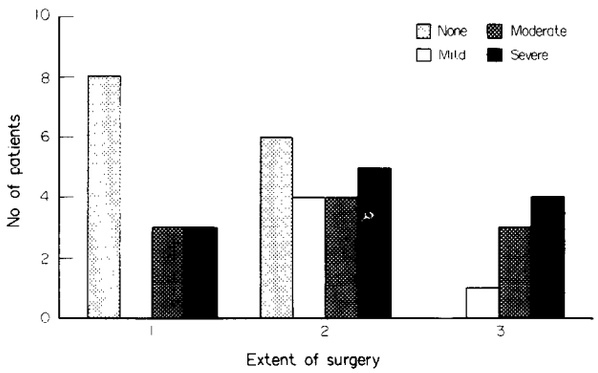

Fig. 1. Restriction in range of movement according to extent of surgery in those patients treated with surgery alone or surgery and conventional doses of radiotherapy.

Table 8. Muscle power by site of tumour and radiotherapy treatment

Grade*	Radiotherapy												
	None				Conventional				High-dose				
	0	1	2	3	0	1	2	3	0	1	2	3	
Buttock	2	1	0	0	0	0	1	0	0	0	1	0	3/5†
Groin	1	0	0	0	1	2	2	0	0	0	0	2	6/8
Thigh	3	3	1	0	1	1	8	5	0	1	1	1	21/25
Knee	0	0	0	0	1	1	0	0	1	0	0	0	1/3
Lower leg	0	0	0	1	0	0	2	1	0	0	1	2	7/7
Foot	0	0	0	0	2	0	1	0	0	1	0	2	4/6
Total	6	4	1	1	5	4	14	6	1	2	3	7	42/54

* 0 = normal; 1 = mild, 2 = moderate, 3 = severe weakness.
† Abnormal/total.

severe reduction in muscle power, and the 3 patients with tumours around the knee one of whom had mild weakness only. 15 of 25 patients with tumours in the thigh (the commonest site) had moderate or severe power loss.

Lymphoedema

38 patients had no detectable lymphoedema. Only 1 patient who had not received radiotherapy had signs of oedema up to the thigh. 2 of the patients with truncal oedema had groin primaries and 2 thigh primaries (both of the latter had proximal thigh lesions and had received radiotherapy). 2 had been treated with a hypofractionated radiotherapy regime which has previously been shown to cause more late normal tissue damage than standard treatment [12]. There was no significant difference between the extent of lymphoedema in patients receiving the high dose radiotherapy regimes and those receiving conventional radiotherapy. On questioning, 21 patients complained that they had experienced swelling of the leg at some time. All but one found that this tended to settle overnight. 16 patients had used a support stocking at some time but only 2 were still using one. Only 2 patients had received other active treatment such as massage, bandaging, flowtron or lymphopress for lymphoedema. 6 reported that the swelling started immediately after surgery, 9 after all treatment had been completed (mean 3 months), and 5 during or following radiotherapy. Objective signs of radiation fibrosis were seen in 29 of 42 patients. This was mild in 13, moderate in 6 and severe in 10.

Gait

12 of 54 patients had an abnormal gait. 7 of these 12 were in the group treated with surgery and high dose radiotherapy. 5 of the 12 patients (4 with lower leg primaries) had problems with dorsiflexion of the foot. 2 patients had leg shortening: 1 following treatment and the other because of an unrelated femoral fracture. 8 patients required a walking aid: 7 used a stick and 1 crutches.

Following the assessment it was clear that 4 patients needed a joint support. However only 1 patient regularly wore a knee splint and this was for osteoarthritis. The other 3, treated for lesions in lower leg (2) and groin (1) were offered a splint following the assessment. 2 required support for the ankle and one for the knee. All patients managed a flight of stairs, 42 without a walking aid.

Pain

10 patients admitted to pain at the time of assessment; 19 said they never had any pain. Of the former 5 scored the severity of

Table 9. Function loss by tumour site and radiotherapy

Impairment	Buttock	Groin	Thigh	Knee	Leg	Foot	Total
Radiotherapy							
None							
None	3	1	7	0	0	0	11
Mild	0	0	0	0	1	0	1
Conventional							
None	0	3	7	1	1	2	14
Mild	1	2	8	1	2	1	15
High-dose							
None	0	0	1	0	0	1	2
Mild	1	1	1	1	3	2	9
Moderate	0	1	1	0	0	0	2

the pain as 1/10, 1 as 2/10, 2 as 4/10 and 2 as 5/10. Pain was intermittent for 30 of the 35 patients still experiencing it at some time and continuous for the remainder. Only 6 patients required regular analgesia (paracetamol in 2, coproxamol in 2, acupuncture in 1 and morphine in 1). Pain interfered with the activity in 11 patients and was present at night in the same number.

Functional questionnaire

Table 9 details the functional loss according to site of the primary and treatment. 27 patients (50%) had normal scores. Only 2 patients scored over 18 and were therefore considered to have moderate functional impairment. The patient with the worst score (20) originally had a 12 × 11 × 6 cm high grade thigh sarcoma treated by compartmental resection and hypofractionated radiotherapy. The second patient had received preoperative radiotherapy for a 10 cm tumour in the groin; the response to this had permitted resection (with a muscle flap for repair) but because of inadequate surgical margins he was given further radiotherapy to a total dose of 80 Gy.

The median functional score of those receiving a dose above 60 Gy was 12.5 compared to 9 (i.e. normal) for those receiving 60 Gy or less ($P < 0.0001$, Mann–Whitney U test).

Figure 2 plots the answers to each section of the questionnaire as the number of patients with each abnormal score. This demonstrates clearly that two-thirds (45/68) of the abnormal

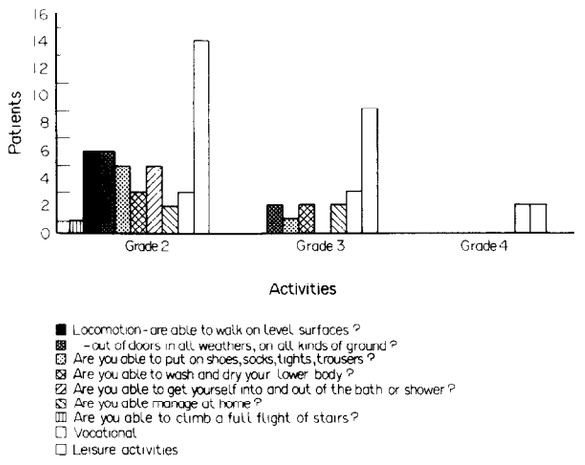

Fig. 2. The number of patients with grades 2, 3 and 4 functional problems.

replies represented only a mild loss of function. Most serious functional losses were in leisure and vocational activities. Overall 26 patients either changed their leisure (25) or vocational activities (8). 2 patients (functional scores 19 and 20) were unable to work at all, 1 of whom was also unable to pursue any of his previous leisure activities.

Statistics

χ^2 testing suggests a significant trend for the use of conventional radiotherapy to be associated with a more severe restriction of range of movement ($P < 0.005$) and a worse overall functional score ($P < 0.01$) than surgery alone.

High-dose/hypofractionated radiotherapy was also associated with poorer muscle power than the use of surgery alone ($P < 0.005$), and with the presence of pain ($P < 0.05$). Significantly more patients in the high-dose radiotherapy group had an abnormal gait compared with each other group. No correlation was found between the use of conventional doses of radiotherapy and muscle power, extent of lymphoedema or for any abnormality of gait. A poor range of movement score was associated with poor muscle power ($P < 0.005$).

The extent of surgery was not related to range of movement, muscle power or functional score in the group as a whole. However, more extensive surgery was significantly associated with a decreased range of movement (but not muscle power or overall function) in the 41 patients treated with surgery alone or surgery and conventional doses of radiotherapy ($P < 0.025$).

Multivariate analysis

Many of the factors determining outcome following treatment of extremity soft tissue sarcoma may be interrelated e.g site and size of tumour with extent of surgery. Log-linear modelling was carried out in an effort to discover which factors might independently contibute to a poor functional outcome. The 54 patients could be divided into two groups; those treated in a conventional manner and those who received high-dose radiotherapy. An analysis including the latter patients gives information on the effect of increased dose on late normal tissue damage and consequent limb function. However, it may not reveal the factors determining outcome in those treated more conventionally. We therefore did the analysis twice; once for the latter group and again for all the patients. The results of these analyses are shown in Table 10.

The site of the tumour, the number of recurrences or operations, the extent of surgery, the type of closure, wound complications and the use of chemotherapy had no significant influence on range of movement, muscle power, gait or functional score in either analysis.

Conventionally-treated group

The only significant independent prognostic factors for poor limb function in this group were increasing age ($P < 0.002$) and the use of radiotherapy ($P < 0.025$). The functional score was predominantly determined by gait ($P < 0.001$), with muscle power and range of movement (clearly interrelated) also being important ($P < 0.001$). Increasing age ($P < 0.02$) and female sex ($P < 0.001$) were significant prognostic factors for development of poor gait, with the use of radiotherapy ($P < 0.001$) the only significant prognostic factor for limitation of both muscle power and range of movement.

All patients

Gait remained the major factor determining the functional score ($P < 0.001$). The dose (2 Gy equivalent) of radiotherapy

Table 10. Independent prognostic factors for development of poor ROM, muscle power, gait, fibrosis and functional score

Endpoint	Significant independent factors			
	Prognostic		Associated	
Function				
All	Dose RT	($P < 0.002$)	Gait	($P < 0.001$)
Conventional	Age	($P < 0.002$)	Gait	($P < 0.001$)
	Use of RT	($P < 0.0025$)	Muscle power	($P < 0.001$)
Gait				
All	None		Muscle power	($P < 0.02$)
Conventional	Female	($P < 0.001$)	Muscle power	($P < 0.001$)
	Age	($P < 0.02$)	ROM	($P < 0.001$)
Muscle power				
All	Physio*	($P < 0.01$)	Fibrosis	($P < 0.01$)
Conventional	Use of RT	($P < 0.001$)	None	
ROM				
All	Use of RT	($P < 0.005$)	Fibrosis	($P < 0.001$)
	Size	($P < 0.02$)	Lympho-	($P < 0.025$)
	Physio*	($P < 0.05$)	edema	
Conventional	Use of RT	($P < 0.02$)	None	
Fibrosis				
All	Dose RT	($P < 0.001$)	None	
	Field length	($P < 0.05$)		

Determined by multivariate analysis of all 54 patients and by a separate analysis of 41 patients treated conventionally.
RT = radiotherapy, ROM = range of movement, Physio = physiotherapy.
* Good prognostic factor.

used was the only other important factor ($P < 0.02$) if gait was included in the model. The probability that this effect might be causal is increased by the confirmation of a significant relationship between dose ($P < 0.001$) and field length ($P < 0.05$) and the degree of fibrosis. The relationship between dose and fibrosis is shown in Fig. 3.

The use of radiotherapy ($P < 0.005$) and increasing tumour size ($P < 0.02$) were risk factors for the development of a reduced range of movement, with the degree of radiation fibrosis ($P < 0.001$) and extent of lymphoedema ($P < 0.025$) the other related factors. Only radiation fibrosis ($P < 0.01$) was significantly associated with poor muscle power. The use of physiotherapy was favourable ($P < 0.01$). Abnormal gait appeared predominantly to be determined by poor muscle power ($P < 0.002$). However, if this factor was not included in the model, radiation fibrosis again became important, reinforcing a possible relationship between the two.

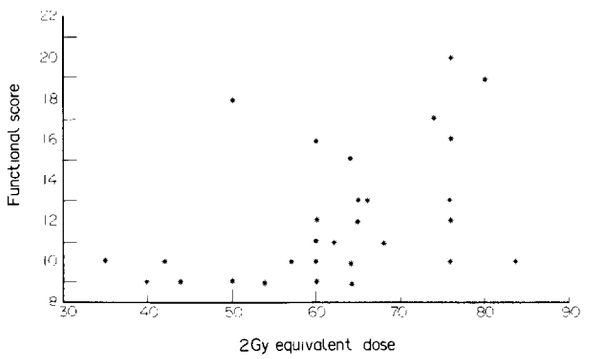

Fig. 3. 2 Gy equivalent dose of radiotherapy against functional score.

DISCUSSION

We have carried out a study of the quality of life and limb function of a group of 54 patients with pelvic girdle or lower limb soft tissue sarcoma who underwent a limb conservation procedure at the Royal Marsden Hospital Sarcoma Unit 2 or more years ago. This was done in an effort to establish the factors determining a good functional outcome. Previous studies of this type have been few in number [9, 20–22].

In 1982 Sugarbaker *et al.* reported detailed psychosocial analysis of their patients anticipating that the limb-conserved group would score more highly for quality of life than amputees [8]. The number of patients in the study was small (21) but the tests were detailed. In the first part of the study those treated by amputation scored significantly better in terms of emotional behaviour, body care/movement, a patient based assessment of daily living and in sexual relationships. In the second part of the study clinical assessments to specifically link treatment consequences to quality of life measures were used in 21 patients (15 limb-spared and 6 amputees) treated for lower limb tumours. These showed no significant difference between the groups in terms of pain, mobility, treatment trauma and sexual relationships. The authors postulated that significant differences in sexual function seen in the first part of the study may have been related to the persistent decreased spermatogenesis and increased follicle stimulating hormone levels in patients undergoing thigh irradiation and chemotherapy [23]. They concluded that there was no evidence for an improved quality of life in those patients whose limbs had been spared.

However, Bell *et al.* prospectively studied the complications and functional results of wide resection and radiotherapy in 19 patients designated as 'difficult' cases [20]. These were patients who might have been candidates for amputation because of size, site or previous treatment. They concluded that almost all soft tissue sarcomas can be managed by limb-salvage techniques with a functional outcome superior to those expected with amputation.

Lampert *et al.* evaluated patients at least 2 years after wide local excision and 1.75 years after high dose radiation [9]. Range of movement and muscle power were assessed along with degree of pain, the presence of oedema, and functional capacity. This study suggested that patients with lower limb sarcomas had more oedema and a poorer functional outcome than those with tumours at other sites. They found that restrictions in range of movement were associated with muscle weakness and decreased functional capacity and that oedema and pain were associated. No conclusion could be drawn about the influence of treatment on these results. They went on to a detailed prospective study of quality of life and limb function in 88 patients entered into randomised trials studying the value of radiotherapy [21]. They noted that limb function, employment status and sexual activity diminished over the 12 months of follow-up. The former comprised both a decrease in joint movement and muscle power. They associated the combination of chemotherapy and radiotherapy with an increase in joint contractures. These were seen only in those patients receiving both chemotherapy and radiotherapy but did not occur in 24 patients with low-grade sarcomas not given chemotherapy or in 15 receiving chemo-

therapy alone. Interestingly, the patients judged there to have been an improvement in overall quality of life during this period.

The major differences between these studies and our own is in their extensive use of adjuvant chemotherapy and our use of unconventional high dose radiotherapy regimes. It is well established that doxorubicin in particular may exacerbate the normal tissue damage [24] and that hypofractionation is associated with increased late normal tissue damage [12].

37 of the 54 (68%) patients in our study with pelvic girdle or lower limb soft tissue sarcomas, assessed 2 years or more after limb sparing treatment, had an excellent functional result (i.e. a score of 9 or 10). 8 of the 17 patients with worse functional scores were in the group treated with high dose or unconventional fractionation. Formal assessment of range of joint movement and muscle power in all 54 patients revealed that 72% and 78%, respectively had significant limitations. Clearly, most patients had overcome these in their day to day activities. Surprisingly, 35/54 patients still occasionally experienced some pain in the treated limb. However, this was usually mild and in all but one of the patients still taking medication it responded to simple analgesia. 21 patients complained of some swelling of the leg and 17 were noted to have lymphoedema. This was also minor and, although 16 patients had worn a support stocking at some time, only 2 had received more active treatment. These patients were all treated before a specialist lymphoedema and physiotherapy team was established at the Royal Marsden Hospital. It is now routine for all patients with limb sarcoma to be evaluated in the Rehabilitation Unit before and after treatment. All undertake active physiotherapy and lymphoedema is treated early.

Initial statistical evaluation suggested that patients receiving radiotherapy had a worse functional outcome. However, multivariate analysis indicates that a number of factors are interrelated in determining the overall functional outcome. When all 54 patients are included the degree of radiation fibrosis, influenced by dose of radiotherapy, is an important factor in the development of both a poor range of movement and poor muscle power. The latter is important in the development of an abnormal gait which (along with radiation dose) is the most important factor in determining functional outcome.

13 patients in this study were treated with unconventional or high dose (> 60 Gy) radiotherapy regimens and had a worse functional outcome than the other patients. We therefore carried out a further analysis based upon the 41 patients treated more conventionally. The results seen in this group are more likely to represent those routinely achieved by an experienced sarcoma team. In this analysis female sex, increasing patient age and the use of radiotherapy were demonstrated to be significant adverse prognostic factors for gait and limb function. Poor muscle power and range of movement (related to the use of radiotherapy) were associated with a poor gait. None of the surgical variables entered into the analysis were found to be independent prognostic factors; although there was an association between extent of surgery and range of movement on univariate analysis. This may be due to the major effect of radiotherapy on limb function or, more likely, that the small number of patients in this study does not permit a definitive assessment of all factors determining functional outcome.

Radiotherapy is an important adjuvant treatment in the management of soft tissue sarcomas. Surgery alone is associated with a high local recurrence rate unless a radical resection is performed. This can rarely be achieved without amputation [25]. Preoperative or postoperative radiotherapy with more conservative surgery reduces the local failure rate to 10–15% [1, 2, 4, 5, 7]. Overall two thirds of our patients with extremity sarcomas have required radiotherapy.

When radiotherapy is indicated it is important to avoid irradiating the full circumference of the limb and to spare joints where at all possible. This often requires the use of an immobilisation device and may be facilitated by the use of CT. The optimum dose is not known but at least 60 Gy is required to control residual disease and a small dose per fraction should be used.

Careful choice of surgical options can also optimise functional outcome. Incisional biopsy should be restricted to that minority of patients in whom histology cannot be obtained by a Trucut needle [26]. When incisional biopsy is performed the site of the incision must be carefully chosen so as not to interfere with the definitive operation which should be performed by a surgeon familiar with limb preservation surgery.

It is apparent, in conclusion, that the majority of these patients compensate for the significant restrictions in range of movement and muscle power seen on objective testing, and thereby retain excellent lower limb function. However, if these results are to be improved it is essential that these patients' treatment is carried out by a multidisciplinary team familiar with the complex problems they present.

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A Meta-analysis of Reported Correlations between Prognostic Factors in Breast Cancer: Does Axillary Lymph Node Metastasis Represent Biology or Chronology?

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A statistical overview of published results on correlations between various prognostic factors in breast cancer was undertaken. A distinction was made between clinical (or anatomical) prognostic factors—namely, axillary lymph node status and tumour size—and eight different biological prognostic factors. The latter included: tumour grade, oestrogen and progesterone receptor status, thymidine labelling index, DNA ploidy, S-phase fraction, epidermal growth factor receptor expression and c-*erb*B-2 gene amplification (or overexpression). 139 articles were eligible for review which reported a total of 432 individual correlations. A simple form of meta-analysis was employed: the counting method, in which the number of studies achieving a statistically significant correlation or not were counted. For each possible correlation examined, the proportion of studies showing a statistically significant correlation was calculated and an exact binomial 99% confidence interval determined for that proportion. If the 99% confidence interval included 5% (the proportion of correlations that would be expected to be statistically significant if the null hypothesis was true), it was taken as failing to exclude the null hypothesis of a zero correlation, while if it excluded 5% it was taken as rejecting the null hypothesis of a zero correlation. A broad agreement was found among published reports on the existence of a statistically significant correlation between the various biological prognostic factors in breast cancer. Of the 20 correlations examined, 18 had a 99% confidence interval excluding 5%, thus rejecting the null hypothesis of a zero correlation. On the other hand, a completely different result was obtained when reports on possible correlations between lymph node status and tumour size on the one hand and the eight biological prognostic factors on the other were analysed. Of the 16 correlations examined, 13 had a 99% confidence interval including 5%, failing to reject the null hypothesis of a zero correlation. These observations suggest the hypothesis that the prognostic influence of node status and tumour size cannot be explained by an analysis of the biology of breast cancer; and is compatible with the contention that axillary node status is merely a reflection of the relative chronological age of breast cancer.
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INTRODUCTION

AXILLARY NODE status has been the traditional prognostic factor used in the clinical management of breast cancer [1]. In recent years, several biological factors have been identified which have been shown to influence the clinical course of the disease, and these are being increasingly used to make treatment decisions [2]. Nevertheless, lymph node status remains the gold standard against which the predictive power of biological prognostic factors are evaluated [2].