ANATOMICAL FACTORS IN ADULT EXTREMITY SOFT TISSUE SARCOMA

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DECLARATION

I declare that this thesis and the work contained in it is my own, except where specifically acknowledged. This thesis has not been submitted for any other degree, postgraduate diploma or professional qualification.

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I would like to thank all the patients who have allowed their data to be analysed and who took the time to fill in questionnaires. I hope that this thesis contributes to improving the lives of those who follow.

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ABSTRACT

This thesis examines the relationship between anatomical location and outcomes in adult extremity soft tissue sarcoma. Four studies address differing aspects of this question by reviewing patients treated at the Musculoskeletal Oncology Unit at the Mount Sinai Hospital, Toronto, Canada.

The anatomical relationships of a tumour may mean that it is resected with a positive surgical margin. The first study looks at the clinical situations in which a positive surgical margin occurs and tests a classification of positive surgical margins. The study shows that positive surgical margins occurring after the resection of a low-grade liposarcoma and planned positive margins against critical anatomical structures are associated with a low risk of local recurrence. However, positive surgical margins occurring during reexcision of a tumour following unplanned excision and unplanned positive margins occurring during primary resection are associated with a significantly higher risk of local recurrence.

The second study examines differences in presentation, treatment and outcomes between soft tissue sarcomas in the upper and lower extremities. It shows that upper extremity tumours are smaller, are more often subjected to unplanned excision before referral and are less often treated with radiotherapy. Upper extremity tumours are more likely to recur locally after treatment, whereas lower extremity tumours are more likely to metastasise.

The third study examines the relationship between the anatomical location of lower extremity soft tissue sarcoma and functional outcome following treatment measured by Musculoskeletal Tumour Society (MSTS (1993)) and Toronto Extremity Salvage Score (TESS) evaluations. It shows that treatment of superficial tumours does not lead to significant changes in functional scores. Treatment of deep tumours, however, leads to significant reductions in functional scores. Aggregated functional scores do not appear to vary with anatomical location, but the items that comprise the aggregated scores do.

The final study examines whether or not the preservation of anatomical structures leads to better functional scores by comparing scores after the planned marginal excision or "shelling out" of a low grade liposarcoma with those seen after the wider resection of a high grade tumour. It shows that the planned marginal excision of a low grade liposarcoma does lead to significant changes in functional scores, although this approach may lead to better TESS evaluations.

These novel, clinically relevant, studies confirm the importance of anatomical location in determining presentation, treatment and outcomes in extremity soft tissue sarcoma.

ETHICAL APPROVAL

The data used in these studies were collected prospectively and reviewed regularly for the purposes of clinical audit and quality control within the Musculoskeletal Oncology Unit at the Mount Sinai Hospital, Toronto, Canada. Functional outcome scores were collected as part of a number of ethically approved studies for which consent was obtained. This consent includes provision for further analysis.

1. INTRODUCTION AND AIMS

Soft tissue sarcomas are rare malignant tumours that exhibit heterogeneity in type, anatomical location and biological behaviour. Most are considered to be of mesenchymal origin, meaning they originate from, and resemble, connective tissues. By convention, this group usually also includes tumours of neural origin but not the cutaneous Kaposi's sarcoma. Soft tissue sarcomas arise most frequently in the extremities and trunk (55%), in the retroperitoneum or viscera (35%) or head and neck (10%) [98]. Lower extremity soft tissue sarcomas are more common than those in the upper extremity [18;72;98;123;128]. The disease occurs at all ages but is most frequently seen in the middle decades of life, at a median of around 50-60 years [4;69;132]. Although local control of extremity tumours can be achieved in up to 90% of patients, 10-year disease-specific survival is between 50 and 60% in most series [33;69;125;138] and has not changed significantly in recent years [134]. Treating patients with these tumours therefore presents a number of challenges; clinical presentation is often delayed, histological diagnosis is specialised, local control requires carefully planned surgery and radiotherapy, there is no highly effective agent for the treatment

of systemic disease and the rarity and heterogeneity of the condition make research difficult. This introduction reviews what is known about adult extremity soft tissue sarcoma, how present treatment regimes have evolved, and describes the aims of this thesis.

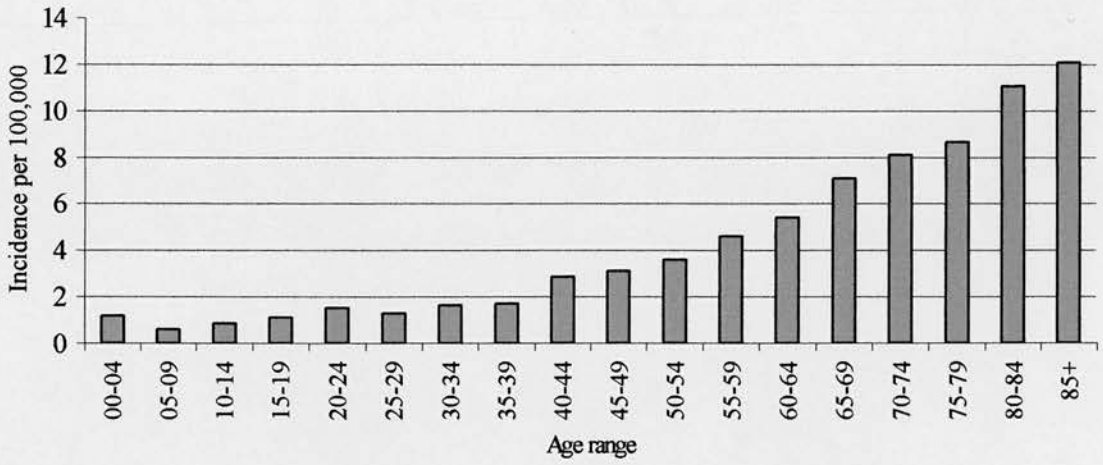
The term "sarcoma" derives from the Greek *sarx*, meaning flesh, as these tumours were originally considered fleshy in appearance. Although malignant tumours were described in the Smith Papyrus, which originated in ancient Egypt in around 1600 BC, the first recognised description of a sarcoma is attributed to Galen in the second century AD [63]. In the eighteenth century the development of the achromatic microscope and thin tissue sectioning techniques lead to the recognition of different embryonic germ layers [63]. The French anatomist Jean Cruveilhier (1791-1874) published illustrations of the gross anatomy of bone and soft tissue tumours, but it was the noted pathologist Rudolf Virchow (1821-1902) who separated sarcomas from carcinomas, defining them as arising from non-epithelial or non-haematogenous tissues. He distinguished six major types of sarcoma: fibrosarcoma, myxosarcoma, gliosarcoma, melanosarcoma, chondrosarcoma and osteosarcoma [94]. The contemporary understanding of the pathology of soft tissue sarcomas has developed as a result of the efforts of, among others, Henry L Jaffe (1896-1979) and Louis Lichtenstein (1906-1977), Dahlin from the Mayo Clinic and Stout, Enzinger and Weiss from the Armed Forces Institute of Pathology, who have published the clinical experience of their centres [94].

Incidence

Although soft tissues and bone comprise around 75% of total body weight, soft tissue sarcomas account for fewer than 1% of all cancers [110;143]. The overall incidence of soft tissue sarcoma increases with age (Figure 1.1). In England and Wales, the Department of Health records around 1200 cases of soft tissue sarcoma in adults [30] and around 80 cases of soft tissue sarcoma per annum in children (under the age of 15) [29]. Figures from the United States show a similar incidence, of 2.8 per 100,000 per annum [100]. Although one study suggests that the incidence of soft tissue sarcoma may be increasing, this has not definitively been demonstrated [142].

Figure 1.1

Incidence of malignant soft tissue tumours by age



Data derive from the United States' Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (1973-2000) and include tumours arising in the heart. These data are available at www.seer.cancer.gov

Aetiology

In most cases of soft tissue sarcoma it is not possible to identify an aetiological cause. However, some genetic and environmental factors have been associated with the disease.

Genetic factors

In the Li-Fraumeni syndrome, families have a predisposition to the early development of malignant tumours. In most cases there is an inherited defect in the p53 tumour suppressor gene [143]. The p53 gene product has a number of roles, including DNA repair, and the p53 pathway is altered in most human cancers [60]. Individuals in these families are thought to have a 50% probability of developing an invasive malignancy by the age of 30 [120]. The spectrum of cancers in this syndrome includes breast cancer, brain tumours, leukaemia, and adrenocortical carcinoma as well as soft tissue sarcoma and osteosarcoma [143].

The retinoblastoma (RB) gene is a tumour suppressor gene subject to unique inactivating mutations in retinoblastoma, osteosarcoma and other sporadic sarcomas[11]. Patients with the inherited form of retinoblastoma have a germline mutation of this gene. Survivors of the inherited form of retinoblastoma have a 10-15% lifetime risk of developing a soft tissue sarcoma [85].

Type 1 neurofibromatosis is an inherited autosomal dominant condition associated with an increased risk of neurogenic sarcomas such as neurofibrosarcoma in adults, and rhabdomyosarcoma in children. Adults with the condition have a 5-10% lifetime risk of developing malignant change within a pre-existing neurofibroma [144]. In

Gardner's syndrome, familial polyposis of the colon is associated with fibromatosis and rarely fibrosarcoma [107].

Environmental factors

Some medical interventions are associated with the development of soft tissue sarcoma. Radiotherapy, especially when given in conjunction with alkylating chemotherapeutic agents is associated with the late (median 8 years) development of secondary sarcoma [76;97]. Secondary sarcomas most often occur within or at the edge of the previously irradiated field and the risk of secondary sarcoma is probably dose-related [143]. The absolute risk of developing a secondary sarcoma has been estimated at between 0.03 and 0.8% [83]. A study of breast cancer survivors found the cumulative incidence of secondary sarcoma at 15 years after diagnosis to be 3.2 per 1000 in patients who had received radiotherapy and 2.3 per 1000 amongst those who had not[140].

Thorotrast (colloidal thorium dioxide) is an alpha-emitting radioisotope once used for the radiographic investigation of blood vessels and has been associated with the development of sarcoma, particularly hepatic angiosarcoma. The cumulative risk of liver malignancy (angiosarcomas and carcinoma) has been estimated at up to 30% at 40 years [143]. There are reports of sarcomas developing at the sites of injection of iron-dextran compounds and chemotherapeutic agents [12;101;133].

Studies of Swedish forestry workers have reported a six-fold increased risk of soft tissue sarcoma following exposure to phenoxyacetic herbicides, chlorophenols and contaminants (dioxins) within them [62;136].

The chronic irritation associated with skin ulceration has been associated with the development of soft tissue sarcoma [44]. Sarcomas have also been reported around metal implants, in particular joint replacements [17;122], although large population-based studies have failed to demonstrate an increased risk of sarcoma in patients who have had joint replacements[49;50;92;112]. Theoretical evidence that metal-on-metal bearings lead to the production of more carcinogenic wear debris has not yet been translated into a higher rate of malignancy amongst patients [130]. Smokeless tobacco, paternal smoking habits and dietary factors have all also been related to the development of soft tissue sarcoma [143].

Clinical Presentation

Most patients with an extremity soft tissue sarcoma present with a painless mass, although pain may make the diagnosis of malignancy more likely [74]. Soft tissue sarcomas are often neglected because neither the patient nor their doctor suspects malignancy. Presentation of an extremity soft tissue sarcoma may be delayed until the mass interferes with normal activities, such as wearing normal clothes.

A significant proportion (approximately 40% in some series) of patients present having had an "unplanned excision", that is removal of the tumour by a surgeon who has not considered beforehand that it may be malignant [79;88]. This is more likely to occur when tumours present in the upper extremity [18;111]. By definition, unplanned excision is performed without regard for preoperative imaging or the necessity to remove a margin of normal tissue covering the tumour and is therefore usually

incomplete [51;52]. These procedures are popularly known as "whoops" operations [73]. Afterwards, residual tumour is difficult to detect with imaging [88]. Local recurrence is highly likely unless residual tumour cells are removed and therefore re-excision of the surgical wound is usually recommended [88].

Despite the strong clinical impression that unplanned excision is likely to compromise oncological outcomes, there is controversy about this in the literature. Some authors associate unplanned excision with higher local recurrence rates [88], some have not found a difference in local control rates [67], and others have reported that unplanned excision followed by re-excision is associated with higher survival rates [51;79].

Despite this controversy, in common with other rare diseases, it is generally accepted that patients with soft tissue sarcomas should have access to an experienced specialist multidisciplinary team. This is an expressed goal of the United Kingdom National Plan for Cancer [31]. Specialist teams allow clinicians to accumulate experience of these rare tumours, to make collaborative decisions about appropriate combinations of different treatment modalities and collect data. There is evidence to suggest that patients treated in specialist centres are likely to receive higher standards of care, undergo fewer operations and are likely to have lower local recurrence rates[15;58;88].

To avoid unplanned excision and to expedite appropriate referrals, guidelines have been developed and circulated. The United Kingdom Department of Health guidelines are reproduced in Figure 1.2 [30]. Guidelines such as these balance the risk

Figure 1.2

Department of Health Guidelines for the referral of soft tissue masses [30]

Soft Tissue Sarcoma

Can occur at any age – more common over 30 years.

Most soft tissue masses are benign (only 1 in 200 are malignant).

Features of a soft tissue mass which are suggestive of malignancy include:

- Size > 5 cms
- Painful
- Increasing in size
- Deep to fascia
- Recurrence after previous excision

Lumps which are superficial and painless and less than 5 cms and static in size are extremely unlikely to be malignant.

of missing a rare but malignant sarcoma against the workload implications of large numbers of referrals for benign tumours. Implementation of these guidelines in Sweden has lead to around 10 benign tumours being referred for every proven malignant soft tissue sarcoma [55]. These guidelines do not account for anatomical location. In particular, malignant tumours in the upper extremity are smaller than those in the lower, and a significant percentage are less than 5 centimetres in maximum diameter [18;57;111].

Pathological characteristics

The diagnosis of soft tissue sarcoma is usually made following the histological examination of tissue obtained at biopsy. Because definitive local treatment involves the removal of the whole tumour and the biopsy track, biopsies must be performed with great care. The histological classification of soft tissue sarcomas is based on the morphological appearance under the light microscope. For example, liposarcomas consist of cells that resemble adipocytes. However, immunohistochemical stains are essential to further characterise tumours, and at present over 130 types are recognised (Appendix 1).

The histological grade of a tumour is one of the best predictors of biological behaviour. However, no consensus exists about the specific criteria that should be used for histological grading. The two most widely used systems are the National Cancer Institute System [20], and the French Federation of Cancer Centres Sarcoma Group System [126]. The former system is based on histological type, location,

necrosis, cellularity, nuclear pleomorphism and mitotic count. The latter generates a score from considerations of tumour differentiation, mitotic rate, and degree of tumour necrosis.

Newer techniques, in particular cytogenetic analysis, have allowed classification to evolve further as some soft tissue sarcomas have characteristic abnormalities (Table 1.1). For example, synovial sarcoma was previously defined by morphological and immunohistochemical features and is now defined by a characteristic X:18 translocation. Similarly, the diagnosis of gastro-intestinal stromal tumours is strengthened if there is overexpression of the c-Kit receptor [45].

Table 1.1

Examples of Chromosomal Translocations in Malignant Soft Tissue Tumours [42]

Tumour type	*Usual and main variant translocations*	*Involved genes*
Synovial sarcoma	t (X;18)(p11.2;q11.2)	SSX1 or SSX2, SYT
Myxoid/round cell liposarcoma	t (12;16)(q13;p11)	CHOP, TLS
	t (12;22)(q13;q12)	CHOP, EWS
Ewing's sarcoma/ primitive neuroectodermal tumour	t (11:22)(q24;q12)	FLI1, EWS
	t (21:22)(q22;q12)	ERG, EWS
	t (7;22)(p22;q12)	ETV1, EWS
	t (2;22)(q33;q12)	FEV, EWS
	t (12;22)(q12;q12)	E1AF, EWS
Clear cell sarcoma	t (12;22)(q13;q12)	ATF1, EWS

Staging Systems

Although heterogeneity in anatomical location and histological type makes it difficult to establish systems that can accurately stage all patients, a number of staging systems are widely used. These include the American Joint Committee on Cancer System (AJCC)[2], and the Musculoskeletal Tumour Society System (MSTS)[36]. These systems use factors of known prognostic significance, including histological grade, size, depth, lymph node involvement and distant metastases. The MSTS system includes the compartmental status of the tumour, which reflects its anatomical location. The Musculoskeletal Tumour Society system is summarised in Table 1.2 and the fifth edition of the AJCC system, in use when these studies in this thesis were completed, is summarised in Table 1.3. Of these two systems, the fifth edition of the AJCC system is of greater value in predicting metastasis-free survival[138].

The sixth edition of the AJCC system has been in use since January 2003. This new edition was developed after further analysis of data from the Memorial Sloan Kettering Cancer Centre, which showed that large deep low grade tumours should be classified along with large superficial low grade tumours as stage 1B rather than IIA, reducing the number of categories in stage II to two. In addition, the new classification excludes the histological types angiosarcoma and malignant mesenchymoma [3].

Table 1.2

Musculoskeletal Tumour Society staging system for primary bone and soft tissue tumours [36]

Definitions

Grade
G1 Low
G2 High

Site
T1 Intracompartmental
T2 Extracompartmental

Metastasis
M0 No regional or distant metastases
M1 Regional or distant metastases present

Stage	*GTM*	*Description*
1A	G1 T1 M0	Low grade Intracompartmental No metastases
1B	G1 T2 M0	Low grade Extracompartmental No metastases
2A	G2 T1 M0	High grade Intracompartmental No metastases
2B	G2 T2 M0	High grade Extracompartmental No metastases
3A	G1/2 T1 M1	Any grade Intracompartmental Metastases
3B	G1/2 T2 M1	Any grade Extracompartmental Metastases

Table 1.3

American Joint Committee on Cancer Staging System for Soft Tissue Sarcoma. Fifth Edition [2]

Tumour grade (G) GX: Grade cannot be assessed G1: Well differentiated G2: Moderately differentiated G3: Poorly differentiated G4: Undifferentiated	***Primary tumour (T)*** TX: Primary tumour cannot be assessed T0: No evidence of primary tumour T1: Tumour 5 cm or less in greatest dimension T1a: Superficial tumour T1b: Deep tumour T2: Tumour more than 5 cm in greatest dimension T2a: Superficial tumour T2b: Deep tumour
Regional lymph nodes (N) NX: Regional lymph nodes cannot be assessed N0: No regional lymph node metastasis N1: Regional lymph node metastasis	***Distant metastasis (M)*** MX: Distant metastasis cannot be assessed M0: No distant metastasis M1: Distant metastasis

Stage IA
Stage IA tumour is defined as low grade, small, superficial or deep.
G1 T1a N0 M0 / G1 T1b N0 M0 / G2 T1a N0 M0 / G2 T1b N0 M0

Stage IB
Stage IB tumour is defined as low grade, large and superficial.
G1 T2a N0 M0 / G2 T2a N0 M0

Stage IIA
Stage IIA tumour is defined as low grade, large and deep.
G1 T2b N0 M0 / G2 T2b N0 M0

Stage IIB
Stage IIB tumour is defined as high grade, small, superficial or deep.
G3 T1a N0 M0 / G3 T1b N0 M0 / G4 T1a N0 M0 / G4 T1b N0 M0

Stage IIC
Stage IIC tumour is defined as high grade, large and superficial.
G3 T2a N0 M0 / G4 T2a N0 M0

Stage III
Stage III tumour is defined as high grade, large and deep.
G3 T2b N0 M0 / G4 T2b N0 M0

Stage IV
Stage IV is defined as any metastasis to lymph nodes or distant sites.
Any G, any T N1 M0 / Any G, any T N0 M1

Although useful, these staging systems can only crudely reflect the complex interaction between tumour and host. It is likely that other indicators of tumour behaviour, such as chromosomal abnormalities or assessments of growth rate will become incorporated into staging systems as understanding of their prognostic value develops [14;56;93]. Likewise, larger studies may allow further refinement of these systems, for example by including more categories for tumour size [90].

Overview of local management of extremity soft tissue sarcoma

Over the last thirty years or so, the local treatment of soft tissue sarcoma has moved away from high rates of amputation towards limb-sparing surgery. A major factor in this change was a study published in 1982 by Rosenberg et al under the auspices of the National Cancer Institute[106]. In this study patients with extremity soft tissue sarcoma were randomised to receive amputation or limb-sparing surgery with radiotherapy. The study showed that although limb-sparing surgery was associated with a higher rate of local recurrence than amputation, disease-free survival and overall survival did not differ significantly between the groups. This has remained the consensus view in the intervening period. Limb sparing surgery is still associated with a higher rate of local recurrence than amputation [132], but combined surgery and radiotherapy has been widely adopted and primary amputation rates remain around 10% [86;96;128;132]. Amputation may still be considered when it is otherwise impossible to obtain adequate clearance, when there are contraindications to radiotherapy or the function of the preserved limb would be poor [91].

Risk factors for local recurrence

The study of risk factors is useful for counselling patients about treatment, in deciding about different treatment options and in enhancing understanding of a disease [84]. Factors shown in multivariate analyses to be associated with local recurrence after treatment for soft tissue sarcoma are summarised in Table 1.4. In these analyses, the effect of a particular factor is usually quoted as "relative risk", which is defined as the incidence in patients with the risk factor, divided by the incidence in those without the relevant risk factor. When calculated from survival curves, the relative risk may be referred to as the "hazard ratio".

Tumour-related factors

Both histological type and grade may influence the risk of local recurrence. Fibrosarcoma has been associated with a relative risk for local recurrence of 2.5, and malignant peripheral nerve sheath tumour with a relative risk for local recurrence of 1.8 in one study [96]. Tumours with higher histological grades are associated with higher risks for local recurrence, with relative risks in multivariate analysis of 1.8 (histological grade 3 of 3 in the French Federation of Cancer Centres (FNCLCC) system) [16], 1.9 (histological grade 3 of 3, system attributed to Myhre Jensen)[132]and 3.0 (grade 3 or 4, Scandinavian Sarcoma Group system) [127]. Extensive histological necrosis, which is reflected in histological grade, has also been associated with local recurrence (relative risk 2.1 [105]).

Table 1.4

Factors predicting local recurrence after treatment of soft tissue sarcoma

Adverse prognostic factor	
Histological type	– Fibrosarcoma [96]
	– Malignant peripheral nerve sheath tumour [96]
High histological grade	– Grade 3 of 3 [16]
	– Grade 3 of 3 [132]
	– Grade 3 or 4 *vs* grade 1 or 2 [127]
Extensive histological necrosis [105]	
Deep anatomical location[16]	
Extracompartmental location [132]	
Advancing age [77;96]	
Local recurrence at presentation [96;102;114]	
Positive surgical margins [16;96;105;114;117;123;127;132]	
Intraoperative tumour violation [123]	
No radiotherapy [16;132]	
Limb sparing surgery compared with amputation [106;132]	

Tumour size is not a significant predictor of local recurrence in the multivariate analyses reviewed, although surrogates for increasing size, such as deep anatomical location (relative risk 1.8 [16]) or extracompartmental location (relative risks 1.9 [105], 2.6 [132]) are. In addition, large tumours are more likely to be resected with positive surgical margins, which is likely to be associated with local recurrence [117]. A tumour which is locally recurrent at presentation is more likely than others to recur again (relative risk 2.0 [96], 7.4 [114]).

Some studies suggest that anatomical location might be important in determining local recurrence by showing a difference in local recurrence rates between tumours in the extremities and those at other sites. Tumours in the extremities or torso have better local control rates than those in the head and neck, retroperitoneum, thorax or viscera, because in these latter sites, complete resection is difficult and the proximity of critical anatomical structures means that local recurrence is more likely to be fatal[16;77;82;116]. However, there is little information about variation in local recurrence rates within the extremities.

Host factors

Advancing age appears to have an adverse effect on the risk of local recurrence [77;96].

Treatment factors

Incomplete resection, assessed by the surgical margin, is one of the strongest predictors of local recurrence [16;77;96;114;117;127;132]. In multivariate analyses, inadequate surgical margins have been associated with a relative risk for local recurrence of 1.8 (microscopically positive margins) [96], 2.2 (intralesional or marginal excisions)[127], 2.4

(positive margin compared with a "clean" margin)[114], 4.0 (microscopically positive margins) [123], 5.3 (intraoperative tumour violation) [123] and 5.9 (marginal surgery, histological grades 3 and 4 only) [105].

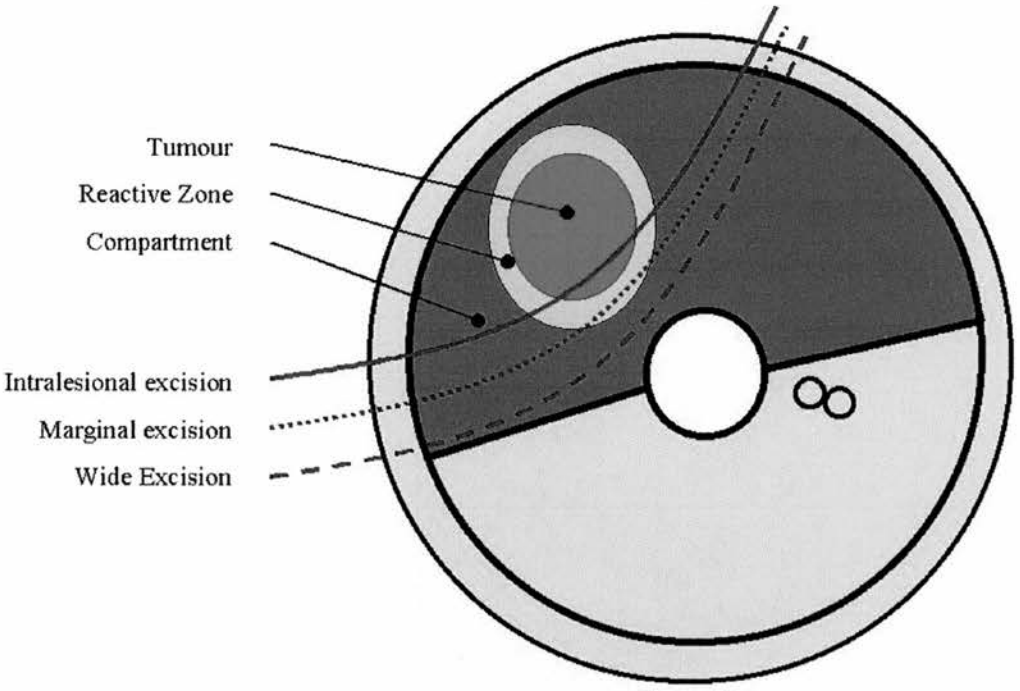
Radiotherapy has been shown to reduce the risk of local recurrence (relative risk (no radiotherapy) 3.7[132] relative risk (radiotherapy) 0.4 [16]).

Defining the surgical margin

It is clear that to control a tumour locally, the whole of the tumour should be removed. Achieving this requires an understanding of the local behaviour of soft tissue sarcomas. Enneking made a major contribution to this field by developing a model in which tumours were considered to be surrounded by a reactive zone of compressed normal tissue, inflammatory and tumour cells (Figure 1.3) [40]. He also recognised that tissues such as bone and fascia resist invasion by tumour, and this observation lead to the concept of anatomical "compartments". These are well-defined anatomical spaces with osteofascial boundaries that tend to contain the local extension of tumours (Table 1.5). Tumours within one of these spaces are said to be "intracompartmental". Other anatomical locations, such as the popliteal fossa, which do not have clearly defined boundaries are known as "extracompartmental" sites. It follows that intracompartmental tumours can be completely excised by removing the whole of the "compartment". This classification remains a useful part of the local staging of musculoskeletal tumours.

Figure 1.3

Diagrammatic representation of a soft tissue tumour within the anterior thigh in cross section



The tumour (red) is surrounded by a reactive zone of compressed normal tissue and inflammatory cells (pink), within an osteofascial compartment (green). Examples of planes of resection are shown. In an intralesional excision, the plane of resection passes through the tumour, in a marginal excision through the reactive zone, and in a wide excision through normal tissue. In a radical excision the whole of the compartment (green) would be excised.

Table 1.5

Examples of intracompartmental and extracompartmental sites for extremity soft tissue sarcoma [113]

Intracompartmental sites	*Extracompartmental sites*
- Intra-articular	
- Superficial to deep fascia	
Osteofascial compartments	*Extrafascial planes or spaces*
- Ray of hand or foot	- Mid- and hindfoot
- Posterior calf	- Popliteal space
- Anterolateral leg	- Groin/femoral triangle
- Anterior thigh	- Intrapelvic
- Medial thigh	- Mid hand
- Posterior thigh	- Antecubital fossa
- Buttocks	- Axilla
- Volar forearm	- Periclavicular
- Dorsal forearm	- Paraspinal
- Anterior arm	- Head and neck
- Posterior arm	
- Periscapular	

Examination of the surgical margin is important to assess whether or not a tumour has been completely excised. In Enneking's system the margins of resection of a tumour were defined in terms of the relationship between the plane of resection, the tumour and its reactive zone, and the anatomical compartment. Resections were defined as *intralesional* when resection was carried out within the reactive zone and through tumour, as *marginal* when resection was carried out through the reactive zone, as *wide* when resection was performed outside the reactive zone through normal tissue and as *radical* when the whole compartment was excised. Although these concepts have their limitations (e.g. compartments such as the posterior thigh do not have clear boundaries at the superior and inferior extent), they are useful in planning the local treatment of soft tissue sarcoma. In Enneking's paper, the rate of local recurrence following surgical treatment alone was 50% after marginal, 25% after wide and 4% after radical excision [40].

These concepts of surgical margins have been developed further by others. Rydholm and Rooser considered an intact muscle to be a distinct anatomical compartment and subclassified wide margins as wide-S (subcutaneous) when a subcutaneous tumour was excised with a cuff of subcutaneous tissue and deep fascia, wide-F (fascia) when a deep tumour was excised with an intact envelope of uninvolved fascia and wide-AM (areolar tissue and muscle) when a deep tumour was excised with a wide margin, some or all of which comprised muscle or areolar tissue. The five-year local recurrence rate was 10% with wide-S and wide-F margins and 30% with a wide-AM margin when patients were treated with surgery alone [108].

Kawaguchi et al. suggested a classification that abandoned the use of compartmental anatomy to describe the resection[71]. Wide margins were classified as *curative*, *adequate* or *inadequate* depending on the width and quality of tissue comprising the margin. Inadequate wide margins did not ensure local control even with adjuvant radiotherapy in high-grade sarcoma, but were sufficient for low-grade tumours [70]. However, this is a complex system which, although used by the Japanese Orthopaedic Association, has not been adopted elsewhere.

As combined management with limb-sparing surgery and adjuvant treatments has developed, the description of surgical margins as simply positive or negative has become more common [6;61;64;78;96;109;114;123]. However, it is likely that all "positive margin" resections do not have the same risk of local recurrence, and this has not been explored in the literature.

The likelihood that a tumour is going to be resected with positive margins depends on a number of factors, such as size and local anatomy [6]. Stojadinovic et al reported that factors associated with a positive surgical margin included anatomical location (retroperitoneum or head and neck), size >10cm, fibrosarcoma histology, and stage T2b (>5cm, deep) [117]. Heslin et al found that resections leading to positive surgical margins were associated with more blood loss and longer operating times than others[64]. Trovik et al reported that adequate resections were associated with patients under 50 years of age, high grade, smaller (<7 cm) tumours, or those in superficial locations or the extremities [127]. After excision of trunk and extremity soft tissue sarcomas, reported positive margin rates vary from 1% [47]to 26% [123]. In a review of

patients treated entirely by an experienced multidisciplinary sarcoma group in Toronto, Wilson reported 9 positive margins in 62 patients, a rate of 14.5% [135].

Adjuvant radiotherapy

Adjuvant radiotherapy is frequently used with surgery to improve local control. In the only randomised controlled trial to address this issue, Yang et al reported local control rates of 80% with surgery alone and 99% when surgery is used with radiotherapy [139]. Although some tumours (particularly those that are small or superficial) can be adequately treated with surgery alone, radiotherapy may be given after consideration of a number of factors, such as histological grade, surgical margin and the anatomical location of the tumour [91].

In the treatment of soft tissue sarcoma, radiotherapy is usually given as external beam therapy or with radioactive wires (brachytherapy). Radiotherapy may be given either preoperatively, rarely intraoperatively, or postoperatively [124]. Postoperative external beam radiotherapy is the most common modality in the United Kingdom. However, there are potential benefits of preoperative radiotherapy. In particular, the extent of the tumour is easier to define, the treatment volume is lower, tissues are better oxygenated and a lower dose of radiotherapy can be given [87;103]. Unfortunately, preoperative radiotherapy leads to a higher rate of wound complications. The largest study to compare pre and postoperative radiotherapy randomised 190 patients across Canada to 50 Gray preoperatively with a 16 Gray postoperative boost to areas where the excision margins were considered inadequate

or 66 Gray postoperatively. The study showed significantly more wound complications amongst patients receiving preoperative radiotherapy (35% vs 17%). The local recurrence rates in both arms of the study were similar [89]. Functional outcome, using a number of measures, appeared to be similar at a year after surgery[24].

Brachytherapy is a technique in which radioactive wires are placed into fine catheters implanted into the wound and has the advantage of delivering radiation to a small volume of tissue. This is most useful in areas where there is a concentration of radiosensitive structures, such as the head and neck, or in the treatment of local recurrence in a previously irradiated area. Local control rates are thought to be equivalent to those achieved with external beam radiotherapy, with a dose of between 42 and 45 Gray [95]. Treatment is given over a shorter period (4 to 6 days) but is more labour intensive.

Endpoints for assessment of systemic disease

Studies that address prognostic factors for systemic disease in soft tissue sarcoma may use the diagnosis of metastasis (metastasis-free survival), death from the disease (disease-specific survival), or survival after the diagnosis of metastasis as endpoints[16;96]. Disease-free survival, in which the diagnosis of local recurrence or metastasis is taken as the event of interest, may be used to reflect systemic metastatic disease in the clinical situation in which local recurrence is unlikely. The time to diagnosis of metastases is likely to be heavily influenced by follow-up protocols.

Patients who are regularly screened, for example with a chest x-ray, are likely to have pulmonary metastases diagnosed earlier than others. Soft tissue sarcomas arising in the extremities usually cause death by pulmonary metastases, and therefore factors associated with the development of these metastases are also those which are likely to be associated with disease-specific survival. This is not the case with retroperitoneal or head and neck sarcomas, which are more likely to cause death by local recurrence, rather than systemic disease[77]. Survival after the diagnosis of metastases is likely to relate to whether or not effective treatment for the metastasis can be administered, which may also relate to how early metastases have been diagnosed. The choice of endpoint depends upon the purpose of the analysis. For the purposes of this introduction, risk factors for disease-specific survival in the literature have been addressed, and then differences between risk factors for metastasis-free survival and disease-specific survival are compared.

Disease specific survival

A number of studies have investigated risk factors for disease specific survival. These are summarised in Table 1.6.

Tumour-related factors

The three most consistent predictors of disease-specific survival are tumour size, histological grade and anatomical depth. In published studies of soft tissue sarcoma, tumour size is usually represented by the maximum single dimension, rather than by estimating tumour volume. Large tumours are associated with an increased risk of

death from disease (>5cm relative risk 1.8 [132]; >10 cm relative risk 2.1 [96]; >7.0 cm relative risk 2.3 [127]; tumour size >=5cm, relative risk not specified [16]). Large tumours tend to be deep, therefore these variables are not independent. Nevertheless, some studies appear to show independent prognostic importance for tumour size and depth [16;96].

The relationship between histological grade and metastatic potential has been confirmed by many studies (grade 3 of 3 (relative risk 2.6 [132]); grade 3 of 3 (relative risk 2.8 [16]); grades 3 or 4 versus grades 1 or 2 (relative risk 3.3, [127]); high grade versus low grade (relative risk 4.0 [96]); high grade versus low grade [77]). Histological type may also influence disease-specific survival. Leiomyosarcoma (relative risk 1.9) and malignant peripheral nerve sheath tumour (relative risk 1.9) have been associated with lower disease-specific survival and liposarcoma associated with a better prognosis in one large study [96]. However, another study did not find an adverse relationship for malignant peripheral nerve sheath tumour, but found adverse effects for Ewings sarcoma, angiosarcoma and synovial sarcoma [114].

Tumours referred to a specialist centre after local recurrence are also associated with poorer disease-specific survival (relative risk 1.5 [96]).

Table 1.6

Factors predicting disease-specific survival after treatment of soft tissue sarcoma

Adverse Prognostic Factor	
Large size [16;96;102;114]	
High histological grade [16;96;102;114;131]	
Histological type	– Leiomyosarcoma, malignant peripheral nerve sheath tumour [96]
	– Ewings sarcoma, synovial sarcoma, angiosarcoma [114]
Deep anatomical location [16;96]	
Lower extremity location [96]	
Proximal extremity site [102]	
Local recurrence at presentation [96;102]	
Older age [114;131;132]	
Male gender [16;105]	
Positive surgical margin [96;116;117]	
Local recurrence after treatment [105]	
No chemotherapy [16]	

A relationship between anatomical location and disease-specific survival has been suggested by a number of studies, although none address this issue directly. Tumours in the proximal extremities or lower extremity (proximal lower extremity, relative risk 1.6 [96]); proximal extremity, hazard ratio 0.8[134]) and those in extracompartmental locations (relative risk 2.1 [132]) have been associated with poorer disease specific survival. Highest disease-specific survival has been reported in upper extremity, then trunk, then lower extremity tumours [132]. Another study found improved survival for extremity tumours when compared to trunk or intraabdominal tumours [68]. The question of how upper and lower extremity tumours differ in terms of their risk of metastasis and survival has not been directly addressed in the literature.

Host factors

Other adverse prognostic factors for disease-specific survival include advancing age (relative risk 1.03 [114]; relative risk 2.3 [132]), and male gender (relative risk 1.9 [16]). Underlying medical conditions may also influence outcomes. For example, type 1 neurofibromatosis appears to be associated with unusually aggressive behaviour of malignant peripheral nerve sheath tumours [32;99].

Treatment factors

Factors related to treatment that may have an effect on disease-specific survival include a positive surgical margin [96;116;117], local recurrence after treatment [105] and the use of chemotherapy [16]. These issues are discussed below.

Differences between risk factors for metastasis and disease-specific survival

In the treatment of adult extremity soft tissue sarcoma, factors predicting metastasis and those that predict death from the disease are similar. Analysis of metastasis-free survival has the benefit of including patients who are alive with systemic disease, thereby increasing the number of events and therefore the power of the survival analysis. However, the literature highlights some interesting differences in studies that have looked at both the metastasis-free rate and disease-specific survival. In the study by Coindre et al that included patients with tumours in all anatomical locations, male gender was associated with an increase in tumour-specific death, but not with the development of distant metastases [16]. Pisters et al reported that microscopically positive surgical margins, lower extremity site and malignant peripheral nerve sheath tumour type were associated with disease-specific survival, but not distant recurrence in extremity soft tissue sarcoma [96]. In a study of small, high grade extremity soft tissue sarcomas, Fleming et al also demonstrated that male gender was associated with lower disease-specific survival, but not metastasis-free survival [43]. Unfortunately, the clinical significance of these differences is not clear.

The relationship between local recurrence and metastasis

Given that limb conservation is associated with a higher rate of local recurrence than amputation [106], the relationship between local recurrence and metastasis is of great interest, but has proved both "controversial" and "enigmatic" [41]. Studies can be quoted selectively to provide arguments for or against a causative relationship between local recurrence and metastasis. In two prospective randomised studies examining the effect of radiotherapy on local control, an increase in local recurrence rates was not associated with an increase in the rate of metastasis[10;106]. Some take the view that local recurrence is an expression of biological activity and therefore metastatic potential, but that local recurrence itself does not increase the risk of metastasis [59]. Others support the view that local recurrence is likely to lead to metastasis, particularly when local recurrence is analysed as a time-dependent variable [35;77;80;119;127].

Clearly, what the surgeon wants to know is whether or not the positive surgical margin that is accepted to preserve function will shorten the life of the patient. The relationship between a positive surgical margin and local recurrence has been well described. However, the relationship between a positive surgical margin, local recurrence and metastasis is less well understood, with opinions varying from no relationship[123;127], to a stronger relationship (Positive surgical margin leads to systemic disease (relative risk 1.7 [96])) or a relationship that is not strong, but increases with time [116].

To summarise, in the management of extremity soft tissue sarcoma, limb sparing surgery appears to be safe and does not have a major adverse impact on survival, although complete resection is the goal of local treatment. Local recurrence indicates that the tumour is biologically aggressive, and may therefore metastasise. Patients who have a local recurrence are at risk of further local or systemic relapse and may benefit from aggressive local or systemic therapy [33].

Systemic therapy

Perhaps the best guide to the effectiveness of chemotherapy comes from the Sarcoma Meta-Analysis Collaboration [125]. This meta-analysis used individual patient data from 1568 patients enrolled in 14 randomised controlled studies of doxorubicin-based chemotherapy. Data were used from patients with tumours at all anatomical sites, including the head and neck, retroperitoneum and uterus. The results suggested chemotherapy lead to statistically significant improvements in local relapse-free survival (hazard ratio 0.73, 95% CI, 0.56 to 0.94 P=0.016), distant metastasis-free survival (hazard ratio 0.70, 95% CI 0.57 to 0.85, P=0.0003) and overall disease-free survival (hazard ratio 0.75, 95% CI 0.64 to 0.87, P=0.0001). Chemotherapy lead to reductions in the absolute risk of local recurrence of 6% at 10 years, in the absolute risk of distant metastases of 10% at 10 years, and in the absolute risk of death of 4% at 10 years. However, the reduction in overall survival did not reach statistical significance. Criticisms of this meta-analysis are that incorporating tumours at all sites might mask a benefit of chemotherapy for particular sites, that tumours of low

or indeterminate grade were included, and that only one of the studies used ifosfamide, which along with the anthracyclines doxorubicin/epirubicin and dacarbazine is one of the three drugs with activity in this disease [9]. For 886 patients with soft tissue sarcoma of the extremities in this study, the hazard ratio for overall survival was 0.80 (P=0.029), equivalent to a 7% absolute benefit at 10 years [9].

These results raise the question of whether individual patients likely to benefit from chemotherapy can be identified. One study randomised patients with high-risk soft tissue sarcoma of the extremities and limb girdles to chemotherapy (ifosfamide and doxorubicin with hydration, mesna and granulocyte colony-stimulating factor) or control (no chemotherapy) groups. High risk tumours were defined as histological grade 3 or 4, and greater than 5cm diameter or any size of recurrent tumour. Median disease-free survival was 48 months in the treatment group and 16 months in the control group (p=0.04). Median overall survival was 75 months for treated and 46 months for untreated patients (p=0.03) [48]. Another study which targeted patients at high risk of systemic relapse with doxorubicin and ifosfamide found no statistically significant difference in disease-free and overall survival between the treated and control groups [53].

A number of approaches have been taken to improving the effectiveness of chemotherapy including the use of docetaxel [129], liposomal doxorubicin [13], high-dose chemotherapy with autologous hematopoetic stem-cell transplantation [7] and cytokines in conjunction with chemotherapy [54].

Evidence that different histological types of soft tissue sarcoma respond differently to chemotherapy is accumulating, and it has been suggested that synovial sarcoma and liposarcoma are more sensitive to chemotherapy than other histological types[115].

New therapeutic agents are showing great promise in the treatment of soft tissue sarcoma. The best known is STI-571 (Imatinib [Gleevec]; Novartis, Basel, Switzerland), an agent that selectively inhibits the c-kit receptor pathway, which is subject to a gain-of-function mutation in gastro-intestinal stromal tumours [45]. Before STI-571, even complete surgical resection of the tumour was associated with a 5-year disease-specific survival rate of 54% [28]. The use of STI-571 has been associated with partial response or stable disease in 88% of patients, and is associated with a rapid biological response, manifest by changes in FDG-positron emission tomography (PET) scanning [27]. Unfortunately, other soft tissue sarcomas do not appear to express c-kit to the same extent and are therefore unlikely to be as responsive [65].

ET-743 is a novel antineoplastic DNA binding agent derived from a marine organism which has shown activity against sarcoma cell lines in vitro and in phase II studies, with clinical response rates of around 8% [21]. However, this agent has recently failed to win marketing approval within the European Union.

Functional outcomes

As limb-sparing treatments have evolved, interest in the "functional outcome" of the patient has increased. Definitions of function have included a variety of measures, including clinical measures of range of motion or muscle strength [75;104], activities of daily living [75], the Musculoskeletal Tumour Society Scale (MSTS 1987) which includes site-specific details of symptoms and clinical measures [37], the revised MSTS, which includes symptoms, mobility and the use of walking aids, generic measures of health status such as the Short-Form 36 (SF 36) questionnaire [22] and the Toronto Extremity Salvage Score (TESS) [26]

The World Health Organisation (WHO) International Classification of Impairments, Disabilities and Handicaps (ICIDH) [137] clarifies what is meant by "function"*. In this classification, impairments are "any loss or abnormality of psychological, physiological, or anatomical structure or function". Disability is "any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being".

MSTS scores most closely follow the definition of impairment in this classification. The MSTS (1993) is completed by the clinician and consists of 6 items; pain, overall function, emotional acceptance, walking ability, walking aids and gait handicap or limp [38] (Appendix 3). Each item is rated on a scale of 1 to 5. The total score is calculated from a sum of the individual items and expressed as a percentage.

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* The ICIDH classification was revised in 2001 to the "International Classification of Function" (World Health Organisation, Geneva, 2001) which emphasises function rather than disabilities. However, for the purposes of the studies in this thesis, the original definitions have been used.

The Toronto Extremity Salvage Score (TESS) is based on the WHO definition of disability and has shown reliability, validity and responsiveness in the extremity sarcoma population (Appendix 4)[22;26]. The TESS questionnaire is completed by the patient and comprises 30 items in which the patient indicates the difficulty experienced in performing a range of everyday activities, such as dressing, grooming, mobility, work, sports and leisure[26]. Each item is rated on a scale of 1 to 5 and the total expressed as a percentage.

Factors predictive of functional scores have been investigated by Davis et al in a study looking at MSTS 1987, MSTS 1993, TESS and SF36 scores in patients treated for lower extremity soft tissue sarcoma[25]. Using multivariate analysis, it was found that different measures had different predictors. Large tumour size, bone resection, motor nerve resection and complications were predictive of lower MSTS 1987 and 1993 scores. Patients with large, high grade tumours requiring motor nerve resection were more disabled, reflected in lower TESS scores. Age and prior surgery were the sole predictors of lower SF-36 scores . Although anatomical site, as defined by the nearest major joint (hip, knee or ankle) was not predictive of functional scores in this analysis, it is likely that anatomical location has a role in determining functional outcome. For example, function after treatment of a buttock tumour is likely to differ from function after treatment of a tumour in the foot or ankle by virtue of anatomical location alone. Knowledge of the likely impact upon function of treating a tumour in any particular anatomical location may be helpful during treatment. This question has not been explored in the literature.

Another question that has not been addressed in the literature is the whether or not the planned marginal excision of low grade liposarcomas leads to better functional outcomes than the wider "negative margin" surgery used for other high grade tumours. Although the preservation of "normal" tissues might be expected to lead to better functional outcomes, the differences between these two approaches have not been investigated.

Aims of this thesis

Review of the literature points to a close relationship between anatomical location and outcome in the treatment of soft tissue sarcoma. There is variation in presentation, with upper extremity tumours being smaller than those in the lower extremity [57]. There is variation in local treatment, with upper extremity soft tissue sarcomas being more often treated by unplanned excision than those in the lower extremity [18;111]. Positive margin rates also vary by anatomical location [117]. The risk of local recurrence and systemic disease differs between tumours in the extremities and those at other sites [16;77;82;118]. Deep or extracompartmental location is associated with local recurrence [16;132] and systemic disease [16;96]. Lower or proximal extremity location is also associated with systemic disease [96;102].

The studies in this thesis examine novel aspects of this relationship. The anatomical relationships of a tumour are major factors in determining the surgical margins, and are major considerations in determining the most appropriate local therapy. Although most studies treat all positive surgical margins as equal, this may not be appropriate,

as the volume of residual disease is likely to relate to the clinical situation in which the positive margin occurs. This has not been addressed in the literature, and the first study in this thesis examines this issue.

The literature suggests that there are differences between the upper and lower extremities in the manner in which soft tissue sarcomas present, are managed and in their oncological outcomes, but this has not been directly addressed in the literature. The second study examines differences in presentation, the characteristics of the tumour, treatment and outcome between the extremities.

The role of anatomical location in determining functional outcome has not been addressed in the literature. The third study in this thesis examines this question in an analysis of tumours in the lower extremity. Preservation of muscle and other non-critical anatomical structures around a tumour may have an influence on functional outcomes. The final study looks at differences in functional outcomes following the planned marginal fashion or "shelling out" of low grade liposarcomas, compared with those following the wider resection of other tumours.

The specific objectives of the studies in this thesis were therefore

1. To classify and determine the risk of local recurrence of a positive surgical margin after the resection of an extremity soft tissue sarcoma.

2. To examine differences in presentation, treatment and oncological outcomes between upper and lower extremity soft tissue sarcomas.

3. To examine the influence of the anatomical location of lower extremity soft tissue sarcomas on functional outcome.

4. To determine the effect of planned marginal surgery on functional outcome.

2. GENERAL METHODS

A clinical database held in the Musculoskeletal Oncology Unit at the Mount Sinai Hospital, Toronto, Canada was used to identify appropriate patients for the studies in this thesis. Data for the studies were extracted from this database and supplemented with additional data from clinical records as required. The studies were therefore secondary analyses of existing data, rather than analyses based on the prospective collection of new data. Preexisting data definitions were therefore accepted.

All of the patients in these studies were adults with extremity soft tissue sarcoma treated at the Musculoskeletal Oncology Unit of the Mount Sinai Hospital in Toronto, Canada between 1986 and 1997. Subjects were selected for each study on the basis of appropriate inclusion and exclusion criteria as stated in the appropriate chapters.

Data collection, validation and storage

The clinical database at the Musculoskeletal Oncology Unit at the Mount Sinai Hospital is password-protected and held on an Apple Macintosh Computer running a Filemaker Pro database. Data have been collected prospectively since 1986 as patients attend clinics and are reviewed at weekly Multi-Disciplinary Team Meetings. This database has been the basis of a large number of publications and the data have been regularly validated as a result. Functional outcome data are prospectively collected in clinics routinely as part of the standard care of patients in the Musculoskeletal Oncology Unit or as part of a number of other studies.

Clinical records relating to patients under the care of the Musculoskeletal Oncology Unit are held within the orthopaedic offices at the Mount Sinai Hospital. This means that records were available for all patients. The recording of surgical procedures is standardised and comprehensive. MRI and CT scans were available as hard copies from other centres or electronically when performed within the Toronto Teaching Hospitals network.

Data in this thesis were initially extracted from the Filemaker Pro database and imported in anonymised form into an Excel spreadsheet on a password-protected Dell computer (Microsoft Excel 97, Microsoft Corporation, Redmond) to which other appropriate data items were added. Data were verified by looking for out-of-range values, for missing values and for logical consistency. For example, if there had been no local recurrence, there should not have been a date for local recurrence in the spreadsheet. When clinical records were reviewed, data already extracted from

the clinical database were verified from the clinical records. When data relating to anatomical location were generated, data items were checked for consistency with the preexisting anatomical coding. Errors detected in this fashion were corrected on the clinical database where appropriate. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows Software Release 10.1.0 Chicago: SPSS inc.

Functional outcome data are stored on a separate Excel spreadsheet within the Musculoskeletal Oncology Unit at the Mount Sinai Hospital. In the studies dealing with functional outcomes, MSTS (93) and TESS item and total scores were extracted from this spreadsheet, linked with other anonymised clinical data and then imported into SPSS for analysis.

Data fields and definition of terms

The data fields extracted from the database are listed in Appendix 2.

Standard definitions were used throughout.

- The upper extremity was defined as commencing at the medial border of the scapula, including pectoral, periscapular and latissimus dorsi muscles. The lower extremity was defined as commencing at the iliac crest.

- Tumours above and not involving the investing fascia of the extremity were considered superficial, while others were considered deep.

- Tumours with a predominant mass above the knee or elbow were considered proximal and those below as distal.

- Compartmental status was defined as described by Enneking [36].

- An unplanned excision was defined as an excisional biopsy or unplanned resection performed without adequate preoperative staging or consideration of the need to remove normal tissue around the tumour [51]. After unplanned excision, tumour size was determined from pathology reports of the first resection, the operative note or preoperative imaging if available.

- A pathologist with an expertise in sarcoma determined the histological type and graded tumours as 1, 2 or 3 [66].

- A positive margin was defined as the presence of viable or non-viable tumour at the inked resection margin or intraoperative exposure of tumour at any stage. Margins were defined as grossly positive when the surgeon or the pathologist could see tumour at the margin of resection with the naked eye, following intralesional surgery or *en face* exposure of the tumour surface. A margin was said to be microscopically positive when tumour could not be seen on visual inspection of the inked surface, but was evident on microscopic examination.

- Surgical margins were assessed in the operating suite by the surgeon and pathologist during the procedure, using frozen sections where appropriate. Positive surgical margins identified in this fashion were revised if appropriate.

- Complications of surgery were defined as major wound dehiscence requiring surgical intervention, infection or fracture.

- Local recurrence was defined as the reappearance of tumour, proven by biopsy, adjacent to or within the previously treated field at any time after initial treatment. The date of biopsy was used as the date of local recurrence.

- Metastatic disease was defined as tumour identified on chest X-ray or CT scan during follow up, or the development of lymphadenopathy containing tumour. The date of metastasis was taken as the date of the chest X-ray or CT scan, or the date on which lymphadenopathy was detected clinically or radiologically.

Principles of local treatment

During the period in which patients in these studies were treated at the Musculoskeletal Oncology Unit of the Mount Sinai Hospital, they were offered limb-sparing surgery whenever possible following multidisciplinary discussion. Amputation was performed where limb-sparing surgery would not have adequately resected the tumour or would have resulted in a limb without useful function. Adjuvant radiotherapy was given for high grade tumours resected with less than a wide surgical margin, or low grade tumours with a deliberately marginal surgical excision.

Following unplanned excision at another centre, an assessment of the extent and adequacy of the initial unplanned excision was made in discussion with the original surgeon and by review of the initial pathology report, the initial operative note, and imaging studies. Re-excision was performed if there was gross residual tumour on clinical examination or imaging or if the resection had been assessed as inadequate.

Follow up protocols

During this period the standard follow up protocol for patients with extremity soft tissue sarcoma included clinical examination and chest x-ray every three months for two years, every four months in the third year, six monthly in years four and five and annually thereafter. Most patients were followed up at the Musculoskeletal Oncology Unit at the Mount Sinai Hospital, or in a peripheral clinic in London, Ontario. A minority, usually for geographical reasons, was followed up closer to home by local clinicians according to the same protocol.

Statistical tests

For each study, descriptive data were calculated using means, medians, standard deviations and ranges for continuous variables and proportions for categorical data. Significance was taken at the 0.05 level throughout. The Student t-test was used to compare means of continuous variables between 2 groups. The paired t-test was

used to compare data before and after an intervention. Differences in mean values between more than two groups were compared using one way analysis of variance (ANOVA) and the Tukey post-hoc test. The Pearson Chi-squared test was used to compare differences in proportions between groups.

Kaplan-Meier survival curves, rather than life tables, were used to compare the local recurrence-free rate, metastasis-free rate and disease specific survival amongst groups. These curves represent events over time graphically. Subjects entered the studies at different time points and length of follow up varied for each patient depending on when a defined event (local recurrence or metastasis) had occurred, the patient had died, or the last attendance at a clinic was recorded. Data were censored at the time of last follow up or death. Censored data points are represented on graphs with a cross and 95% confidence intervals are shown where appropriate. The date of surgery was taken as the origin for survival analyses. The Log Rank test was used to compare Kaplan-Meier curves.

The Cox Proportional Hazards Model was used to investigate whether there were differences in survival in two or more groups having adjusted for other variables. The Cox Proportional Hazards Model assumes that the hazard ratio for each co-variable is proportional over time. These graphs were plotted in order to ensure this was the case. The rule of thumb attributed to Harrell, that there should be more than 10 events for each variable entered into the analysis [63], was applied. A stepwise entry method in which all variables were entered into the model at the start of the calculation was used with multiple iterations. Tables of results are presented which show the P value for selection into the model (which tests the null hypothesis that the

relative risk for that variable is 1), the relative risk and the 95% confidence intervals of the relative risk.

Non-parametric data (i.e. TESS and MSTS scores) were analysed using the Mann-Whitney test, or the Wilcoxon test for paired data. The Kruskal-Wallis Test was used to compare scores for non-normally distributed data across more than two groups.

Multiple linear regression was used to determine the contribution of anatomical location to functional outcomes whilst compensating for factors already shown to have an influence on functional outcome. Once more, Harrell's guide, that there should be more than 10 patients for each variable entered in multiple regression analysis was applied [63]. In these analyses, comparisons were only performed when there was a complete set of relevant data items for each patient. Postoperative functional scores were taken at one year or at two years if the one year value was missing. An entry method in which all variables were entered at the start of the analysis was used. In this analysis, "dummy" variables were assigned to each of the nine anatomical locations, in which the value 0 or 1 was assigned as appropriate. Tables of results are presented which show the standardised β coefficient, the t statistic and significance values for each variable in the analysis. The standardised β coefficient allows the variables to be compared with each other for their effect on the outcome variable. The t statistics and the significance values reflect the relative importance of each variable in the model.

Each study was designed to incorporate as many of the patients in the database as possible. Therefore formal *a priori* power calculations were not performed.

3. ANALYSIS OF POSITIVE SURGICAL MARGINS

Introduction

The purpose of this study was to evaluate the clinical significance of a positive surgical margin by considering the clinical situations in which a positive surgical margin occurs and the risk of local recurrence associated with each situation. In particular, it was hypothesised that when a positive surgical margin is accepted by an experienced surgeon against a critical anatomical structure the risk of local recurrence is likely to be relatively low.

Patients and methods

Four mutually exclusive clinical groups representing situations in which a positive surgical margin occurs after limb-sparing surgery for extremity soft tissue sarcoma were defined (Figure 3.1).

Figure 3.1

Clinical situations in which positive surgical margins occur and hypothesised risk of local recurrence

Group 1. *Low grade liposarcomas (Low Risk)*

The positive margin followed an intentionally marginal excision of a low-grade liposarcoma.

Group 2. *Planned positive margins against critical structures (Low Risk)*

In order to preserve a functional extremity, a positive margin was accepted against one or more critical structures (i.e. major nerve, vessel or bone).

Group 3. *Positive margins during re-excision after prior unplanned excision (High Risk)*

An intralesional or marginal unplanned excision was performed prior to referral. A positive margin followed re-excision.

Group 4. *Unplanned positive margins (High Risk)*

A positive margin was unexpectedly found during primary resection of the tumour, usually following a surgical error.

Clinical groups

Group 1. Low-grade liposarcomas

The first group included all patients with a diagnosis of low-grade, well-differentiated liposarcoma. When these tumours originate in the extremity they seldom recur locally after treatment and rarely metastasise [55;141]. Therefore they can be treated safely by planned marginal excision or "shelling out", unlike other tumours which require wider, negative margin excision. Low-grade liposarcomas are often large and may involve critical structures such as nerves, vessels or bones. In this situation positive margins may be accepted in order to preserve normal anatomy (Figure 3.2).

Group 2. Planned positive margins against critical structures

This group included patients who had positive surgical margins against one or more critically important anatomical structures (nerve, vessel or bone) that were planned preoperatively as part of a primary resection. The decision to accept a positive margin was made in advance by the multidisciplinary team as an acceptable compromise between tumour clearance and surgical morbidity and was confirmed after resection by the surgeon and pathologist (Figure 3.3).

Group 3. Positive margin during re-excision after prior unplanned excision

Patients in this group underwent unplanned excision of a sarcoma at another institution before referral, and a positive surgical margin occurred during re-excision at the Musculoskeletal Oncology Unit of the Mount Sinai Hospital.

Figure 3.2

Axial CT scan showing a homogenous fat lesion in the proximal thigh (indicated by arrow), which underwent excision with positive margins. Final pathology confirmed low-grade liposarcoma.

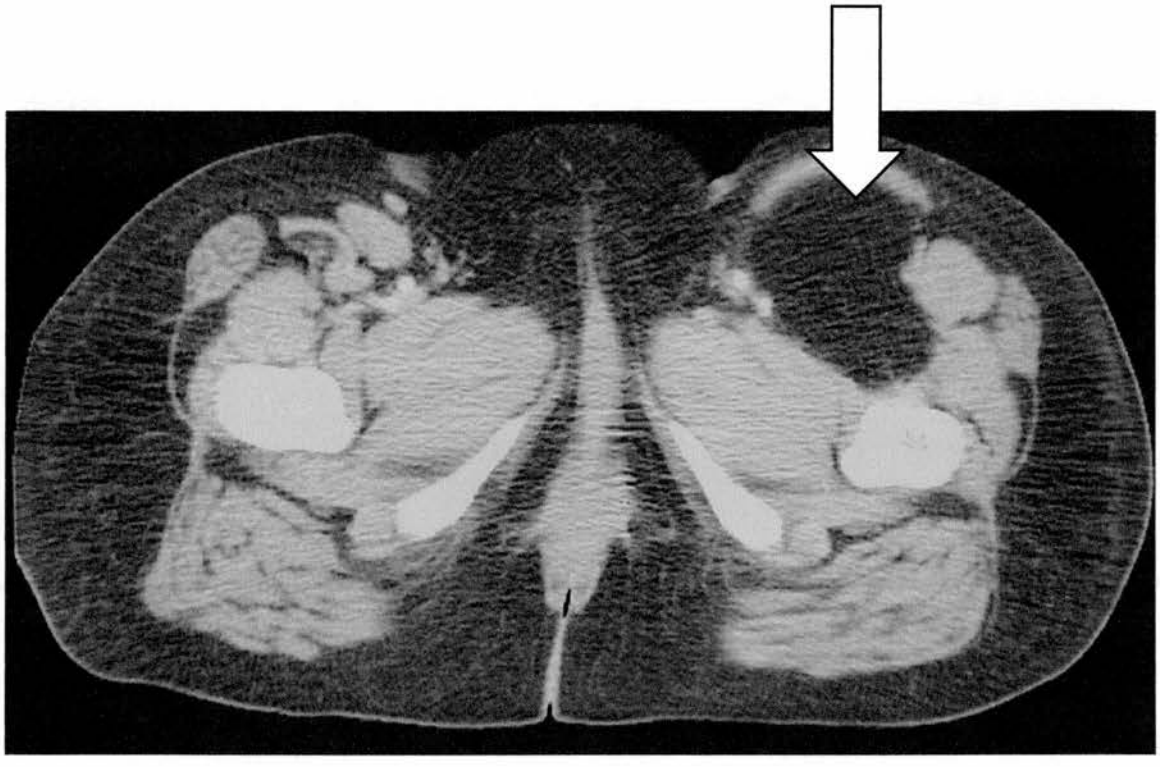
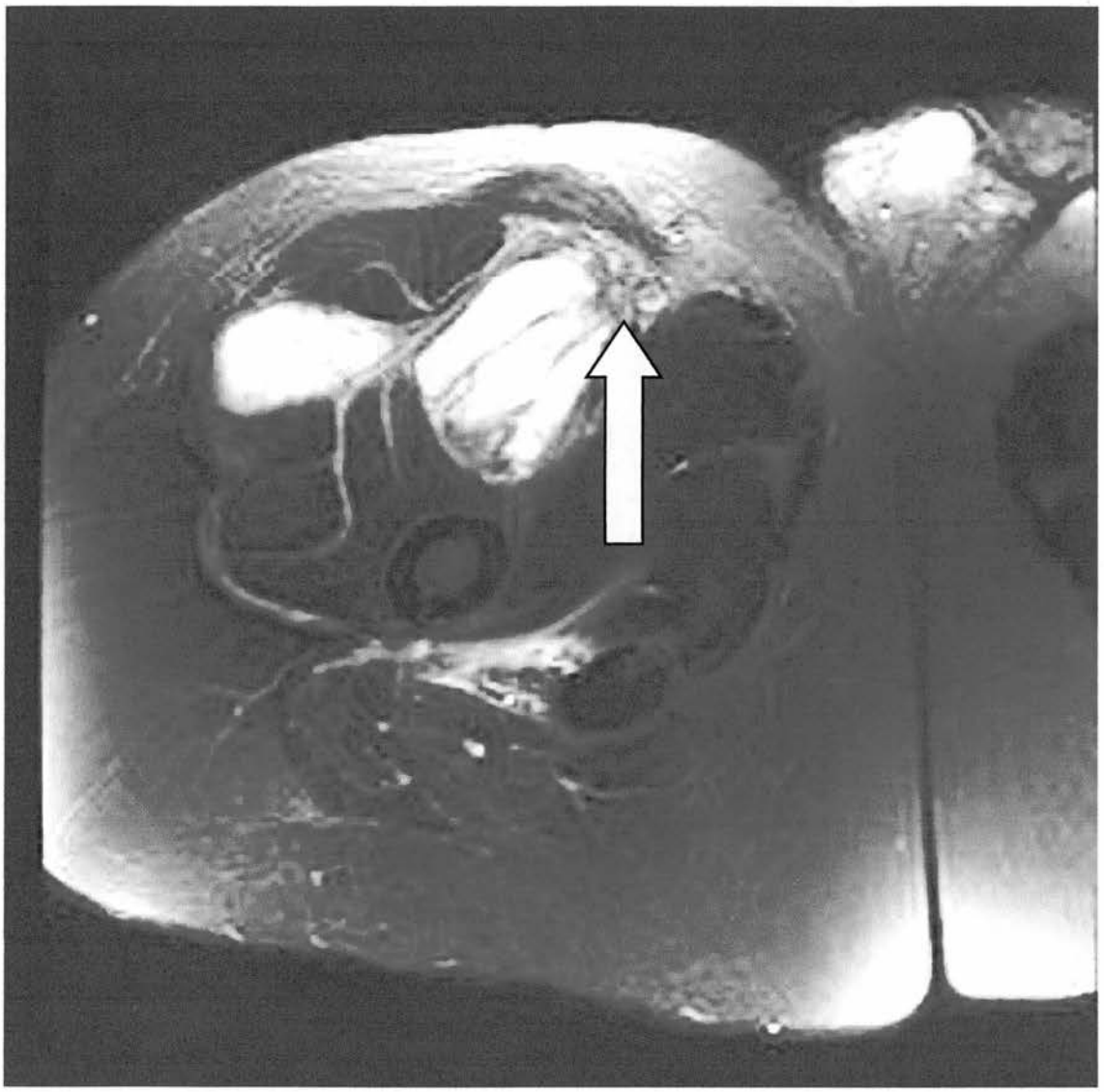


Figure 3.3

T2 weighted axial MRI scan demonstrating a myxoid liposarcoma in the proximal thigh, excised with a planned positive margin along the femoral artery (indicated by arrow).



Group 4. Unplanned positive margins

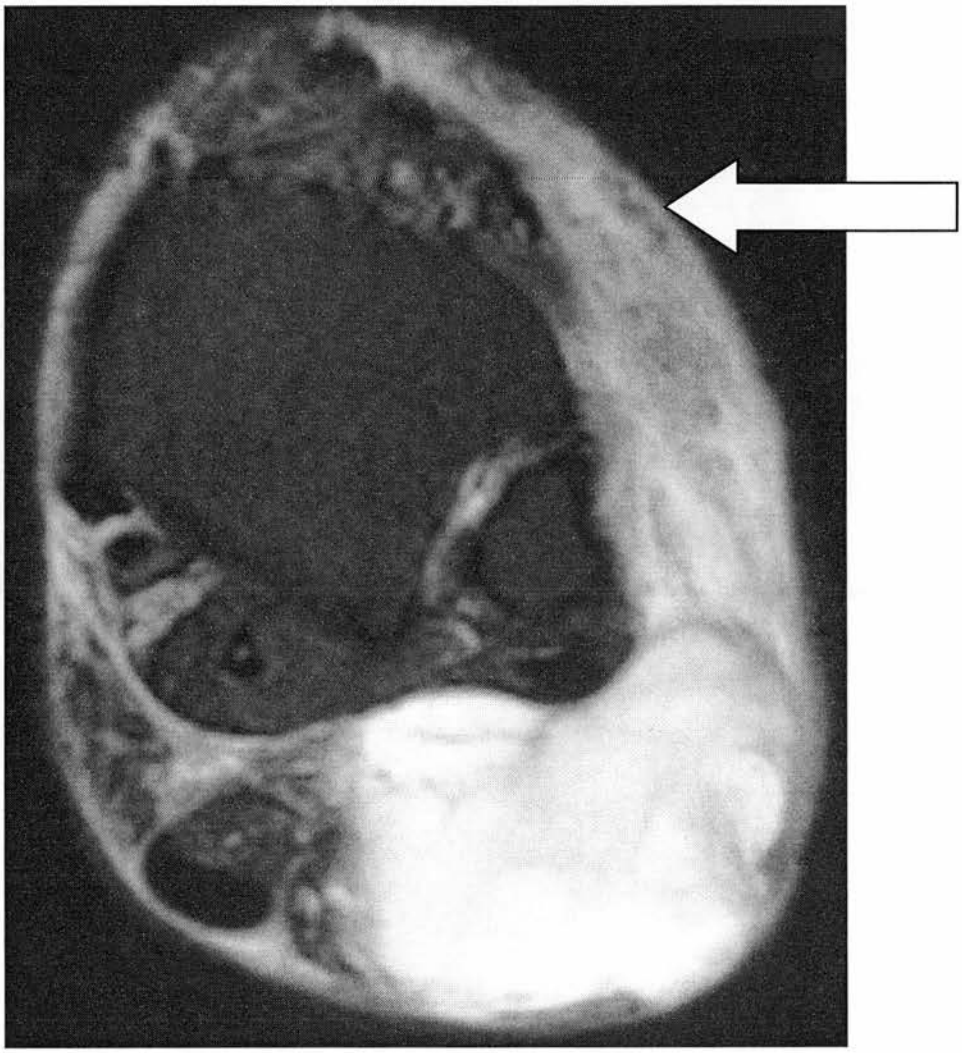
In this group, during primary resection at the Musculoskeletal Oncology Unit of the Mount Sinai Hospital, a positive margin occurred that had not been planned (Figure 3.4). This rare and unexpected event usually followed an error in assessing the extent of the primary lesion despite review of local site imaging (usually MRI).

The presence of a positive surgical margin was recognised at one of three times: (1) intraoperatively during dissection of the tumour, (2) in the pathology suite immediately after removal and gross and microscopic inspection of the resected tumour or (3) after final histological examination of the inked margins.

If the positive margin was recognised during or immediately after surgery, further tissue at the site of the positive margin was re-excised if this did not compromise critical structures. If the positive margin was recognised following definitive histological evaluation, a further wide excision was always considered. No patients had grossly evident tumour left in the wound at the completion of surgery.

Figure 3.4

T2 weighted axial MRI scan demonstrating a myxoid liposarcoma in the lateral ankle with considerable subcutaneous oedema. The anterior resection margin was positive in the subcutaneous tissues (indicated by arrow).



The hypothesis was that Groups 1 and 2 would be at low risk of local recurrence and that Groups 3 and 4 would be at higher risk. The database was used to identify patients meeting the following inclusion criteria: (1) a diagnosis of soft tissue sarcoma, other than dermatofibrosarcoma protuberans, (2) location in an extremity, (3) limb-sparing surgery with curative intent, (4) a positive surgical margin, (5) (neo)adjuvant radiotherapy. All patients underwent surgery between January 1986 and April 1997 so that there was potential for a minimum of three years of follow up.

Patients who received chemotherapy because of histological type or metastatic disease were excluded, as this might have an impact on local control. Patients who had not received "standard" adjuvant external beam radiotherapy (either 50 Gy preoperatively with a postoperative boost of 16 Gy if there was a positive margin, or 66 Gy postoperatively by a reducing field technique, in 2 Gy daily fractions) because of previous radiotherapy, comorbidity or contraindications were also excluded for this reason. Because this study was designed to assess local control rates, patients with metastases at presentation were included.

The following items were extracted from the database and verified against clinical records: age at surgery, gender, status at presentation, unplanned excision, extremity, histological type and grade, maximum diameter, depth, and whether the margin(s) were grossly or microscopically positive. Data relating to oncological outcomes were specifically excluded from this part of the analysis. Data about tumour biopsy and compartmental status were retrieved from clinical records.

That part of the clinical record that would have been available at the time of the multidisciplinary conference was reviewed. Information relating to outcome was, once more, excluded. These data were used to assign each patient to one of the four groups whilst being blinded to outcome. All low-grade liposarcomas were assigned to Group 1 and all patients who had an unplanned excision prior to referral were assigned to Group 3 regardless of further management. Following this initial classification, the operating surgeons (RSB and JW) reviewed the classification of each tumour to ensure consensus. Two patients were reclassified in this fashion. Both were thought to have had low grade liposarcomas and had been placed in Group 1. However, the resected tumours were higher grade and both patients were therefore placed into Group 2. Once all patients had been assigned to groups, the number, timing and further management of local recurrences were reviewed using database fields and clinical records.

Analysis

Given that low-grade liposarcomas (Group 1) differ in their biological behaviour and management from tumours of other histological types they were analysed separately. The remainder (Groups 2 to 4) were compared for differences in age, gender, local recurrence at presentation, histological grade, length of follow up, histological type, depth, compartmental status, upper or lower extremity location, and the local recurrence-free rate. To assess differences in systemic disease between these groups, disease-specific survival was used rather than metastasis-free survival because patients presenting with metastases had not been excluded from the analysis.

Results

There were a total of 566 patients entered in the database between January 1986 and April 1997. 112 had positive surgical margins of whom 25 patients were excluded; 12 who did not receive standard radiotherapy, seven who received chemotherapy, four with advanced metastatic disease who had palliative procedures, one with a positive margin following primary amputation and one who underwent exploration of an extensive sarcoma in the foot secondarily treated by amputation. Of the 12 patients who did not receive standard radiotherapy, seven had received external beam radiotherapy before referral and could not be irradiated further, and in the remaining five cases radiotherapy was not used because of patient preference, or wound healing complications. Chemotherapy was given for a diagnosis of Ewing's sarcoma/ primitive neuroectodermal tumour (PNET) or alveolar soft part sarcoma in four patients, and advanced metastatic disease in three.

Eighty-seven patients remained, 42 men and 45 women, with a mean age of 60 years (21 to 95). Clinical records relating to all patients were available. The mean follow up of 55 surviving patients was 5.4 years (3.0 to 9.5). Twenty-four patients died of metastatic disease at a mean of 1.8 years (0.3 to 6.6), and eight died of unrelated causes at a mean of 2.1 years (0.2 to 7.7 years).

24 patients with low-grade liposarcomas were placed in Group 1. None had grossly positive margins. There was one local recurrence (4.2%, 95% confidence interval 0 to 12.2) at four months, which was re-excised at the time of relapse. All patients were alive and free of disease at a mean follow-up of 5.1 years (3.2 to 9.3).

Of the remaining patients, 28 were allocated to Group 2 (planned positive margins against critical structures), nineteen to Group 3 (positive margins after previous unplanned excision) and sixteen to Group 4 (unplanned positive margins)(Table 3.1). When Groups 2, 3 and 4 were compared, Group 3 tumours were significantly smaller than Group 4 (mean diameter 4.8 cm vs 9.6cm p=0.04), and Group 4 tumours were smaller than Group 2 (mean diameter 9.6cm vs 14.7cm, p=0.02). There were more proximal limb tumours in Group 2 than Group 3 (22 of 28 (79%) vs 8 of 19 (42%), p=0.01) and Group 4 (7 of 16 (44%), p=0.02). However, groups 2, 3 and 4 did not differ significantly for age, gender, local recurrence at presentation, grade and length of follow-up. No difference in the distribution of histological types across the groups could be detected. In particular, the number of leiomyosarcoma, angiosarcoma, fibrosarcoma and malignant peripheral nerve sheath tumours, which may predispose to local failure [18;80;96] did not differ significantly between the three groups. There was no significant difference between the groups when deep and superficial, intracompartmental and extracompartmental, and upper and lower extremity tumours were compared.

Table 3.1

Summary of characteristics of patients and tumours at presentation

		1. Low grade liposarcomas	*2. Planned positive margin against a critical structure*	*3. Positive margin during re-excision after prior unplanned excision*	*4. Unplanned positive margin*
Number of cases		24	28	19	16
Mean age		54.8	62.5	66.7	57.5
Proportion male		54%	54%	37%	44%
Presentation with local recurrence		4	3	2	1
Presentation with metastases		-	1	-	1
Open biopsy		5	11	19	9
Grade of tumour	1	24	1	-	2
	2	-	8	9	6
	3	-	19	10	8
Mean max diameter (cm)		14.4	14.7	4.8	9.6
Histological type	MFH*	-	13	8	6
	Liposarcoma	24	8	6	3
	Other	-	7	5	7
Location	Upper extremity	6	6	5	6
	Lower extremity	18	22	14	10
	Proximal extremity	19	22	8	7
	Distal extremity	5	6	11	9
	Superficial	-	-	2	-
	Deep	24	28	17	16
	Intracompartmental	10	6	1	3
	Extracompartmental	14	22	18	13

* MFH= Malignant fibrous histiocytoma.

In Group 2 (planned positive margins against critical structures), one of 28 cases developed a local recurrence (3.6%, 95% confidence interval 0 to 10.4) at two months. This case was one of 25 with microscopically positive margins. There were no local recurrences in three patients with grossly positive margins. Twelve patients in the group were alive at a mean of 5.2 years (3.0 to 7.4), eleven died of metastatic disease at a mean of 1.6 years (0.3 to 2.8) and five died of other causes at a mean of 1.6 years (0.2 to 4.7) (Table 3.2).

In Group 3 (positive margin after prior unplanned excision), there were six local recurrences in 19 cases (31.6%, 95% confidence intervals 10.7 to 52.5). The mean time to local recurrence was 34.5 months (2.7 to 82.0)(Table 3.2). Eleven patients in this group had a residual tumour mass identified on clinical examination or imaging before re-excision. In five of these eleven cases, the positive margins were planned against critical structures adjacent to the residual tumour mass and one of these had a local recurrence. In comparison, an unplanned positive margin occurred during resection of the other six of eleven cases with a residual tumour mass, and three of these had local recurrences. In eight patients without a residual tumour mass there were two local recurrences (Figure 3.5).

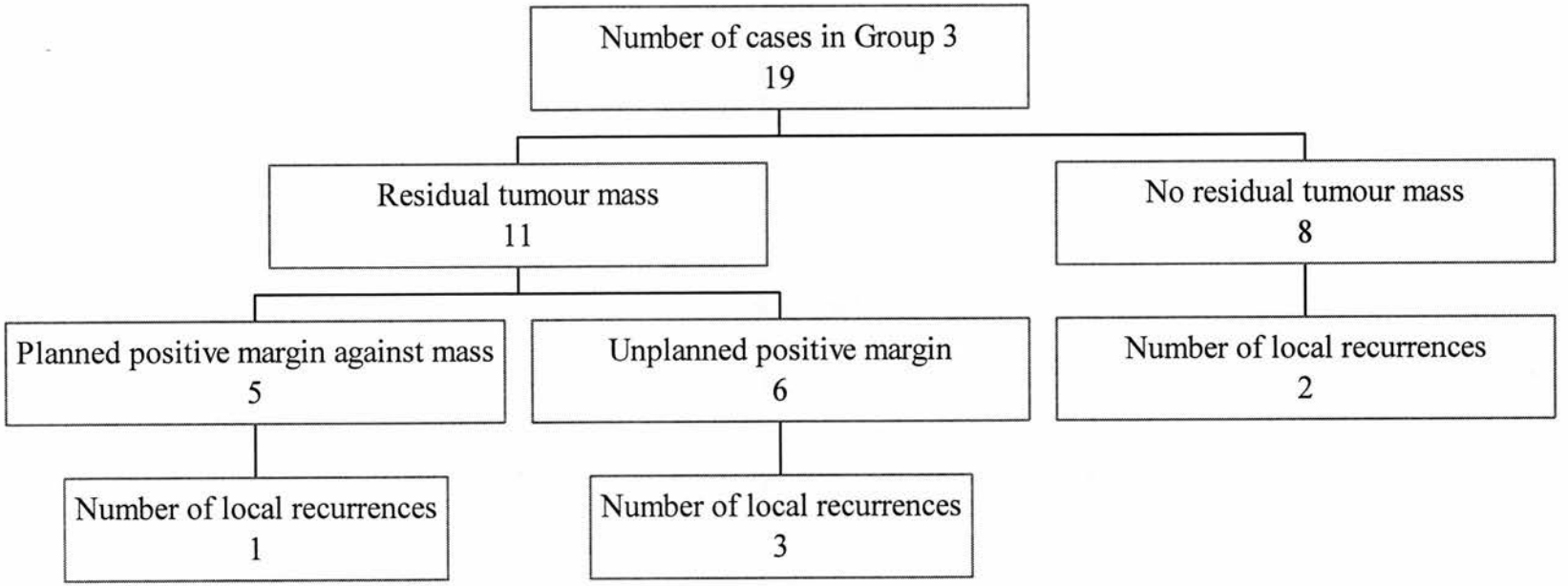
Table 3.2

Summary of surgical margins, local recurrence and systemic disease

		1. Low grade liposarcomas	*2. Planned positive margin against a critical structure*	*3. Positive margin during re-excision after prior unplanned excision*	*4. Unplanned positive margin*
Number of cases		24	28	19	16
Type of positive margin	Microscopically positive	24	25	17	12
	Grossly positive	0	3	2	4
Number of local recurrences		1 (4.2%)	1 (3.6%)	6 (31.6%)	6 (37.5%)
Mean time to local recurrence (months)		4	2	35	25
Mean follow up of surviving patients (years)		5.1	5.2	6.3	5.6
Final status	Alive, without disease	24	10	9	8
	Alive with disease	-	2	1	1
	Died of disease	-	11	6	7
	Died of other causes	-	5	3	-

Figure 3.5

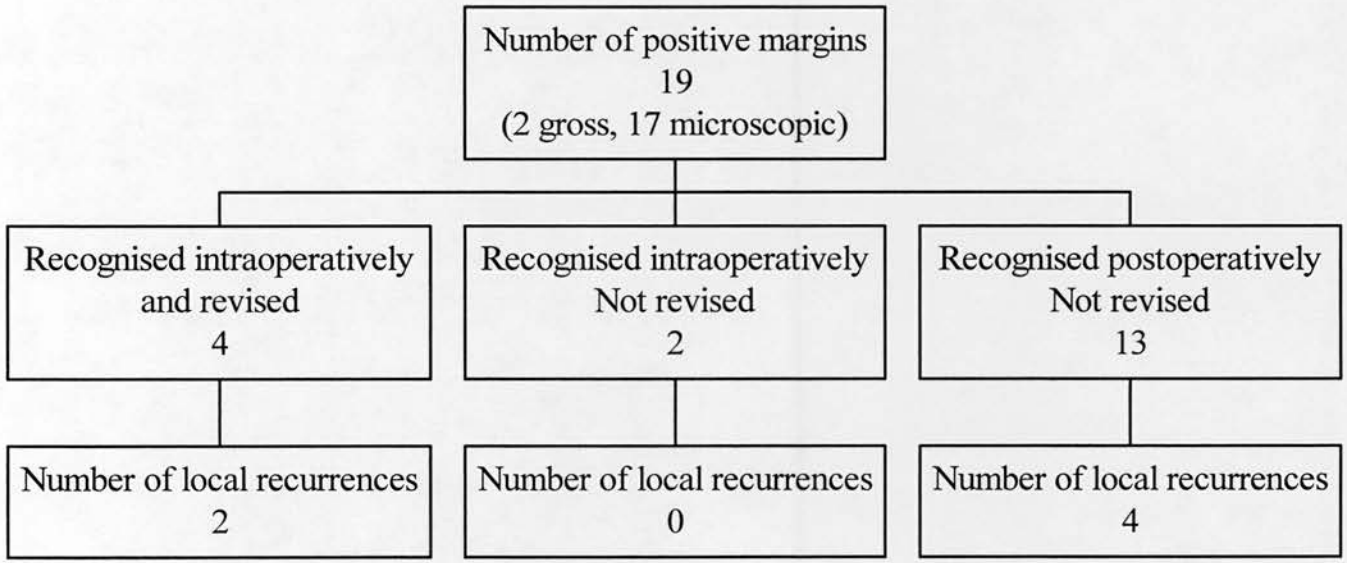
Group 3. Positive surgical margin following unplanned excision. Subgroup analysis. Effect of residual tumour mass



Of all nineteen patients in Group 3, two had grossly positive margins and both had local recurrences, compared with four local recurrences in seventeen patients with microscopically positive margins. In four cases, the positive margin was recognised intraoperatively, and the margin was revised during the same procedure. Two of these four patients had a local recurrence. In two cases, the positive margin was recognised intraoperatively but the margin could not be revised with acceptable morbidity. Neither of these patients had a local recurrence. In thirteen cases, the positive margin was recognised after definitive histological examination of the specimen. None of these margins were revised surgically. Four of these thirteen patients had a local recurrence (Figure 3.6). Of all nineteen patients, ten were alive at a mean of 6.3 years (3.5 to 9.4), six died of metastatic disease at a mean of 1.7 years (0.7 to 3.2) and three died of other causes at a mean of 3.1 years (0.7 to 7.7) (Table 3.2).

Figure 3.6

Group 3. Subgroup analysis. Positive surgical margin following unplanned excision. Time of recognition of positive surgical margin



In Group 4 (unplanned positive margins), there were six local recurrences in sixteen cases (37.5%, 95% confidence interval 13.8 to 61.2). The mean time to local recurrence was 24.9 months (5.9 to 68.1)(Table 3.2). One of four patients with grossly positive margins and five of twelve patients with microscopically positive margins had a local recurrence. In nine cases, the positive margin was recognised intraoperatively, and the margin was revised during the same procedure. Four of these nine patients had a local recurrence. In three cases, the positive margin was recognised intraoperatively but the margin could not be revised with acceptable morbidity. None of these three patients had a local recurrence. In four cases, the positive margin was recognised after definitive histological examination of the specimen. Three of these had no further surgery, and two of these three had a local recurrence. In the fourth case, a second wide excision was performed to revise the margin and there has not been a local recurrence (Figure 3.7). Of sixteen cases in Group 4, nine were alive at a mean of 5.6 years (3.0 to 8.9) and seven died of metastatic disease at a mean of 2.0 years (0.3 to 6.6).

The crude local recurrence rate in Group 2 was significantly lower than in Group 3 ($p=0.03$) and Group 4 ($p=0.01$). The crude local recurrence rates in Group 3 and Group 4 were not significantly different. The local recurrence-free rate was significantly different between groups 2 and 3 ($p=0.01$) and groups 2 and 4 ($p=0.02$), but not between groups 3 and 4 ($p=0.64$) (Figure 3.8). Disease-specific survival in groups 2, 3 and 4 did not differ significantly ($p=0.74$) (Figure 3.9).

Figure 3.7

Group 4. Unplanned positive margin. Subgroup analysis. Time of recognition of positive surgical margin

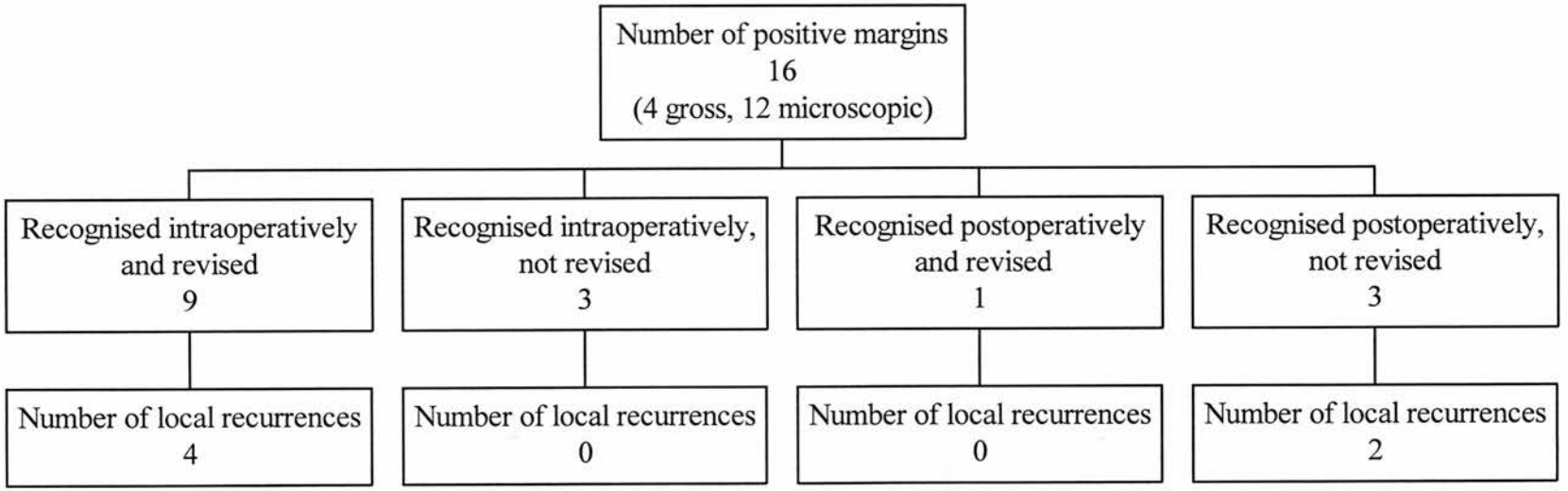
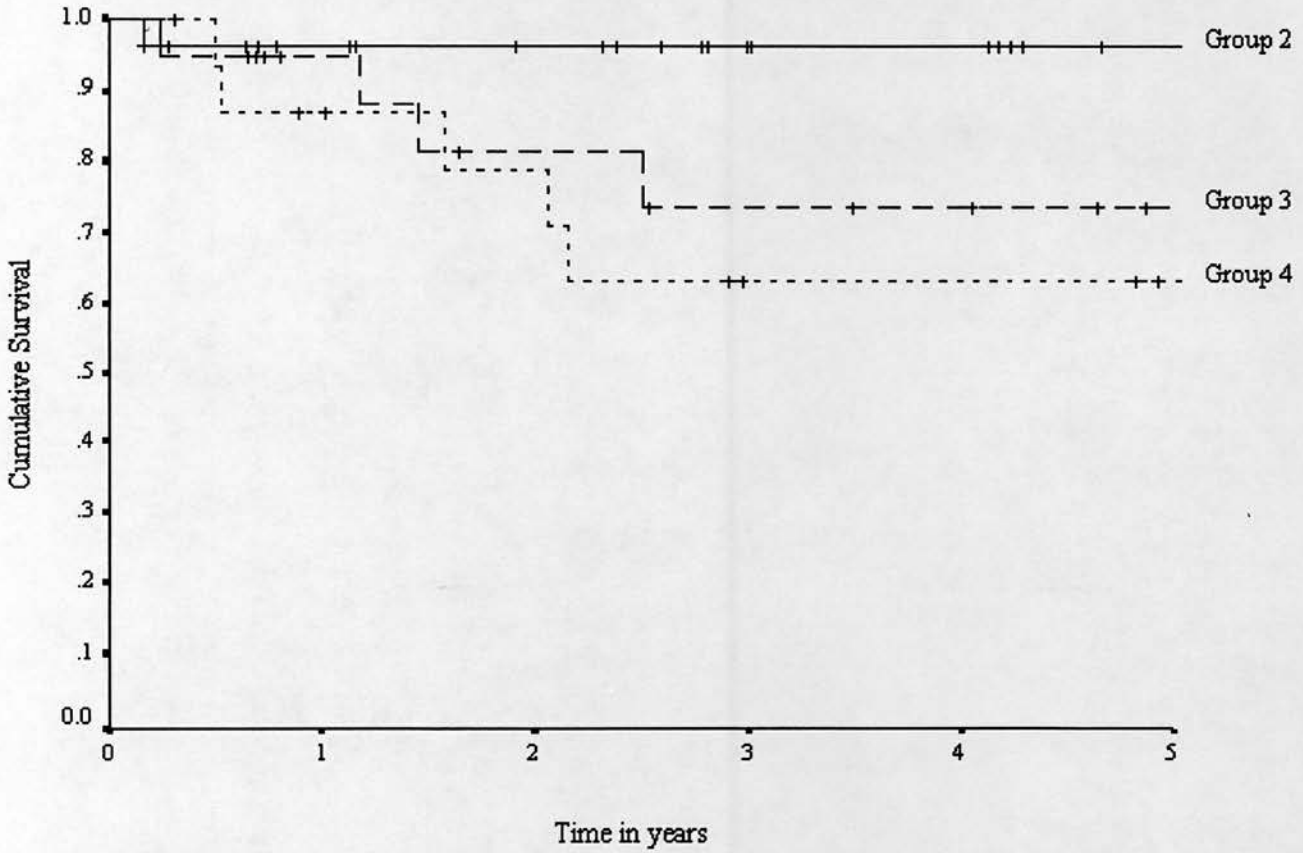
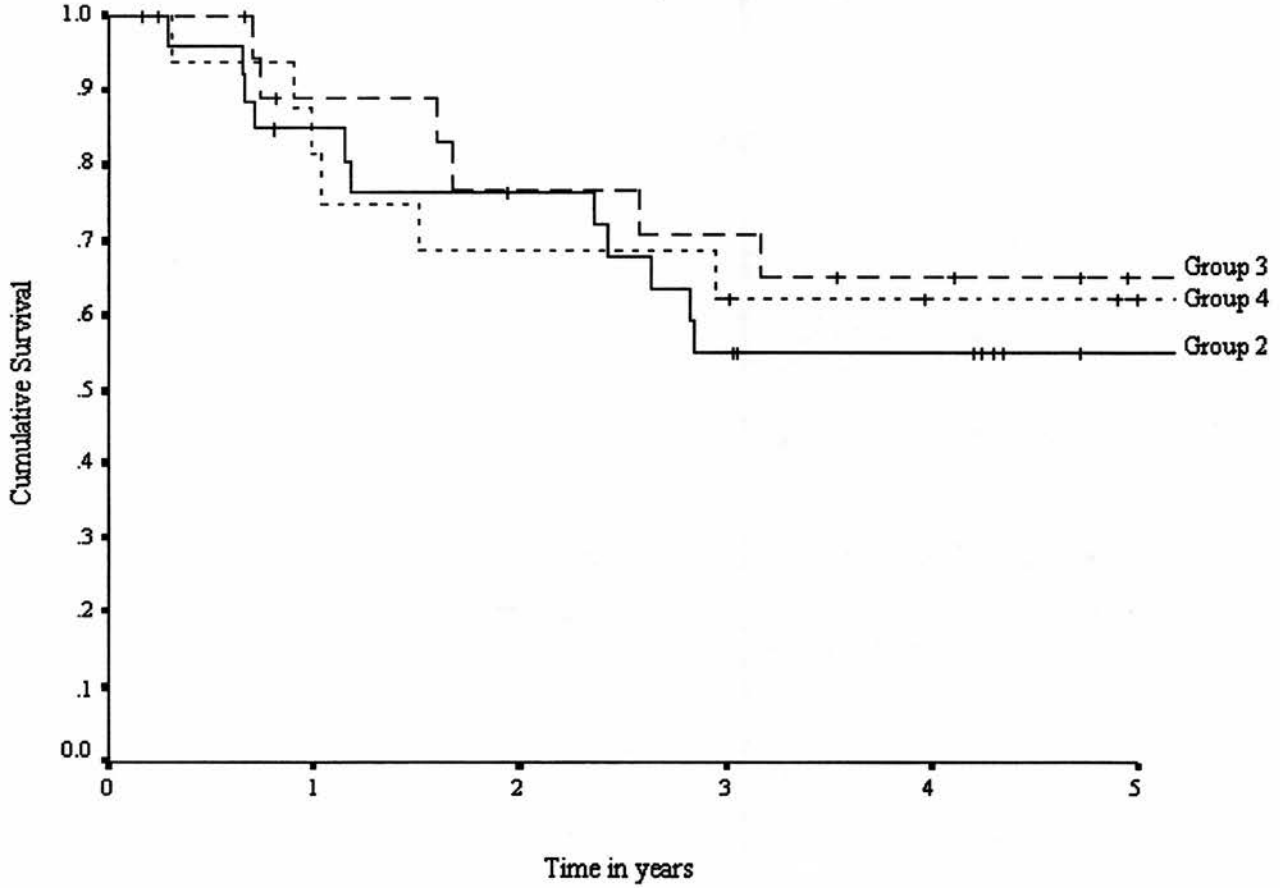


Figure 3.8 Kaplan-Meier estimate for local recurrence-free rate



Tick marks represent censored cases.

Figure 3.9 Kaplan-Meier estimate for disease-specific survival



Tick marks represent censored cases.

Discussion

This analysis has shown that the significance of a positive surgical margin after resection of extremity soft tissue sarcoma depends on the clinical situation, and that patients can be classified into groups that reflect the risk of local recurrence. Low-grade liposarcomas are recognised as biologically different, requiring a different treatment approach from other soft tissue sarcomas and have a low risk of local recurrence despite marginal excision. Planned positive margins against critical structures during primary resection, in association with adjuvant radiotherapy, are associated with a low risk of local recurrence. Positive margins following re-excision of a sarcoma treated by unplanned excision before referral, as well as unplanned positive margins during primary resection are associated with a higher risk of local tumour relapse.

The overall positive margin rate (112 of 566 patients, 19.8%) is within published rates which vary from 1% [47] to 26% [123]. The higher rate of positive margins after resection of low-grade liposarcomas in this study (27 of 49 patients, 55%) reflects a philosophy of deliberate marginal excision and confirms that this approach, with adjuvant radiotherapy, is associated with a low rate of local recurrence at this length of follow-up. The only recurrence occurred after resection of an extensive tumour in the axilla. There were no local recurrences in 22 low-grade liposarcomas treated by excision with a negative surgical margin. The positive margin rate for other histological types (85 of 518 cases, 16%) is within the accepted range.

The fact that a planned positive margin against a critical anatomical structure is associated with a low risk of local recurrence shows that this is a safe approach for many tumours. However, the experience of the multidisciplinary team is important in making the decision to approach a tumour in this fashion and may contribute to better outcomes in specialised centres.

All patients who had undergone an unplanned excision were offered re-excision unless the margins could be reliably assessed as adequate [88]. If there was a residual mass after unplanned excision it acted as a visual and palpable guide to re-excision and if the mass was adjacent to a critical anatomical structure, a positive margin was planned. There was one local recurrence in five such cases in this study. If there is a residual mass and the positive margin was not planned, the local recurrence rate may be even higher (three of six cases). If there was no residual mass, the extent of contamination is difficult to determine and re-excision was planned based on an estimate of the area at risk and the morbidity of the excision. A positive margin not only means there is residual tumour, which is itself a risk factor for local recurrence, but that the area involved with tumour has been underestimated [23].

Exposure of tumour during primary resection because of an error in surgical judgement is associated with a high risk of local recurrence in this and other series [39]. Of sixteen cases in which an unplanned positive margin occurred, four had grossly positive margins, one of whom went on to local recurrence. The remaining twelve had microscopically positive margins and five of these went on to local recurrence, suggesting that microscopically positive margins are also associated with a high risk of local failure in this situation.

The distinction between microscopically positive and grossly positive margins is one of degree. In this study, grossly positive margins have been defined as recognisable with the naked eye, which is not the same as leaving gross residual disease in the wound. However, the potential for wound contamination is greater when margins are grossly rather than microscopically positive. In Group 3, both patients with an identifiable mass and grossly positive margins had a local recurrence, compared with 4 of 17 patients with microscopically positive margins. The distinction between grossly and microscopically positive margins was less clear in Group 4, where 1 of 4 patients with grossly positive margins had a local recurrence compared with 5 of 12 with microscopically positive margins, not significantly different.

It is recognised that the assessment of a surgical margin as "positive" or "negative" depends upon careful examination of the specimen. The reliability and validity of this process in the treatment of extremity soft tissue sarcomas has not been formally assessed. Sampling errors, particularly with very large tumours, may lead to an error in assessment of the true margin. However, the approach described here, in which the surgeon can orientate the specimen and indicate areas of concern to the pathologist whilst the patient is still on the table, leads to a consensus, which is likely to be a more accurate assessment than when the pathologist works in isolation. It is interesting that despite this assessment at the time of surgery, a significant number of positive margins (13 of 19 patients in Group 3 and 4 of 16 in Group 4) were not recognised until after definitive examination of the specimen.

This study was not designed to assess the effect of revision of a positive margin. However, it is of interest that amongst patients who could not have revision of the

positive margin because of local anatomical constraints there were no local recurrences. It may be that a positive margin against a structure such as muscle that is readily revised is associated with more residual disease than a positive margin against a critical structure such as bone, nerve or vessel, which is not easily resected and which may be more resistant to tumour invasion. When margins were revised intraoperatively, the data in Figures 3.6 and 3.7 appear to show that there is still a significant risk of local recurrence (two local recurrences in four revisions in Group 3, four local recurrences in nine revisions in Group 4).

One of the most significant differences between groups 2, 3, and 4 was tumour size. The smallest tumours were those treated by initial unplanned excision, which has also been the experience of other authors [47]. However, given that the largest tumours in this study were in the group with the lowest local recurrence rate (Group 2), size is unlikely to have adversely influenced the results.

Patients who received chemotherapy were excluded because it may have an effect on local recurrence [8;125]. As the number of patients who received chemotherapy is small, this is unlikely to have influenced the results of this study. The decision to exclude patients who did not receive "standard" radiotherapy was made on the basis that radiotherapy is an effective adjuvant and without it the surgeon may attempt to achieve wider margins [1;81;121]. This excluded patients presenting with a local recurrence after prior treatment that included radiotherapy. Although presentation with locally recurrent disease is associated with lower local control rates, after excluding the group of patients who had "non-standard" radiotherapy, the number of patients presenting with a local recurrence was similar in groups 2, 3 and 4.

No difference in disease-specific survival between the groups was demonstrated in this series at a mean follow-up of 5.3 years, confirming that the association between local recurrence and metastatic disease is weak. However, it is possible that a difference may become apparent with longer follow-up.

To summarise, this study has shown that the clinical significance of a positive surgical margin depends upon the clinical situation in which it occurs, and it is possible to classify positive surgical margins in this fashion. This is a novel finding. Differences in positive margins of this kind have not been demonstrated previously. This is highly relevant in the clinical situation in which the approach to an extremity soft tissue sarcoma is being planned. In particular it shows that a planned positive margin to preserve a critical anatomical structure is safe and associated with a low risk of local recurrence, and that a positive surgical margin after reexcision of a soft tissue sarcoma previously treated by unplanned excision is associated with a high risk of local recurrence. This may influence the choice of local treatments and allow a more aggressive approach to the management of positive surgical margins in high-risk groups.

4. COMPARISON OF THE UPPER AND LOWER EXTREMITIES

Introduction

The purpose of this study was to examine differences in presentation, treatment and outcomes between upper and lower extremity soft tissue sarcomas.

Patients and Methods

The database was used to identify and retrieve information about patients who had an extremity soft tissue sarcoma treated by limb-sparing surgery between January 1986 and April 1997 and therefore had the potential for a minimum of 3 years follow-up. Patients with metastatic disease at presentation or with the histological types

dermatofibrosarcoma protuberans, Ewing's sarcoma/ primitive neuroectodermal tumour or rhabdomyosarcoma were excluded.

The following fields were extracted from the database: age at surgery, gender, unplanned excision before referral, status at presentation, maximum tumour diameter, histological type and grade, surgical margin status, radiotherapy given or chemotherapy given. Fields relating to local recurrence and metastasis were used to derive data for whether or not local relapse or metastasis had occurred and the time to that event. Length of follow up was derived from the database and checked against clinical records.

The following data relating to anatomical location were retrieved: extremity, anatomical site (nearest joint) and depth. Location within the extremity was recorded in the database as proximity to the closest major joint (shoulder, elbow, wrist/hand, hip, knee and foot/ankle).

Data were first used to define the characteristics of the whole group and the anatomical distribution of tumours. Next, differences in presenting features, tumour characteristics and treatment between the extremities were determined. The local recurrence-free rate in the extremities was compared using the methods of Kaplan and Meier and the log-rank statistic. The Cox proportional hazards model was then used to investigate first whether maximum tumour diameter and then whether surgical margin status, extremity and unplanned excision before referral were predictive of time to local recurrence. Thereafter exploratory analyses examined the

influence of unplanned excision before referral, surgical margin status and radiotherapy on local recurrence.

To assess the rate of systemic disease, metastasis-free rate was used in preference to disease-specific survival in order to maximise the number of events in the survival analysis, and was compared using the methods of Kaplan and Meier and the log-rank statistic. The Cox proportional hazards model was used to investigate whether histological grade, maximum tumour diameter, depth and extremity were predictive of time to metastasis.

Results

566 patients were entered into the database between January 1986 and April 1997. There were six primary amputations in 168 upper extremity tumours (3.6%) and 22 primary amputations in 398 lower extremity tumours (5.5%). A further 58 patients were excluded; 34 presenting with metastatic disease, 12 with a diagnosis of dermatofibrosarcoma protuberans, seven with primitive neuroectodermal tumour and five with rhabdomyosarcoma. 480 patients remained in the study.

There were 261 men (54.4%) and 219 women of median age 56 years (15 to 96). Malignant fibrous histiocytoma (MFH) (163 cases, 34.0%) and liposarcoma (107 cases, 22.3%) were the most common histological types. Tumours were grade one in 83 (17.3%) cases, grade two in 172 (35.8%) and grade three in 225 (46.9%).

Forty-eight patients (10.0%) had a local recurrence at a median of 1.4 years (0.1 to 9.2). No patients died of local recurrence. 131 patients (27.3%) developed metastases at a median of 1.0 years (0.1 to 12.8), 86 of whom died of metastatic disease at a median of 1.5 years (0.1 to 6.8). Nineteen patients died from causes other than metastatic disease at a median of 1.0 years (0.0 to 7.7). Three of these nineteen patients died in the immediate postoperative period following a pulmonary embolus. Median follow-up for the 375 surviving patients was 4.8 years (0.1 to 12.9).

Anatomical distribution

There were 139 (29.0%) tumours in the upper extremity and 341 (71.0%) in the lower (Table 4.1). Seventy-four (15.4%) were around the shoulder, 41 (8.5%) the elbow, 24 (5.0%) the hand or wrist, 154 (32.1%) the hip, 148 (30.8%) the knee and 39 (8.1%) the ankle or foot (Table 4.2). Three hundred and seventy seven (78.5%) were deep to or involving the investing fascia of the extremity.

Table 4.1

Summary of presenting features and treatment by extremity

		Upper extremity	*Lower extremity*
Number of cases		139	341
Median age at surgery (range)		54 (17 to 86)	56 (15 to 96)
Proportion of males		84 (60.4%)	177 (51.9%)
Mean maximum tumour diameter (cm)		6.0 (1 to 26)	9.3 (1 to 40)
Deep to or involving investing fascia		97 (69.8%)	280 (82.1%)
Histological grade	1	30 (21.6%)	53 (15.5%)
	2	44 (31.7%)	128 (37.5%)
	3	65 (46.8%)	160 (46.9%)
Unplanned excision before referral		89 (64.0%)	160 (46.9%)
Presentation with a local recurrence		18 (12.9%)	38 (11.1%)
Positive surgical margins		28 (20.1%)	71 (20.8%)
Adjuvant radiotherapy		98 (70.5%)	289 (84.8%)

Table 4.2

Summary of local recurrence and systemic disease by extremity

	Upper extremity	*Lower extremity*
Median follow-up of survivors in years	4.9 (0.1 to 11.1)	4.7 (0.2 to 12.9)
Number of patients with local recurrence	23	25
Median time to local recurrence (years)	1.3 (0.2 to 9.2)	1.6 (0.1 to 6.6)
Local recurrence-free rate at 5 years	82%	93%
Number of patients developing metastases	26	105
Median time to metastasis (years)	1.0 (0.1 to 6.7)	1.0 (0.1 to 12.8)
Metastasis-free rate at 5 years	82%	69%

Differences between the extremities

Upper extremity tumours were more often treated by unplanned excision before referral than lower extremity tumours (89 (64.0%) vs. 160 (46.9%), p<0.001). The proportion of patients presenting with a local recurrence was similar in each extremity (18 (12.9%) vs. 38 (11.1%), p=0.576). Upper extremity tumours were significantly smaller than lower extremity tumours (6.0 cm vs. 9.3cm, p<0.001) and were less often deep to or involving the investing fascia (97 (69.8%) vs. 280 (82.1%), p=0.003) (Table 4.1). Mean tumour diameter decreased from proximal to distal in both extremities (Table 4.3). There was a relative excess of synovial sarcoma, epithelioid sarcoma and fibrosarcoma in upper extremity sites and of liposarcoma and myxoid liposarcoma in the lower extremity (Table 4.4). Histological grade did not differ significantly between the upper and lower extremities (p=0.219) (Table 4.1).

Table 4.3

Summary of results by anatomical location within each extremity

Location	*Number of cases*	*Mean tumour diameter (cm)*	*Unplanned excision before referral*	*Positive surgical margins (percentage rate)*	*Adjuvant radiotherapy given*	*Local recurrences*	*Number developing metastases*
Shoulder	74	6.5	47	7 (9.5%)	45	13 (17.6%)	19
Elbow	41	6.3	26	16 (39.0%)	34	5 (12.2%)	6
Wrist/hand	24	3.9	16	5 (20.8%)	19	5 (20.8%)	1
Hip	154	10.6	65	28 (18.2%)	125	11 (7.1%)	45
Knee	148	9.0	73	35 (23.6%)	128	10 (6.8%)	49
Ankle/foot	39	5.3	22	8 (20.5%)	36	4 (10.3%)	11
Whole group	480	8.3	249	99 (20.6%)	387	48 (10.0%)	131

Table 4.4 Distribution of histological types by extremity

Histological type	*Upper extremity*			*Lower extremity*		
	Number	Percentage within extremity	Local recurrences	Number	Percentage within extremity	Local recurrences
Malignant Fibrous Histiocytoma	56	40.3%	7	107	31.4%	12
Liposarcoma, otherwise undesignated	21	15.1%	3	86	25.2%	6
Synovial sarcoma	14	10.1%	0	18	5.3%	1
Malignant peripheral nerve sheath tumour	10	7.2%	3	22	6.5%	2
Leiomyosarcoma	10	7.2%	2	27	7.9%	3
Fibrosarcoma	9	6.5%	3	11	3.2%	0
Epithelioid sarcoma	4	2.9%	2	3	0.9%	0
Angiosarcoma	2	1.4%	1	3	0.9%	0
Myxoid liposarcoma	1	0.7%	0	29	8.5%	1
Other	12	8.6%	2	35	10.3%	0
Total	139	100%	23	341	100%	25

The proportion of patients with a positive surgical margin did not differ significantly between the upper and lower extremities (28 (20.1%) vs. 71 (20.8%), p=0.868)(Table 4.1). However, within the upper extremity positive surgical margins were more frequent around the elbow (16 of 41 (39.0%)), than the wrist and hand (5 of 24 (20.8%)) or shoulder (7 of 74 (9.5%), p<0.001)(Table 4.3).

Overall, radiotherapy was given less often for upper than lower extremity tumours (98 (70.5%) vs. 289 (84.8%) p<0.001)(Table 4.1). This was because tumours around the shoulder were not treated with adjuvant radiotherapy (45 of 74 (60.8%)) as often as tumours around the elbow (34 of 41 (82.9%)) or wrist (19 of 24 (79.2%), p=0.048) (Table 4.3). The proportion of patients given adjuvant chemotherapy did not differ significantly between the upper and lower extremities (2 of 139 (1.4%) vs. 8 of 341 (2.3%), p=0.528)

Median follow-up for survivors was 4.9 (0.1 to 11.1) years in the upper and 4.7 (0.2 to 12.9) years in the lower extremity.

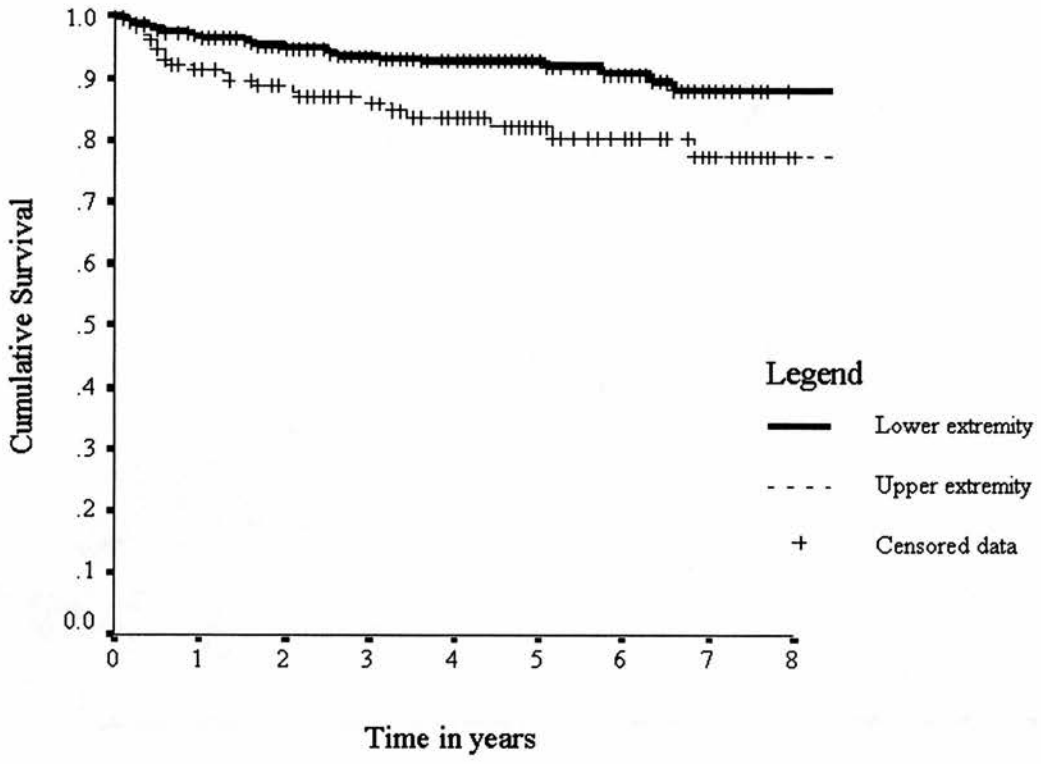
Local recurrence

There were 23 local recurrences in the upper extremity and 25 in the lower. The median time to local recurrence was 1.3 (0.2 to 9.2) years in the upper extremity and 1.6 (0.1 to 6.6) years in the lower. The local recurrence-free rate at five years was 82% in the upper and 93% in the lower extremity (log-rank test, p=0.002) (Figure 4.1).

The difference in the local recurrence-free rate between the extremities was investigated with a Cox proportional hazards regression model. First, recognising the difference in tumour size between the extremities, regression was performed using tumour diameter as a single continuous variable. This did not reach significance (p=0.074), confirming that tumour size is not a significant determinant of local recurrence. A second model was constructed using, in this order, categorical variables for surgical margin status (negative or positive), extremity (lower or upper), unplanned excision before referral (no or yes) and an interaction variable of extremity and unplanned excision before referral. Plots for each variable confirmed proportionality of the hazard ratio over time. Surgical margin status reached significance in the model (p<0.001) with a hazard ratio of 3.16 (95% confidence interval 1.76 to 5.69) associated with a positive margin. Extremity, unplanned excision before referral and the interaction variable of extremity and unplanned excision before referral did not reach significance (p=0.127, 0.056 and 0.868)(Table 4.5).

Figure 4.1

Kaplan-Meier estimate for the local recurrence-free rate



Tick marks represent censored cases.

Table 4.5

Results of Cox regression analysis for local recurrence

Variable	*Selection into Cox Model (score P)*	*Relative risk*	*95% Confidence intervals for relative risk*
Positive surgical margin (No/Yes)	<0.001	3.164	1.758-5.695
Extremity (Lower/Upper)	0.127	2.347	0.786-7.010
Unplanned excision before referral (No/Yes)	0.056	2.229	0.980-5.070
Interaction variable of extremity and unplanned excision	0.868	0.896	0.248-3.243

An exploratory analysis of the relationship between an unplanned excision before referral, surgical margin status and local recurrence compared crude local recurrence rates in four groups (Table 4.6). Amongst patients who had primary excision of a tumour with a positive surgical margin, those with upper extremity tumours were more likely to have local recurrence than those with lower extremity tumours (3/13 (23.1%) vs. 2/46 (4.3%), p=0.032).

A further exploratory analysis examined the effect of radiotherapy on local recurrence by calculating how many patients with local recurrences in these four groups had received radiotherapy (Table 4.6). Six of 11 patients with upper extremity tumours treated by unplanned excision before referral and re-excision with negative margins who had a local recurrence had not received radiotherapy. In three cases, all located around the shoulder, this was because radiotherapy had been given on a previous occasion, precluding further radiotherapy. In two of the remaining patients radiotherapy was not given because no tumour was identified in the re-excision specimen. The sixth patient had a low-grade fibrosarcoma around the shoulder, thought to have been completely excised.

Table 4.6

Exploratory analysis of the relationship between unplanned excision before referral, surgical margin status and local recurrence

Group	*Upper extremity*			*Lower extremity*			*P value for difference in local recurrence rates between extremities*
	Number of cases	Number of local recurrences	Local recurrences not given radiotherapy	Number of cases	Number of local recurrences	Local recurrences not given radiotherapy	
Primary excision with negative surgical margins	37	2 (5.4%)	1	135	7 (5.2%)	0	0.957
Primary excision with positive surgical margins	13	3 (23.1%)	1	46	2 (4.3%)	0	0.032
Unplanned excision before referral, re-excision with negative margins	74	11 (14.9%)	6	135	9 (6.7%)	2	0.054
Unplanned excision before referral, re-excision with positive margins	15	7 (46.7%)	0	25	7 (28.0%)	1	0.231

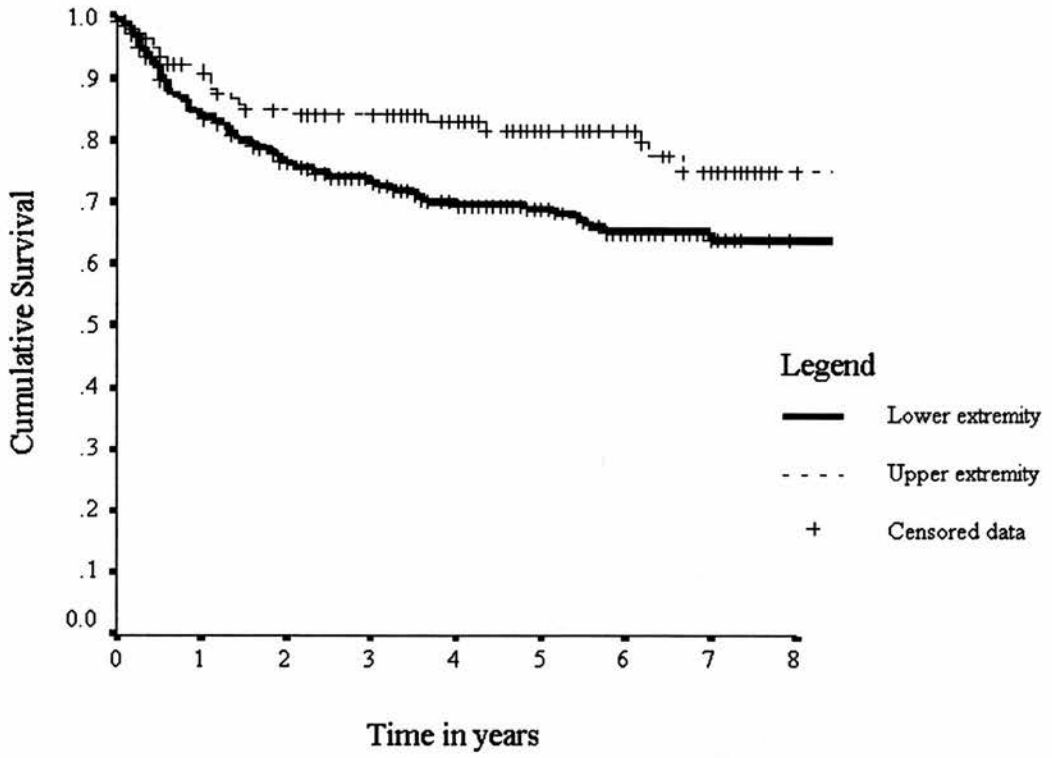
Metastasis-free survival

Twenty-six of 139 patients with upper extremity tumours developed a metastasis compared with 105 of 341 with a lower extremity tumour. The median time to metastasis was 1.0 (0.1 to 6.7) years after surgery in the upper and 1.0 (0.1 to 12.8) years after surgery in the lower extremity. The metastasis-free rate at five years was 82% in the upper extremity and 69% in the lower (log-rank test, p=0.013)(Figure 4.2). There was a trend towards fewer metastases in the distal extremities (Table 4.2).

To investigate the difference in metastasis-free rates between the extremities a Cox proportional hazards model was constructed using, in this order, histological grade (low (grade 1) or high (grade 2 or 3)), maximum tumour diameter in centimeters, depth (superficial or deep), and extremity (upper or lower). The hazard ratio for each variable was plotted to confirm proportionality over time. There was an increased risk of metastasis with high histological grade (hazard ratio 17.28 (95% confidence interval 4.26 to 70.10), p<0.001), maximum tumour diameter (increased hazard ratio of 1.05 (95% confidence interval 1.02 to 1.08) per centimeter increase, p<0.001) and deep location (hazard ratio 1.93 (95% confidence interval 1.07 to 3.48), p=0.028). The variable for extremity did not reach significance (p=0.211)(Table 4.7).

Figure 4.2

Kaplan-Meier estimate for the metastasis-free rate



Tick marks represent censored cases.

Table 4.7

Results of Cox regression analysis for metastasis-free rate

Variable	*Selection into Cox Model (score P)*	*Relative risk*	*95% Confidence intervals for relative risk*
Histological grade (low/high)	<0.001	17.278	4.259-70.096
Tumour diameter	0.001	1.050	1.020-1.081
Depth (superficial/deep)	0.028	1.934	1.075-3.480
Extremity (upper/lower)	0.211	1.344	0.846-2.135

Discussion

This study has compared the presentation, treatment, local recurrence-free and metastasis-free rates of upper and lower extremity soft tissue sarcomas in this group of patients. The study shows that upper extremity tumours are smaller, more often treated by unplanned excision before referral, are of different histological types, and less often meet the criteria for adjuvant radiotherapy. The study also shows that after treatment of extremity soft tissue sarcoma, the local recurrence-free rate and metastasis-free rate vary with anatomical location. In particular, local recurrence is more frequent after treatment of an upper extremity sarcoma. Conversely, lower extremity sarcomas are associated with an increased metastatic rate.

A number of factors may contribute to the higher local recurrence rate in the upper extremity. These include differences in tumour characteristics, such as histological type, and differences in treatment, such as the effect of unplanned excision before referral and the use of radiotherapy. The strongest predictor of local recurrence in many studies is a positive surgical margin, which implies the presence of residual disease [6;109;123;127]. The Cox model confirms this relationship in this series, and shows that after incorporating the effect of a positive surgical margin, the effect of an unplanned excision before referral, or the upper rather than lower extremity location of a soft tissue sarcoma do not reach significance. Sadoski et al suggested that the relationship between a positive surgical margin and local recurrence is stronger in the upper than the lower extremity [109]. However, in our series there was a higher local recurrence rate in the upper extremity in both positive and negative margin cases (Table 4.4).

The proportion of patients with a positive surgical margin was particularly high (16 of 41 cases) for tumours around the elbow, which may reflect local anatomy. Despite this the local recurrence rate in this group was not as high as in other upper extremity sites (Table 4.2). The reason for this may be that four patients in this group had low grade liposarcomas, and were therefore at low risk of local recurrence.

Although it is a subgroup analysis and should therefore be treated with caution, it is interesting that there was a significant difference in local recurrence rates between the extremities amongst patients treated by primary excision with positive margins. There are a number of possible explanations. The previous study shows that an unexpected positive margin following a surgical error is associated with a higher risk of local recurrence than a planned positive margin against a critical structure (such as nerve, vessel or bone) or a planned marginal resection of a low grade liposarcoma. In five of 16 (31.3%) patients undergoing primary resection of an upper extremity sarcoma with a positive surgical margin, the positive margin was unexpected compared with eight of 48 (16.7%) in the lower extremity. This suggests that primary resection of a soft tissue sarcoma in the upper extremity is technically more demanding, or that in order to preserve function, the surgeon is prepared to operate closer to the tumour in the upper extremity. Another explanation for the difference in local recurrence rates is that there were more low grade liposarcomas in the lower extremity, which are at low risk of local recurrence (17 of 48 (35.4%) in the lower extremity vs. four of 16 (25%) in the upper)[141].

The distribution of histological types may have contributed to the difference in local recurrence rates between the extremities in another way. The histological types

angiosarcoma and malignant peripheral nerve sheath tumour have been associated with an increased risk of local recurrence [18;19]. Both of these types were relatively more frequent amongst upper compared to lower extremity tumours. Within the upper extremity, these histologic types were associated with four of 23 (17.4%) local recurrences, compared with two of 25 (8.0%) lower extremity tumours (Table 4.3).

Variation in the use of radiotherapy may also have influenced the local recurrence rate. In particular, tumours around the shoulder did not meet the criteria for radiotherapy as often as those in other upper extremity sites. This is likely to be because a proportion of soft tissue sarcomas around the shoulder occur in muscle (such as deltoid) where they can be excised with an adequate margin more readily than in other upper extremity sites. Therefore an unplanned excision is more likely to have been successful in removing all identifiable tumour and adjuvant radiotherapy is not indicated after re-excision. It was also more common for the shoulder to have been treated with radiotherapy previously, both for the presenting tumour and for unrelated conditions, such as Hodgkin disease.

Upper extremity tumours more frequently undergo unplanned excision before referral, possibly because they are smaller and more often superficial. However, this study does not conclusively prove an adverse influence of unplanned excision on local recurrence in the Cox model.

The finding that lower extremity tumours are associated with a higher rate of metastasis confirms that of other authors[57;68;96]. The Cox model suggests that that most of this difference is accounted for by recognised risk factors for metastasis,

namely grade, size and depth [16;68;96;127;138], rather than another hitherto unrecognised feature of lower extremity sarcomas. The analysis makes the assumption that after the treatment of an extremity soft tissue sarcoma, local recurrence and metastasis are independent and not competing events. Length of follow-up of survivors was similar in the upper and lower extremities, and therefore it is unlikely that the higher local recurrence rate of upper extremity tumours was caused by an increased death rate and shorter follow up of lower extremity tumours.

There were more lower than upper extremity tumours in this series, an experience shared by other authors [18;72;98;123;128]. This probably reflects the greater volume of mesenchymal tissue in the lower extremity.

Tumours in the upper extremity are smaller probably either because the smaller volume of the extremity allows tumours to be detected earlier or because the upper extremities are exposed and abnormal swellings are identified readily. However, this study, like others, suggests that tumour size is not a strong predictor of local recurrence [16;96;127]. This study was not designed to assess delays in referral, and it is therefore not possible to conclude if upper extremity tumours present earlier than those in the lower extremity. The smaller size of upper extremity tumours supports the suggestion that the threshold above which a mass should be treated as potentially malignant should be lower in the upper extremity [57]. The larger size of lower extremity tumours probably explains why they more often involve the investing fascia of the limb and are therefore classified as deep.

This study is novel in directly comparing upper and lower extremity soft tissue sarcomas treated in one centre. It highlights differences in treatment and outcomes despite the fact that the treating clinicians felt that they were applying similar principles in both locations. It shows that in this group of patients, upper extremity sarcomas are associated with a higher local recurrence rate than those in the lower extremity probably because of differences in histological type, the use of radiotherapy and local anatomy. Although upper extremity sarcomas are more often treated by unplanned excision before referral, the study does not conclusively prove that this has an adverse effect on local tumour control. In contrast, lower extremity sarcomas tend to be larger, and more often deep than upper extremity sarcomas, and therefore have an increased risk of metastasis. This study also shows that in this patient population, the higher rate of local recurrence in the upper extremity was not matched by a higher rate of metastatic disease. This supports the philosophy of preserving function in the upper extremity where possible. These results are directly relevant to the management of patients with extremity soft tissue sarcoma.

5. ANATOMICAL LOCATION AND FUNCTIONAL OUTCOME

Introduction

The purpose of this study was to explore the relationship between anatomical location and functional outcome scores in lower extremity soft tissue sarcoma.

Patients and Methods

It was decided at the outset to exclude patients with upper extremity tumours from this study because they were too few in number to allow meaningful analysis. Functional outcome was assessed using MSTS (1993) and TESS evaluations. The MSTS (1987) evaluation is site-specific (i.e. pelvis/hip/proximal thigh, distal thigh/knee/proximal leg and distal leg/ankle/foot) and was therefore not suitable for this study. The generic general health status measure Short-Form 36 (SF-36) was not used because it is not sensitive to local treatment factors[25].

The TESS was first used in April 1994 and therefore patients treated before this date were excluded. A minimum of 1 year follow up for functional evaluation was required, at which point functional scores plateau[5;24]. Patients were also excluded if they had metastases at presentation, had a local or systemic relapse before functional assessment at 1 year or received chemotherapy, as all of these factors are likely to have an adverse effect on functional scores.

The database was used to identify suitable patients and the following data were extracted from it; age, gender, status at presentation, unplanned excision, histological type and grade, maximum tumour diameter, depth, type of procedure, and complications of surgery. Resection of bone, resection of major motor nerve, MSTS and TESS item and aggregated scores were extracted from the function database.

Anatomical definitions

Tumours were first categorised as superficial or deep, as defined previously. Next, deep tumours were assigned to one of nine anatomical regions in the lower extremity. These regions were based upon the concept of anatomical compartments developed by Enneking as these have both oncological and functional significance [40]. The thigh compartments as described by Enneking were used and the following anatomical regions were defined; the groin/femoral triangle, the buttock, the popliteal fossa, anterolateral leg, posterior calf, and foot and ankle. The boundaries and contents of these anatomical regions are described in Table 5.1. The anatomical location of the tumour was determined by review of the operating note and imaging. A tumour involving more than one region was assigned to the region containing the greatest part of the tumour.

Table 5.1 Anatomical regions within the lower extremity

Region	*Anatomical boundaries and contents*
Groin/femoral triangle	Proximally the inguinal ligament, posteriorly iliopsoas and anterior hip capsule, laterally the tendon of rectus femoris. Contains proximal extent of femoral artery, vein, nerve and inguinal nodes.
Buttock	Proximally the posterior brim of pelvis, medially the sacrum, anteriorly the posterior border of tensor fascia lata, anterior border of gluteus medius, and as the deep boundary, the outer table of pelvis. Contains gluteus maximus, minimus, medius, quadratus femoris, and the proximal extent of the sciatic nerve.
Anterior thigh	Proximally the brim of pelvis, distally the patella, and laterally the intermuscular septum. Contains quadriceps including patella and patellar tendon, sartorius, tensor fascia lata, femoral artery, vein, and nerve.
Medial thigh	Proximally the pubic rami and ischial tuberosity, anterolaterally the adductor canal and medial intermuscular septum, posteriorly the posterior surface of adductor magnus, distally the pes anserinus. Contains gracilis, adductors brevis, longus, magnus, pectineus, and profunda femoris vessels.
Posterior thigh	Laterally the intermuscular septum, medially the adductor magnus fascia, proximally the ischial tuberosity, distally the musculotendinous junctions of the hamstring muscles, anteriorly the linea aspera and posterior face of femur. Contains semimembranosus, semitendinosis, and biceps femoris.

Table 5.1 continued

Region	*Anatomical boundaries and contents*
Popliteal fossa	Superficially the deep fascia, anteriorly the posterior capsule of knee joint and the heads of gastrocnemius, distally the confluence of gastrocnemius and proximally the musculotendinous junctions of hamstrings. Contains sciatic nerve, popliteal vessels and lymph nodes.
Posterior calf	Anteriorly, the posterior surface of the tibia, interosseous membrane, posterior aspect of fibula and posterior intermuscular septum. Posteriorly, the deep fascia of the calf. Superiorly the confluence of gastrocnemius, distally the commencement of the tendo Achilles. Contains gastrocnemius, plantaris, soleus, popliteus, flexor digitorum longus, flexor hallucis longus, tibialis posterior, and the posterior tibial vessels and nerve.
Anterolateral leg	Anteriorly, the deep fascia of the leg, posteriorly the lateral surface of the tibia, the interosseous membrane, the fibula and the posterior intermuscular septum. Proximally the proximal extent of the insertion of tibialis anterior into the tibia, distally the superior extensor retinaculum of the ankle. Contains peroneus longus and brevis, peroneus tertius, extensor digitorum longus, extensor hallucis longus, tibialis anterior, the anterior tibial vessels and deep peroneal nerve.
Foot and ankle	Proximally this space in bounded by the superior extensor retinaculum anteriorly and commencement of the tendo Achilles posteriorly.

Data entry

To minimise transcription errors, data relating to anatomical location were entered twice into a spreadsheet and checked for compatibility with the pre-existing anatomical classification in the database in which tumours were grouped by their proximity to the nearest major joint.

Analysis

Initially, descriptive variables were calculated for the whole group of eligible patients. Next the characteristics, MSTS (1993) and TESS evaluations of superficial and deep tumours were compared. Factors influencing MSTS (1993) and TESS scores for deep tumours alone were then investigated using linear regression. Models were constructed using variables previously shown to be predictive of functional outcome [25] and adding further variables for anatomical location. Therefore, to investigate the effect of anatomical location on postoperative MSTS (1993) scores, the linear regression model used variables for tumour diameter, high histological grade (N/Y), resection of bone (N/Y), resection of motor nerve (N/Y), complications of surgery (N/Y) and dummy variables for each of the nine anatomical locations. The regression model for postoperative TESS used variables for tumour diameter, high histological grade (N/Y), motor nerve resection (N/Y) and dummy variables for each of the nine anatomical locations.

To investigate variation in pre- and postoperative MSTS (1993) and TESS score items for deep tumours by anatomical location an exploratory analysis compared the mean scores for each item across the anatomical locations.

To assess the effect of missing MSTS and TESS results, patients with and without postoperative MSTS and TESS results were compared for characteristics which might have an effect on these scores, namely tumour diameter, bone resection, motor nerve resection, complications of surgery and anatomical location.

Results

Between April 1994 and March 1999, data relating to 397 patients were entered in the database. Ninety-seven of these had upper extremity tumours, and 17 had an amputation and were therefore excluded. The following patients were also excluded; 22 with metastases at presentation, 32 who developed metastases before functional evaluation, two who died of other causes, three with a local recurrence in the first year, and ten patients who received chemotherapy. Seven patients had no function data available. Therefore 207 patients were included in this study.

Characteristics of the whole group

There were 106 (51.2%) females and 101 males of median age 54 (15 to 89) years. Twelve patients (5.8%) presented with a local recurrence after treatment elsewhere. Seventy-six patients (36.7%) had been treated by unplanned excision before referral. The distribution of histological types was similar to that in other series, with malignant fibrous histiocytoma in 48 (23.2%), liposarcoma otherwise undesignated in 49 (23.7%) and myxoid liposarcoma in 28 (13.5%). Tumours were grade one in 40 (19.3%) cases, grade two in 76 (36.7%) and grade three in 91 (44.0%). The median maximum tumour diameter was 8.0 cm (0.3 to 36.0).

A tissue transfer or split-skin graft was used for wound closure in 40 (19.3%) cases, and 170 (82.1%) patients received adjuvant radiotherapy. Resection of bone was required in twelve (5.8%) cases and resection of a major motor nerve in twelve (5.8%) cases. Forty-eight (23.2%) patients had a wound complication and three (1.4%) had a fracture.

After anatomical classification there were 58 (28.0%) superficial and 149 (72.0%) deep tumours. Superficial tumours were significantly smaller than deep tumours (4.6 vs 11.2 cm, $p<0.001$)(Table 5.2). Of the deep tumours, six were located in the groin/femoral triangle, eight in the buttock, 52 in the anterior thigh, 22 in the medial thigh, 20 in the posterior thigh, ten in the popliteal fossa, thirteen in the posterior calf, eleven in the anterolateral leg and seven in the foot and ankle (Table 5.3). Of the deep tumours, 119 (79.9%) involved one site only, 28 (18.8%) involved 2 sites and 2 (1.3%) involved three sites.

Table 5.2

Differences in characteristics and functional scores between deep and superficial tumours

Site	*No. of cases*	*Mean diameter in cm (SD)*	*Complic-ations of surgery*	*Radiotherapy*	*MSTS (1993)*		*TESS*	
					Mean Preop Score	*Mean postop score*	*Mean preop score*	*Mean postop score*
Superficial	58	4.6 (3.2)	10	35	90.6 (32.0-100.0	93.0 (23.0-100.0)	86.4 (29.2-100.0)	90.9 (41.7-100.0)
Deep	149	11.2 (6.6)	41	135	86.9 (16.0-100.0)	83.0 (23.0-100.0)	81.8 (15.0-100.0)	79.5 (25.8-100.0)
		p<0.001	p=0.123	p<0.001	p=0.271	p<0.001	p=0.081	p<0.001

P values are shown for comparison of values between superficial and deep tumours. Range for functional scores shown in parentheses.

Table 5.3 Characteristics of deep tumours, treatment and functional scores by anatomical location

Anatomical location	*No. of cases*	*Mean diameter in cm (SD)*	*Major motor nerve resection*	*Bone resection*	*Compl-ications of surgery*	*Radio-therapy*	*MSTS (1993)*		*TESS*	
							Mean preop (range)	Mean postop (range)	Mean preop (range)	Mean postop (range)
Groin/femoral triangle	6	8.8 (1.9)	2	1	4	6	58.6 (16-80)	64.3 (27-90)	54.9 (15.0-89.2)	63.8 (25.8-82.5)
Buttock	8	8.1 (4.1)			2	8	86.8 (33-100)	90.0 (77-100)	79.2 (19.4-100)	77.8 (54.2-99.1)
Anterior thigh	52	11.8 (6.3)	4	1	12	47	89.8 (20-100)	80.1 (23-100)	80.7 (21.7-100)	77.5 (25.8-100)
Medial thigh	22	13.5 (8.5)			9	17	84.9 (27-100)	88.0 (37-100)	81.2 (24.1-100)	83.1 (35.8-100)
Posterior thigh	20	14.9 (6.5)	2		1	18	90.4 (67-100)	80.5 (43-100)	85.9 (54.4-100)	75.7 (54.2-96.7)
Popliteal fossa	10	9.5 (5.7)		1	3	10	93.8 (80-100)	92.3 (67-100)	90.6 (71.7-100)	83.3 (43.5-100)
Posterior calf	13	8.8 (4.8)	1	1	5	13	79.8 (24-100)	87.0 (60-100)	76.2 (15.0-100)	88.3 (68.3-100)
Anterolateral leg	11	8.7 (5.5)	1	6	2	10	91.8 (48-100)	84.4 (50-100)	90.6 (66.7-100)	80.2 (39.2-97.5)
Foot and ankle	7	4.6 (1.7)		2	3	6	77.7 (24-100)	84.2 (57-100)	90.4 (67.5-100)	88.1 (73.3-100)

Differences between deep and superficial tumours

Functional scores grouped according to whether the tumour was superficial or deep are shown in Table 5.2. There was no significant difference in MSTS (1993) or TESS at presentation when superficial and deep tumours were compared (mean MSTS (1993) 90.6% for superficial tumours vs. 86.9% for deep tumours, p=0.271; mean TESS 86.4% for superficial tumours vs. 81.8% for deep tumours, p=0.081).

Treatment of superficial tumours was not associated with a significant change in MSTS (1993) (mean MSTS (1993) 90.6% preoperatively vs 93.0% postoperatively, p=0.566) and TESS (mean TESS 86.4% preoperatively vs 90.9% postoperatively, p=0.059). However, treatment of deep tumours was associated with a significant reduction in MSTS (1993) and TESS (mean MSTS (1993) 86.9% preoperatively vs. 83.0% postoperatively, p<0.001; mean TESS 81.8% preoperatively vs. 79.5% postoperatively, p=0.015). MSTS (1993) and TESS differed significantly between superficial and deep tumours after treatment (mean MSTS (1993) 93.0% for superficial tumours vs 83.0% for deep tumours, p<0.001; mean TESS 90.9% for superficial tumours vs 79.4% for deep tumours, p<0.001).

Variation in characteristics of deep tumours by anatomical location

Variation in tumour size, type, treatment and functional scores amongst deep tumours by anatomical location is summarised in Table 5.3. Comparison of MSTS (1993) and TESS scores by anatomical location revealed no significant differences in preoperative MSTS (1993) (p=0.120) or TESS (p=0.282). Significance values from the regression model for postoperative MSTS (1993) are shown in Table 5.4. The only factor to reach significance was resection of motor nerve (p<0.001). The

variables for anatomical location did not reach significance. Significance values from the linear regression analysis for postoperative TESS are shown in Table 5.5. Once more, the only variable to reach significance was resection of motor nerve ($p=0.002$). The variables for anatomical location did not reach significance.

Table 5.4

Significance values from linear regression analysis for postoperative MSTS (1993)

	Standardised β coefficient	*t*	*Significance*
High or low histological grade	-0.037	-0.417	0.678
Resection of motor nerve	-0.349	-4.169	<0.001
Groin/femoral triangle	-0.064	-0.738	0.462
Buttock	0.068	0.817	0.416
Medial thigh	0.146	1.633	0.105
Posterior thigh	0.044	0.495	0.622
Popliteal fossa	0.134	1.591	0.114
Posterior calf	0.103	1.197	0.233
Anterolateral leg	0.124	1.256	0.212
Foot and ankle	0.040	0.457	0.649
Maximum tumour diameter	-0.161	-1.764	0.080
Any complication of surgery	-0.106	-1.234	0.220
Resection of bone	-0.122	-1.242	0.217
Excluded variable			
Anterior thigh			

Table 5.5

Significance values from linear regression analysis for postoperative TESS

	Standardised β coefficient	*t*	*Significance*
High or low histological grade	0.012	0.123	0.902
Resection of motor nerve	-0.306	-3.242	0.002
Groin/femoral triangle	-0.130	-1.354	0.179
Buttock	-0.045	-0.467	0.641
Medial thigh	0.075	0.729	0.468
Posterior thigh	0.002	0.016	0.987
Popliteal fossa	0.041	0.429	0.669
Posterior calf	0.139	1.373	0.173
Anterolateral leg	0.026	0.265	0.791
Foot and ankle	0.069	0.712	0.478
Maximum tumour diameter	-0.134	-1.328	0.187
Excluded variable			
Anterior thigh			

Comparison of MSTS (1993) and TESS items by anatomical location

Exploratory analysis of score items showed significant variation by anatomical location for the pain and gait items of the preoperative MSTS (1993) (Figure 5.1). Tumours in the groin/femoral triangle were associated with more pain than those in other locations. All patients with tumours in the groin/femoral triangle required analgesia, with most requiring narcotic analgesia. The lowest mean score for gait was for tumours in the groin/femoral triangle, followed by the posterior calf, the foot and ankle and the anterolateral leg (Figure 5.1).

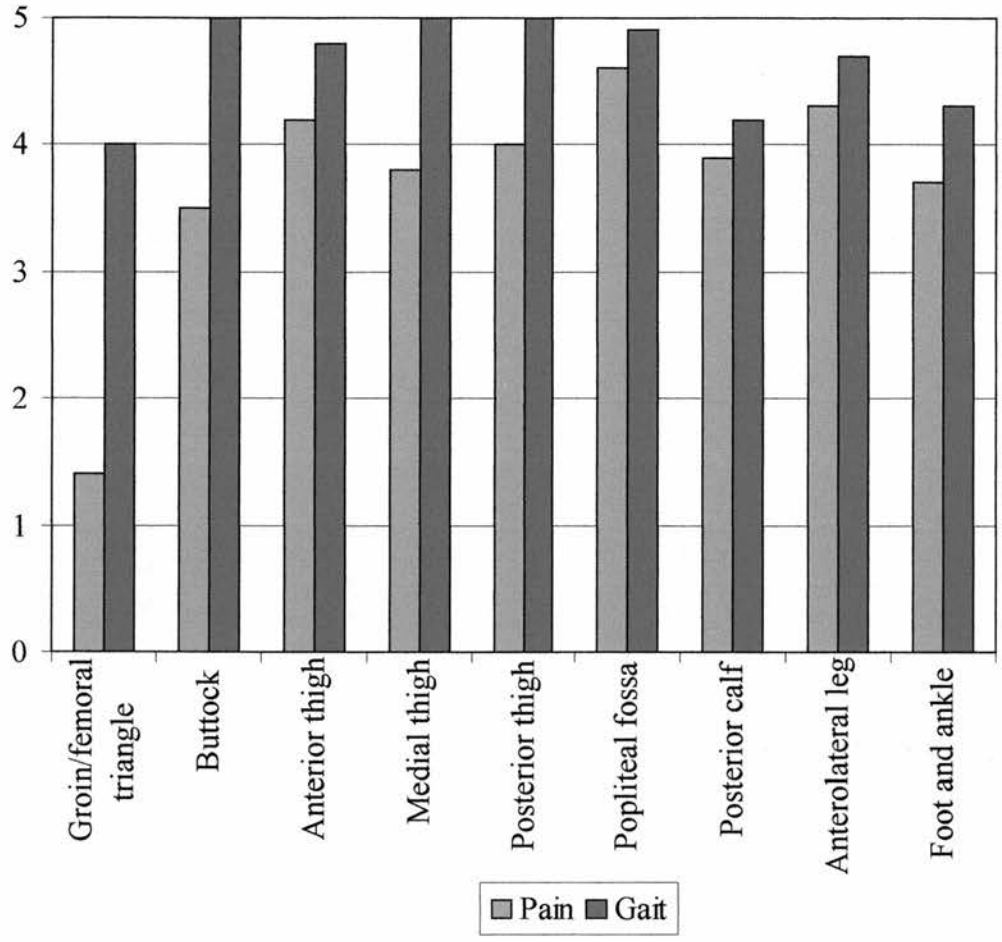
In the postoperative MSTS (1993), significant variation was also seen in item scores for gait. Once more, the lowest scores were seen in tumours in the groin/femoral triangle. Patients with tumours in the medial thigh, popliteal fossa, posterior calf and foot and ankle all walked normally (Figure 5.2). In the preoperative TESS, exploratory analysis did not identify items with significant variation by anatomical location although the item score for sitting approached significance. Patients with tumours in the groin/femoral triangle, buttock and posterior thigh had the greatest difficulty with sitting (Figure 5.3).

In the postoperative TESS significant variation was seen in the items for putting on pants (trousers), putting on socks or stockings, getting in and out of the bath, or bending to pick something up off the floor. Once more, patients with tumours in the groin/femoral triangle had the greatest difficulty with these activities. Putting on socks and stockings also appeared to be difficult for those with posterior thigh or buttock tumours (Figure 5.4). Getting in and out of the bath was also difficult for those with posterior thigh or anterolateral leg tumours. Bending to pick something up

off the floor was most difficult for patients with tumours in the groin/femoral triangle, buttock and the posterior thigh (Figure 5.5).

Figure 5.1

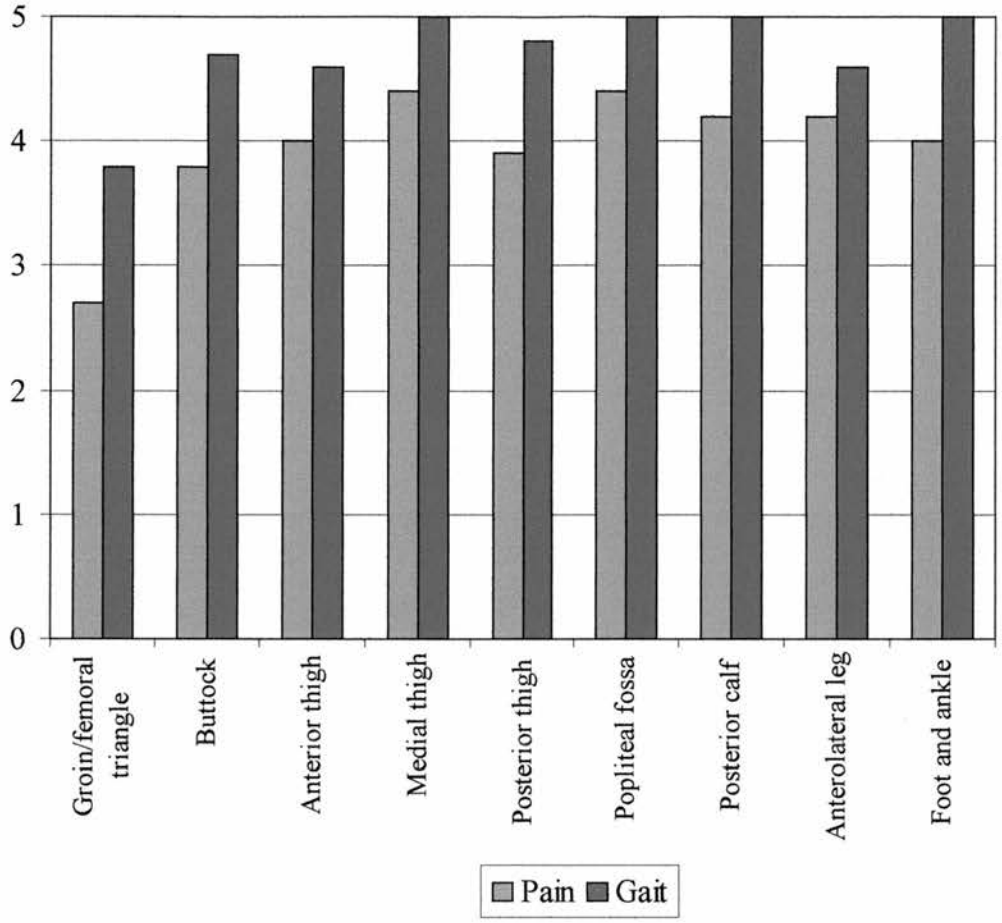
Mean preoperative MSTS (1993) "pain" and "gait handicap or limp" items by anatomical location



Anatomical location		Groin/ Fem. triangle	Butt-ock	Ant. thigh	Med. thigh	Post. thigh	Pop. fossa	Post. calf	Ant. lat leg	Foot and ankle
MSTS (1993) preop, mean scores	Pain	1.4	3.5	4.2	3.8	4.0	4.6	3.9	4.3	3.7
	Gait	4.0	5.0	4.8	5.0	5.0	4.9	4.2	4.7	4.3

Figure 5.2

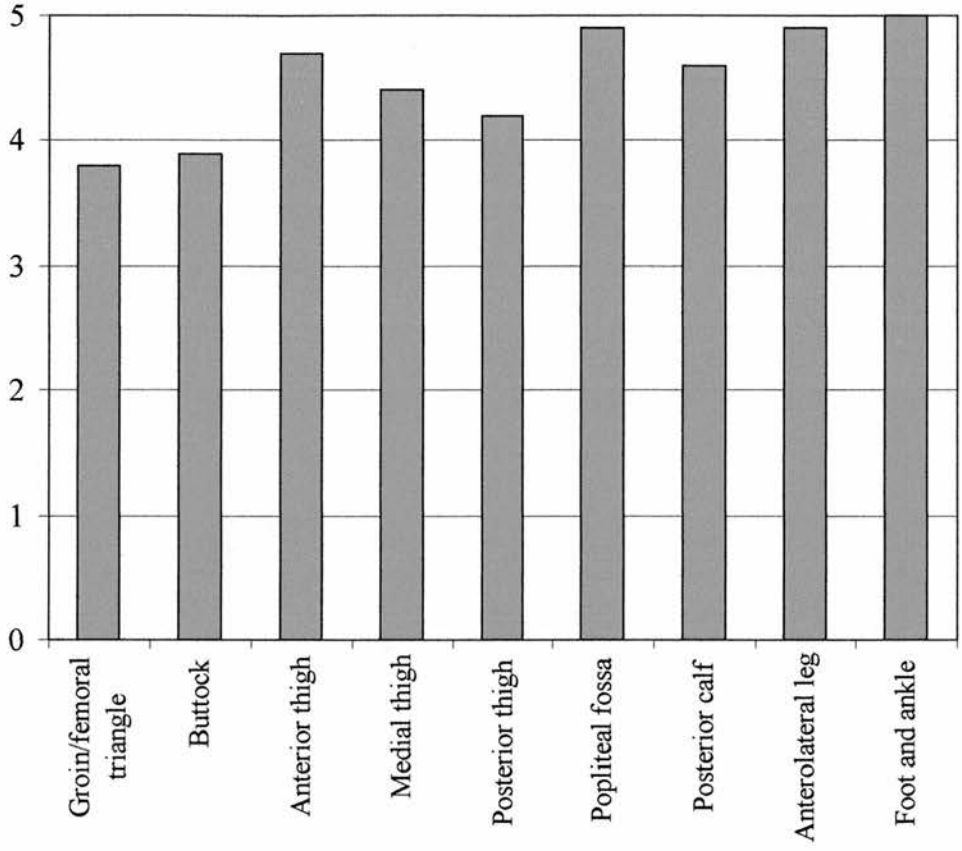
Mean postoperative MSTS (1993) "pain" and "gait handicap or limp" items by anatomical location



Anatomical location		Groin/ Fem. triangle	Butt-ock	Ant. thigh	Med. Thigh	Post. thigh	Pop. fossa	Post. calf	Ant. lat leg	Foot and ankle
MSTS (1993) postop, mean scores	Pain	2.7	3.8	4.0	4.4	3.9	4.4	4.2	4.2	4.0
	Gait	3.8	4.7	4.6	5.0	4.8	5.0	5.0	4.6	5.0

Figure 5.3

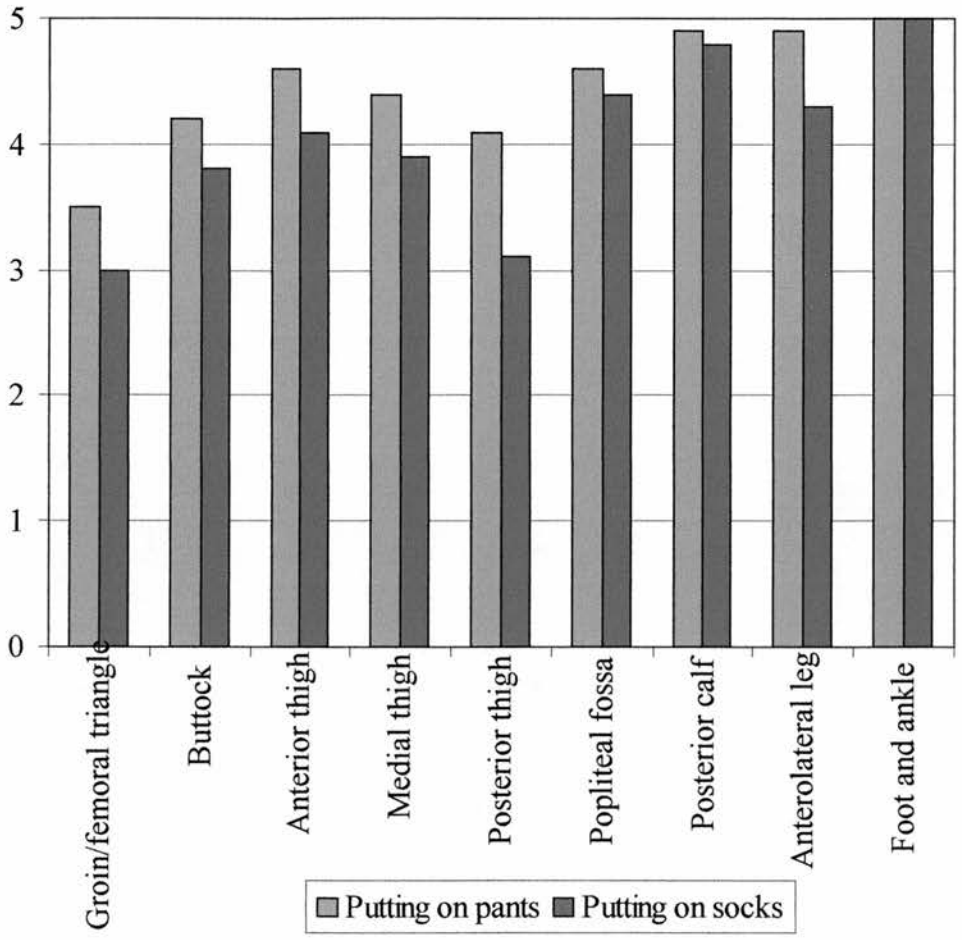
Mean postoperative TESS "sitting" item scores by anatomical location



Anatomical location	Groin/ femoral triangle	Butt-ock	Ant thigh	Medial thigh	Post thigh	Pop fossa	Post calf	Ant. lat leg	Foot and ankle
Preoperative TESS "sitting" item score	3.8	3.9	4.7	4.4	4.2	4.9	4.6	4.9	5.0

Figure 5.4

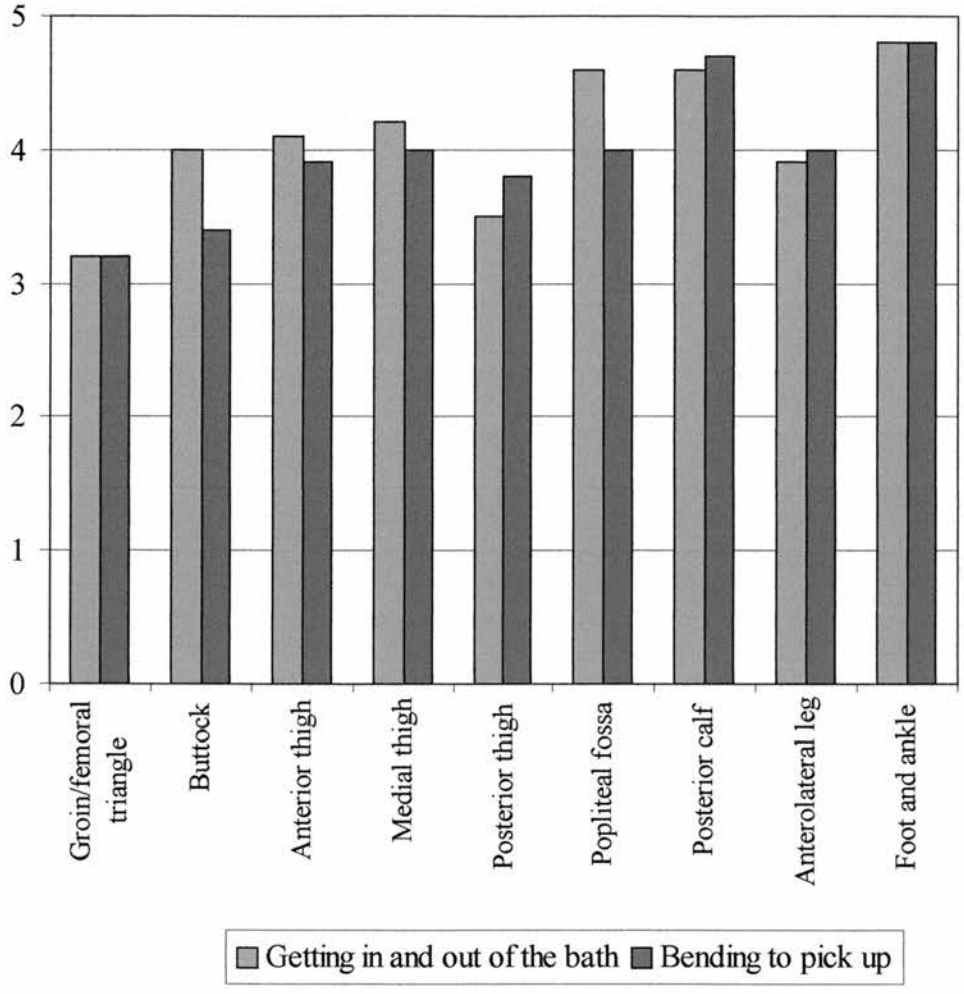
Mean postoperative TESS "pants" and "socks" items by anatomical location



Anatomical location		Groin/ Fem. triangle	Butt -ock	Ant. thigh	Med. Thigh	Post. thigh	Pop. fossa	Post. calf	Ant. lateral leg	Foot and ankle
TESS postop mean item scores	Pants	3.5	4.2	4.6	4.4	4.1	4.6	4.9	4.9	5.0
	Socks	3.0	3.8	4.1	3.9	3.1	4.4	4.8	4.3	5.0

Figure 5.5

Mean postoperative TESS "bath" and "bending" items by anatomical location



Anatomical location		Groin/ Fem. triangle	Butt-ock	Ant. thigh	Med. Thigh	Post. thigh	Pop. fossa	Post. calf	Ant. lateral leg	Foot and ankle
TESS postop mean item scores	Bath	3.2	4.0	4.1	4.2	3.5	4.6	4.6	3.9	4.8
	Ben-ding	3.2	3.4	3.9	4.0	3.8	4.0	4.7	4.0	4.8

Completeness of function data

Preoperative MSTS (1993) results were available for 203, and 1 or 2 year MSTS (1993) results were available for 189 patients. Preoperative TESS results were available for 172 and 1 or 2 year TESS results were available for 155 patients. Of the patients for whom 1 or 2 year TESS results were not available, twenty did not speak English, eleven were lost to follow up, seven were infirm and unable to complete the questionnaire and fourteen had no data for other reasons.

Differences in the characteristics of patients with postoperative MSTS (1993) evaluations and those without are summarised in Table 5.6. There were no significant differences in factors thought to have an influence in determining MSTS (1993) scores when patients with and without postoperative MSTS (1993) evaluations were compared.

Differences between patients with and without postoperative TESS evaluations are summarised in Table 5.7. The analysis shows that patients with incomplete postoperative TESS data had larger tumours than others, but fewer major motor nerve resections.

Table 5.6 Comparison of patients with and without postoperative MSTS(1993) scores

		Postoperative MSTS (1993) not available	*Postoperative MSTS (1993) available*	*P*
Number of patients		25	189	
Mean tumour diameter (cm)		10.0 (1.5-26.0)	9.2 (0.3-36.0)	0.564
High histological grade	No	4	37	0.669
	Yes	21	152	
Resection of bone	No	25	177	0.195
	Yes	0	12	
Resection of major motor nerve	No	24	178	0.710
	Yes	1	11	
Complications of surgery	No	22	141	0.140
	Yes	3	48	
Depth	Superficial	7	53	0.996
	Deep	18	136	
Groin/femoral triangle		0	6	0.582
Buttock		2	6	
Anterior thigh		5	49	
Medial thigh		1	21	
Posterior thigh		4	18	
Popliteal fossa		1	9	
Posterior calf		2	12	
Anterolateral leg		1	10	
Foot and ankle		2	5	

P-value for difference between patients with and without postoperative MSTS scores

Table 5.7

Comparison of patients with and without postoperative TESS scores

		Postoperative TESS not available	*Postoperative TESS available*	*P*
Number of patients		59	155	
Mean tumour diameter (cm)		11.1 (1.0-28.0)	8.7 (0.3-36.0)	0.015
High histological grade	No	15	26	0.151
	Yes	44	129	
Resection of major motor nerve	No	59	143	0.028
	Yes	0	12	
Depth	Superficial	16	44	0.854
	Deep	43	111	
Groin/femoral triangle		0	6	0.551
Buttock		3	5	
Anterior thigh		16	38	
Medial thigh		5	17	
Posterior thigh		9	13	
Popliteal fossa		3	7	
Posterior calf		4	10	
Anterolateral leg		1	10	
Foot and ankle		2	5	

P-value is for difference between patients with and without preoperative TESS scores

Discussion

The purpose of this study was to examine the influence of anatomical location on function as measured by MSTS (1993) and TESS evaluations. The study shows differences between MSTS (1993) and TESS evaluations for superficial and deep tumours, that anatomical location does not appear to be predictive of aggregated MSTS (1993) and TESS, but that MSTS (1993) and TESS items do vary with anatomical location.

Although a proportion of MSTS (1993) and TESS evaluations were not available, the analysis suggests that patients with missing postoperative MSTS (1993) data did not differ significantly from those with data available for factors likely to have an impact on MSTS (1993) evaluations. However, patients without postoperative TESS evaluations appeared to have larger tumours, but fewer motor nerve resections when compared to those with postoperative TESS evaluations. Large size has an adverse effect on function whereas preservation of major motor nerves is associated with better functional scores. It has been assumed that these missing data items would not have changed the conclusions of this study.

Higher MSTS (1993) and TESS evaluations for superficial tumours likely reflects their smaller size and the fact that treatment does not involve major muscle, motor nerve or bone resection. In fact, the treatment of superficial tumours was associated with an increase in MSTS (1993) and TESS although this did not reach statistical significance. Treatment of deep tumours when considered as a group was, as expected, associated with a significant decrease in MSTS (1993) and TESS. However, it is of note that the change in total scores varied with anatomical location.

In some locations, such as the groin/femoral triangle, the medial thigh, and the posterior calf, treatment of deep tumours was associated with an increase in functional scores, but treatment of tumours in the anterior thigh, the posterior thigh, the popliteal fossa and the anterolateral leg all lead to a decrease in functional scores. This may in part reflect the relative importance of these anatomical compartments in determining functional scores.

In the regression model, variables for anatomical location were not predictive of aggregated postoperative MSTS (1993) or TESS scores for deep tumours in this group of patients using these anatomical definitions. The exploratory analysis, however, indicates that individual score items do show variability with anatomical location. Tumours in the groin/femoral triangle were associated with more preoperative pain, as measured by the MSTS (1993) item for pain than those in other locations. This may be related to the relatively high rate of major nerve involvement in this location (2 of 6 patients requiring major motor nerve resection). Other than those in the groin, tumours located below the knee appeared to be associated with the lowest preoperative gait handicap or limp scores, reflecting the contribution of these compartments to normal gait. The lowest mean postoperative MSTS (1993) gait handicap or limp scores were seen in tumours in the groin/femoral triangle, although the group included one patient who had undergone a major femoral nerve resection and scored zero for gait postoperatively.

The TESS evaluation contains a greater number of items than the MSTS (1993) and some items, such as the ability to sit, have an intuitive relationship with anatomical location. Tumours in the buttock and posterior thigh were associated with greater

difficulty in sitting than those in other locations, likely reflecting the discomfort experienced when sitting directly on a tumour. Patients with tumours in the groin/femoral triangle also had difficulty sitting normally, perhaps because of restriction of normal hip flexion. The postoperative TESS evaluation confirms that after treatment, patients with tumours in the groin/femoral triangle continue to score lower for the items putting on socks, getting out of the bath and bending to pick up, all of which involve hip flexion.

The anatomical definitions in this study are based on Enneking's compartments as these have both oncological and functional significance. The muscles in any one compartment tend to have similar functions. This classification lead to the use of nine anatomical regions, which in turn meant the numbers of patients with tumours in any one compartment was small. Additionally, tumours were assigned to one compartment for this analysis, although they may have involved more than one. The validity of this classification has not been tested. Other anatomical classifications may have lead to different conclusions, although it is of note that in another study, in which the anatomical location was defined by the proximity of the tumour to the nearest major joint, anatomical location was not a significant predictor of functional scores [25].

This study therefore shows that the anatomical location of a lower extremity soft tissue sarcoma has a role in determining the function of the patient after treatment. This question has not been directly addressed in the literature before. The treatment of superficial tumours is associated with little change in functional scores, a fact that is likely to be helpful when counselling patients about treatment. Treatment of deep

tumours leads to a decrease in functional scores. Anatomical location does not appear to have an effect on aggregated MSTS and TESS item scores, but may influence score items.

6. THE EFFECT OF PLANNED MARGINAL EXCISION ON FUNCTIONAL OUTCOME

Introduction

The purpose of this study was to investigate whether the preservation of "normal" non-critical anatomical structures around a tumour associated with the "shelling out" or planned marginal excision of low-grade liposarcomas leads to better functional outcomes than the wider, negative margin surgery performed for higher grade malignant tumours.

Patients and Methods

The same criteria were used to select patients for this analysis as in the previous study of functional outcome and anatomical location. Patients with upper extremity tumours were excluded as were those treated before the TESS was first used in April 1994, and those without a minimum of 1 year of follow up. Patients were also

excluded if they had metastases at presentation, had a local or systemic relapse before functional assessment at 1 year or received chemotherapy. Superficial tumours were excluded as treatment does not lead to significant changes in MSTS and TESS evaluations. The following data were derived from the database; age, gender, status at presentation, unplanned excision, histological type and grade, maximum tumour diameter, depth, type of procedure, and complications of surgery. Resection of bone, resection of major motor nerve, MSTS and TESS item and aggregated scores were extracted from the function database.

Patients were assigned to two groups; those with a diagnosis of low-grade liposarcoma and others. The diagnosis of low-grade liposarcoma was suspected preoperatively on the basis of CT and/or MRI scanning. These tumours are characterised by their homogenous fat content, and biopsy was not usually performed, the diagnosis being confirmed after definitive resection. The surgical management of these tumours usually involves approaching the surface of the lesion and resecting the tumour covered with a thin film of normal tissue. The surgical margin is usually positive in parts, but an attempt is always made to obtain complete resection whilst preserving normal tissues. Occasionally, neurovascular structures are involved in these tumours, and may be resected with the tumour to obtain clearance. This differs from the treatment of higher grade tumours, when an attempt is usually made to resect the tumour with a mobile covering of normal tissue such as muscle or fascia outside the reactive zone. Radiotherapy was given based on the perceived risk of local recurrence, following multidisciplinary assessment of the predicted or actual surgical margins and the histological appearance of the tumour.

Initially the characteristics of the two groups and pre-and postoperative aggregated MSTS (1993) and TESS values were compared. Next, regression models were constructed with postoperative MSTS (1993) and TESS values as dependent variables using factors previously shown to be predictive of them with the addition of a variable for low grade liposarcoma. Given that there was a difference in the use of radiotherapy between the groups, a variable for the use of radiotherapy was also added. Therefore the model for postoperative MSTS (1993) contained variables for tumour diameter, high histological grade (N/Y), resection of bone (N/Y), resection of motor nerve (N/Y), complications of surgery (N/Y), low grade liposarcoma (N/Y) and radiotherapy (N/Y). The model for postoperative TESS included variables for tumour diameter, high histological grade (N/Y), motor nerve resection (N/Y), low grade liposarcoma (N/Y) and radiotherapy (N/Y).

Results

As stated in the previous study, data relating to 397 patients were entered in the database between April 1994 and March 1999. The following patients were excluded; 97 with upper extremity tumours, 17 who had an amputation, 22 with metastases at presentation, 32 who developed metastases before functional evaluation, two who died of other causes, three who had a local recurrence in the first year, and ten patients who received chemotherapy. 60 patients with superficial tumours were also excluded. Of the 154 patients remaining, five had no function data available, leaving 149 patients in this analysis.

Of the 149 patients in this study, 27 had low-grade liposarcomas (Table 6.1). The mean age of the 149 patients was 52 years (15 to 89). 71 were male. Mean age and gender did not differ significantly between patients with low-grade liposarcomas and the rest (58.0 vs 51.2 years, p=0.082; 45.9% vs 55.6% male, p=0.363). Low grade liposarcomas were significantly larger than other tumour types (mean maximum diameter 16.5 vs 10.0 cm, p<0.001). However, the two groups of patients did not differ significantly in the number requiring resection of major motor nerves or bone (Table 6.1). Four of 27 patients with low-grade liposarcomas had complications of surgery (one fracture and 3 wound complications). 37 of 122 patients in the other group had complications of surgery (2 fractures, 35 wound complications), also not significantly different (p=0.102). However, radiotherapy was used significantly less often in the treatment of low-grade liposarcomas than other tumours (21 of 27 vs 114 of 122, p=0.012).

There were no significant differences in aggregated preoperative MSTS (1993), preoperative TESS, postoperative MSTS (1993) and postoperative TESS evaluations when low-grade liposarcomas and other tumour types were compared. Treatment of low-grade liposarcomas was associated with a significant decrease in MSTS (1993) and TESS (93.7 vs. 84.9, p=0.010; 86.8 vs. 80.7, p=0.044). Treatment of other tumours was associated with a significant decrease in MSTS (1993) (85.4 vs. 82.6; p=0.016) and a decrease in TESS which did not reach statistical significance (80.9 vs. 79.3, p=0.068)(Table 6.2).

Table 6.1

Differences in characteristics between low-grade liposarcomas and other tumours

	No. of cases	*Mean age*	*Mean diameter in cm (SD)*	*Major motor nerve resection*	*Bone resection*	*Complications of surgery*	*Radiotherapy*
Low grade liposarcomas	27	58.0	16.5 (6.2)	1	0	4	21
Other tumour types	122	51.2	10.0 (6.1)	9	12	37	114
		p=0.082	p<0.001	p=0.490	p=0.089	p=0.102	p=0.012

P values are shown for comparison of values between low-grade liposarcomas and other tumours.

Table 6.2

Differences in functional scores between low-grade liposarcomas and other tumours

	MSTS (1993)		*TESS*	
	Mean preop score	Mean postop score	Mean preop score	Mean Postop score
Low grade liposarcomas	93.7 (52-100)	84.9 (30-100)	86.8 (50-100)	80.7 (55.4-98.3)
Other tumour types	85.4 (16-100)	82.6 (23-100)	80.9 (15-100)	79.3 (25.8-100)
	p=0.058	p=0.617	p=0.606	p=0.778

P values are shown for comparison of values between low-grade liposarcomas and other tumours. Range for functional scores shown in parentheses.

In the regression model for postoperative MSTS (1993), the variable for resection of motor nerve was the only one to reach significance (Table 6.3). In the model for postoperative TESS, the variables for histological grade, resection of motor nerve and low-grade liposarcoma all reached significance (Table 6.4).

Completeness of function data

Of the 154 patients eligible for this study, postoperative MSTS (1993) evaluations were not available for 18. Differences in the characteristics of patients with postoperative MSTS (1993) evaluations and those without are summarised in Table 6.5. There were no significant differences in factors thought to have an influence in determining MSTS (1993) scores when patients with and without postoperative MSTS (1993) evaluations were compared.

Postoperative TESS evaluations were not available for 43 patients in this analysis. Differences between patients with and without postoperative TESS evaluations are summarised in Table 6.6. As in the previous study, patients with incomplete postoperative TESS data had larger tumours than others, but fewer major motor nerve resections.

Table 6.3

Significance values from linear regression analysis for postoperative MSTS (1993)

	Standardised β coefficient	*t*	*Significance*
High or low histological grade	0.090	0.553	0.581
Resection of motor nerve	-0.388	-4.868	<0.001
Maximum tumour diameter	-0.162	-1.908	0.059
Low grade liposarcoma	0.077	0.468	0.640
Resection of bone	-0.070	-0.865	0.389
Any complication of surgery	-0.077	-0.945	0.347
Radiotherapy	-0.127	-1.559	0.121

Table 6.4

Significance values from linear regression analysis for postoperative TESS

	Standardised β coefficient	*t*	*Significance*
High or low histological grade	0.422	2.299	0.024
Resection of motor nerve	-0.346	-3.934	<0.001
Maximum tumour diameter	-0.147	-1.618	0.109
Low grade liposarcoma	0.414	2.259	0.026
Radiotherapy	-0.121	-1.345	0.181

Table 6.5

Comparison of patients with and without postoperative MSTS(1993) scores

		Postoperative MSTS (1993) not available	*Postoperative MSTS (1993) available*	*P*
Number of patients		18	136	
Mean tumour diameter (cm)		12.1 (2.0-26.0)	11.0 (2.0-36.0)	0.498
High histological grade	No	4	30	0.987
	Yes	14	106	
Resection of bone	No	18	124	0.189
	Yes	0	12	
Resection of major motor nerve	No	17	127	0.864
	Yes	1	9	
Complications of surgery	No	15	98	0.309
	Yes	3	38	
Low grade liposarcoma	No	14	112	0.636
	Yes	4	24	

P-value for difference between patients with and without postoperative MSTS scores

Table 6.6

Comparison of patients with and without postoperative TESS scores

		Postoperative TESS not available	*Postoperative TESS available*	*P*
Number of patients		43	111	
Mean tumour diameter (cm)		13.2 (2.0-28.0)	10.4 (2.0-36.0)	0.016
High histological grade	No	14	20	0.051
	Yes	29	91	
Resection of major motor nerve	No	43	101	0.042
	Yes	0	10	
Low grade liposarcoma	No	31	95	0.051
	Yes	12	16	

P-value is for difference between patients with and without preoperative TESS scores

Discussion

The aim of this analysis was to assess whether the "shelling out" of low-grade liposarcomas in which almost all normal tissue is preserved is associated with better functional outcomes that the more extensive, "negative margin", surgery used for other tumours in the lower extremity. This question has not been addressed elsewhere in the literature. This study shows that the planned marginal excision of low-grade liposarcomas still leads to a decrease in MSTS (1993) and TESS evaluations, despite a more conservative surgical approach. Although aggregated functional scores do not differ significantly between patients with low-grade liposarcomas and other tumours, the regression analysis suggests that the planned marginal excision of low-grade liposarcomas may be associated with higher TESS evaluations.

This analysis uses multiple regression to compensate for the effect of variables previously shown to have an effect on functional scores. However, it is clear that the oncological significance of a diagnosis of low-grade liposarcoma is very different to the diagnosis of malignant soft tissue sarcoma. It is not clear what effect this may have had on patient responses to function questionnaires. This difference might have had an effect on functional scores. The regression analysis suggests that other differences between these groups, particularly tumour diameter and the use of radiotherapy do not have a significant effect on functional scores.

The regression analysis also suggests that the treatment of low-grade liposarcomas does not lead to better postoperative MSTS (1993) evaluations, but may be

associated with improved postoperative TESS evaluations. This may reflect differences in what the scores measure (MSTS(1993) is a measure of impairment, TESS of handicap), or in their ability to discriminate between patients.

It is interesting to note that the surgery of low-grade liposarcomas has a complication rate similar to the surgery of other soft tissue sarcomas. One patient had a large (26cm in maximum diameter) low-grade liposarcoma in the proximal thigh treated with preoperative radiotherapy and partial resection of the femoral nerve. This was followed by a femoral fracture treated with internal fixation. Despite this, the TESS score of this patient increased from 82.4 preoperatively to 87.0 after treatment. All three patients with low-grade liposarcomas who had wound complications received radiotherapy, two preoperatively and one postoperatively.

The effect of missing functional data is difficult to evaluate. Comparison of the characteristics of patients with missing data with others suggests that missing MSTS (1993) evaluations are unlikely to have adversely influenced the results. The proportion of patients with missing TESS evaluations was higher however, and patients for whom these were missing appeared to have had larger tumours and fewer motor nerve resections than the rest, which may have influenced the results.

In summary, this study shows that the planned marginal excision of low-grade liposarcomas is associated with significant changes in functional scores and complication rates, similar to those seen after the resection of other tumours. This has not been shown previously in the literature. This information is helpful in counselling patients about the likely effects of treatment, and confirms that removing the tumour

alone, without other tissues, has a significant impact on patient function. The treatment of low-grade liposarcomas is not associated with better MSTS scores. However, this approach is associated with improved TESS scores, supporting the proposition that the preservation of normal non-critical anatomical structures leads to better function for patients.

7. CONCLUSIONS AND FUTURE DIRECTIONS

This thesis confirms that anatomical location is an important determinant of the presentation, treatment and outcome of adult extremity soft tissue sarcoma, and a number of novel aspects of this relationship have been demonstrated. It has been shown that the significance of positive surgical margins depends on the clinical context in which they occur, and in particular, that important anatomical structures adjacent to soft tissue sarcomas can be safely preserved. It has been shown that soft tissue sarcomas of the upper and lower extremities differ in presentation, treatment and outcome. Tumours in the upper extremities have a higher local recurrence rate, but a lower rate of metastasis than tumours in the lower extremities, and there are differences in surgical margins and the use of radiotherapy. Furthermore it has been shown that functional outcome scores are influenced by anatomical location, and in particular, that the treatment of superficial tumours does not lead to significant changes in functional scores, unlike the treatment of deep tumours. Finally, it has

been shown that the preservation of non-critical anatomical structures during the planned marginal excision of a low-grade liposarcomas may have a beneficial effect on TESS evaluations.

Are these findings justified?

The studies in this thesis rely on the retrospective analysis of clinical data from a single centre. There are a number of weaknesses inherent in this kind of analysis. For example, the data were not collected with these specific research questions in mind, and a prospective study specifically designed to answer each of the questions in turn would strengthen the conclusions. In addition, the experience of a single centre may not be applicable to others. There is likely to be significant variation between centres in surgical technique, the assessment of surgical margins, the histological classification of tumours (particularly low-grade fatty tumours) and the use of radiotherapy. In particular, the decision making process by which a positive surgical margin is deemed acceptable or not is highly dependent on the experience of the local team, and it is difficult to standardise this kind of assessment across patients and between centres. To confirm whether these conclusions are applicable to other centres and other groups of patients would require prospective, possibly multicentre studies and standardisation of the major variables. Furthermore, where they have been performed, the statistical analysis of subgroups should be treated with caution, particularly in the functional score studies, in which the analysis of large numbers of item scores increases the chance of a false positive result.

In order to accumulate sufficient numbers of these rare tumours for meaningful analyses, the combination of a large number of different histological types of soft tissue sarcoma into studies is common throughout the literature. However, this is a potential flaw in these and other studies. It is becoming clear that not all histological types of tumour behave in the same fashion. For example, the histological types fibrosarcoma and malignant peripheral nerve sheath tumour are locally infiltrative and perhaps require wider margins than other histological types. The effect of this variation on these studies may only become clear in the future, when larger studies of single histological types are performed.

The length of follow-up of patients is similar in the studies and has been determined by the length of time over which the Musculoskeletal Oncology Unit at the Mount Sinai Hospital has been in existence. It has been suggested that the effect of local treatment variables, such as a positive surgical margin, may become more significant over time [116]. It is therefore possible that, in the longer term, further differences may become apparent in local and systemic relapse between patients with different classes of positive surgical margin, between the upper and lower extremities, and in functional outcomes. Patients treated at the Mount Sinai Hospital are often involved in clinical trials. A study comparing preoperative and postoperative radiotherapy was in progress at the time that these patients were treated. Although the results of this study appear to show little difference in tumour control and 1-2 year functional scores between groups, it is possible that a difference will become apparent at longer term follow up.

To be scientifically rigorous, questionnaires or other scoring systems used in clinical practice should be reliable, valid and responsive. These attributes have been tested for the TESS evaluation [26]. However, less is known about these factors in the MSTS evaluation, which was developed without patient input. The fact that clinicians rather than patients complete the MSTS introduces another potential source of bias.

Implications for practice

These studies have a number of clinical implications. Consideration of the anatomical location may allow patients to be better counselled about what to expect, in terms of tumour control and functional outcomes. The understanding that not all positive surgical margins have the same risk of local recurrence may allow appropriate patients to be treated more aggressively, in the hope that a local recurrence might be avoided.

It has been suggested by Pisters (plenary session, Connective Tissue Oncology Society, Barcelona 2003) that the classification of positive surgical margins developed in this thesis could be useful in developing or refining staging systems for local recurrence. Whether or not anatomical location might be a useful part of staging systems for systemic disease is not clear.

Knowledge that superficial tumours can be treated without a major impact on functional scores is useful for patients. When discussing the functional outcome expected after treatment of a deep tumour, patients may find a discussion of how

their ability to perform particular activities will be changed (in other words, changes in score items), rather than changes in aggregated scores. When considering low grade fatty tumours, the surgeon also needs to emphasise that there will be adverse changes in function after treatment, despite the preservation of non-critical anatomical structures.

In conclusion, just as extremity and retroperitoneal soft tissue sarcomas differ in terms of their anatomical location and therefore their clinical behaviour, the anatomical location of an extremity soft tissue sarcoma appears to have an influence on its presentation, management and outcomes. Anatomical location is therefore an important consideration in the management of extremity soft tissue sarcomas.

Future directions

This thesis suggests a number of avenues for further research, both clinical and biological. Clinical studies might be usefully divided into those concerned with local control and others concerned with systemic disease. It is clear that there is a need for an effective systemic agent for the treatment of soft tissue sarcoma, and it is to be hoped that the future will bring developments in this regard. However, given that the studies in this thesis were more concerned with local anatomy, this will not be discussed further here.

Considering how local treatment may develop in future, it is likely that clinical studies will continue to support the trend towards more "conservative" surgery and closer surgical margins. However, this will require a deeper understanding of what represents an adequate margin, and the refinement of the present systems for describing surgical margins into systems that are reproducible and better reflect the volume of residual disease. The direct assessment of residual disease may become feasible, perhaps by using targeted antibodies in the operating theatre, or postoperatively with more sensitive scanning techniques than those presently available. Further clinical research is likely to demonstrate that the adequacy of a surgical margin is dependent on the histological type of tumour.

The future is likely to bring developments in local imaging techniques, which may allow the tumour to be better defined and allow surgery to be better planned. As clinical experience of presently available techniques, such as MRI grows, radiologists may be better able to define the extent of the tumour[34]. The ability to

deliver radiotherapy to the tumour and not normal surrounding tissues is likely to improve with the development of new technologies, for which knowledge of the anatomical extent of the tumour is also critical.

The major aim of pursuing closer surgical margins is to achieve better functional outcomes for patients. This requires objective measures of function that can discriminate between patients. It is likely that the assessment of function will develop further towards measures known to be valid and reproducible, such as TESS. The MSTS system, with the inherent disadvantages of being completed by clinicians, and summating item scores for fundamentally different variables, such as "gait handicap or limp" and "emotional acceptance" is likely to fall into disuse without a major revision. The reporting of patient outcomes is likely to broaden, to include measures of how patients adapt and function in society, rather than measures of physical function alone. However, explaining these scores to patients in a meaningful way remains a major challenge.

Further evolution in the staging systems used to classify patients for their risk of oncological endpoints, such as local recurrence and metastasis is likely. Although disease-specific survival is the endpoint of most current staging systems, the development of a staging system to predict local recurrence, perhaps using variables for histological type, classification of positive surgical margins and anatomical location may be a useful development in the local management of these patients.

This thesis suggests a number of directions for biological research in soft tissue sarcoma. One potential avenue of research is would be to investigate why particular

types of soft tissue sarcoma are more likely to arise in one anatomical location than another, suggested in the study comparing upper and lower extremity tumours. There is likely to be variation in tissue types or exposure to environmental carcinogens between the extremities. Further research in this field may shed light on the pathogenesis of soft tissue sarcomas. The study of positive surgical margins suggests, as did Enneking, that tissues vary in their resistance to tumour invasion. It is not clear why this should be at a cellular level. Further research into tumour/host interactions may encourage different approaches to the surgery of soft tissue sarcomas. Tumours that express biological markers of locally aggressive behaviour may, for example, spread easily along tissue planes and may require wider surgical margins than others. An understanding of this interaction may enhance surgical practice.

All of these developments will benefit greatly from the combination of experience from more than one centre. Agreement about standard definitions, such as the assessment of histological grade and surgical margins is a key component of this. Biological studies require access to tumour tissue, and it is to be hoped that specimens will be banked routinely in all centres for this purpose in future. However, there is no doubt that these developments will be built on a foundation of closer co-operation between clinicians and scientists in different centres and different countries. We must work together to improve the lot of our patients.

8. BIBLIOGRAPHY

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APPENDIX 1

World Health Organisation classification of soft tissue tumours [46]

ADIPOCYTIC TUMOURS	**Benign**	Lipoma
		Lipomatosis
		Lipomatosis of nerve
		Lipoblastoma/ Lipoblastomatosis
		Angiolipoma
		Myolipoma
		Chondroid lipoma
		Extrarenal angiomyolipoma
		Extra-adrenal myelolipoma
		Spindle cell/ Pleomorphic lipoma
		Hibernoma
	Intermediate (locally aggressive)	Atypical lipomatous tumour/ Well differentiated liposarcoma
	Malignant	Dedifferentiated liposarcoma
		Myxoid liposarcoma
		Round cell liposarcoma
		Pleomorphic liposarcoma
		Mixed-type liposarcoma
		Liposarcoma, not otherwise specified
FIBROBLASTIC/ MYOFIBRO-BLASTIC TUMOURS	**Benign**	Nodular fasciitis
		Proliferative fasciitis
		Proliferative myositis
		Myositis ossificans
		Fibro-osseous pseudotumour of digits
		Ischaemic fasciitis
		Elastofibroma
		Fibrous hamartoma of infancy
		Myofibroma/Myofibromatosis
		Fibromatosis colli
		Juvenile hyaline fibromatosis
		Inclusion body fibromatosis
		Fibroma of tendon sheath
		Desmoplastic fibroblastoma
		Mammary-type myofibroblastoma
		Calcifying aponeurotic fibroma
		Angiomyofibroblastoma
		Cellular angiofibroma
		Nuchal-type fibroma
		Gardner fibroma
		Calcifying fibrous tumour
		Giant cell angiofibroma

FIBROBLASTIC/ MYOFIBRO-BLASTIC TUMOURS (Continued)	**Intermediate (locally aggressive)**	Superficial fibromatoses (palmar/plantar)
		Desmoid-type fibromatoses
		Lipofibromatosis
	Intermediate (rarely metastasising)	Solitary fibrous tumour and haemangiopericytoma (incl. lipomatous haemangiopericytoma)
		Inflammatory myofibroblastic tumour
		Low grade myofibroblastic tumour
		Myxoinflammatory fibroblastic sarcoma
		Infantile fibrosarcoma
	Malignant	Adult fibrosarcoma
		Myxofibrosarcoma
		Low grade fibromyxoid sarcoma, hyalinising spindle cell tumour
		Sclerosing epithelioid fibrosarcoma
SO-CALLED FIBRO-HISTIOCYTIC TUMOURS	**Benign**	Giant cell tumour of tendon sheath
		Diffuse-type giant cell tumour
		Deep benign fibrous histiocytoma
	Intermediate (rarely metastasising)	Plexiform fibrohistiocytic tumour
		Giant cell tumour of soft tissues
	Malignant	Pleomorphic 'MFH'/ Undifferentiated pleomorphic sarcoma
		Giant cell 'MFH' / Undifferentiated pleomorphic sarcoma with giant cells
		Inflammatory 'MFH'/ Undifferentiated pleomorphic sarcoma with prominent inflammation
SMOOTH MUSCLE TUMOURS		Angioleiomyoma
		Deep leiomyoma
		Genital leiomyoma
		Leiomyosarcoma (excluding skin)
PERICYTIC (PERIVASCULAR) TUMOURS		Glomus tumour (and variants)
		Malignant glomus tumour
		Myopericytoma
SKELETAL MUSCLE TUMOURS	**Benign**	Rhabdomyoma Adult type Fetal type Genital type
	Malignant	Embryonal rhabdomyosarcoma (inclu. Spindle cell, botyroid, anaplastic)
		Alveolar rhabdomyosarcoma (incl. solid, anaplastic)
		Pleomorphic rhabdomyosarcoma

VASCULAR TUMOURS	**Benign**	Haemangiomas of subcut/deep soft tissue Capillary Cavernous Arteriovenous Venous Intramuscular Synovial
		Epithelioid haemangioma
		Angiomatosis
		Lymphangioma
	Intermediate (locally aggressive)	Kaposiform haemangioendothelioma
	Intermediate (rarely metastasizing)	Retiform haemangioendothelioma
		Papillary intralymphatic angioendothelioma
		Composite haemangioendothelioma
		Kaposi sarcoma
	Malignant	Epithelioid haemangioendothelioma
		Angiosarcoma of soft tissue
CHONDRO-OSSEOUS TUMOURS		Soft-tissue chondroma
		Mesenchymal chondrosarcoma
		Extraskeletal osteosarcoma
TUMOURS OF UNCERTAIN DIFFEREN-TIATION	**Benign**	Intramuscular myxoma (incl. cellular variant)
		Juxta-articular myxoma
		Deep ('aggressive') angiomyxoma
		Pleomorphic hyalinising angiectatic tumour
		Ectopic hamartomatous thymoma
	Intermediate (rarely metastasizing)	Angiomatoid fibrous histiocytoma
		Ossifying fibromyxoid tumour (incl. atypical/malignant)
		Mixed tumour /Myoepithelioma /Parachordoma
	Malignant	Synovial sarcoma
		Epithelioid sarcoma
		Alveolar soft part sarcoma
		Clear cell sarcoma of soft tissue
		Extraskeletal myxoid chondrosarcoma ("chordoid" type)
		PNET/ Extraskeletal Ewing tumour
		Desmoplasitc small round cell tumour
		Extra-renal rhabdoid tumour
		Malignant mesenchymoma
		Neoplasms with perivascular epithelioid cell differentiation (PEComa) Clear cell myomelanocytic tumour
		Intimal sarcoma

APPENDIX 2

Data fields extracted from clinical database

Data item	*Values*
Gender	Male Female
Age at surgery (years)	Continuous variable
Status at presentation	Primary tumour present, no metastases Local recurrence, no metastases Primary tumour present, metastases Local recurrence, metastases Metastases only
Unplanned excision	No Yes
Anatomical site (nearest joint)	Shoulder Elbow Wrist/hand Hip Knee Foot/ankle Pelvic girdle
Extremity	Upper Lower
Histological type	Malignant Fibrous Histiocytoma Synovial sarcoma Liposarcoma Angiosarcoma Clear cell sarcoma Epithelioid sarcoma Fibrosarcoma Hemangiopericytoma Leiomyosarcoma Malignant peripheral nerve sheath tumour Myxoid liposarcoma Pleomorphic liposarcoma Not otherwise specified Primitive neuroectodermal tumour/Ewings Rhabdomyosarcoma Alveolar soft parts sarcoma Chondrosarcoma Extraskeletal osteosarcoma Fibrosarcoma Dermatofibrosarcoma protuberans
Histological grade	1 (1 of 3 or 1 of 4) 2 (2 of 3 or 2 of 4) 3 (3 of 3, 3 and 4 of 4)
Maximum diameter	Value in centimetres
Depth	Superficial Deep
Age at surgery	Continuous variable

Type of procedure	Excision/ re-excision Hindquarter amputation/ hip disarticulation Above knee amputation Below knee amputation Forequarter amputation/ shoulder disarticulation Above elbow amputation Below elbow amputation Tissue transfer/ split thickness skin graft
Vascular reconstruction	No Yes
Surgical margin	Negative Microscopically positive Grossly positive
Chemotherapy given	No Yes
Radiotherapy given as part of definitive treatment	No Yes
Complications	None Wound Fracture Other
Treatment of complications	Not applicable Debridement Dressings Split thickness skin graft Flap No treatment Other
First relapse	None Local recurrence Systemic disease
Surgical treatment of first relapse	Not applicable No surgery Excision Thoracotomy Tissue transfer Amputation
Radiotherapy for first relapse	Not applicable None Radiotherapy given
Chemotherapy for first relapse	Not applicable None Chemotherapy given
Second relapse	None Local recurrence Systemic disease
Surgical treatment of second relapse	Not applicable No surgery Excision Thoracotomy Tissue transfer Amputation
Radiotherapy for second relapse	Not applicable None Radiotherapy given

Chemotherapy for second relapse	Not applicable None Chemotherapy given
Final status	Alive, no evidence of disease Alive with evidence of disease Died of disease Died of other causes
Disease free survival after surgery (months)	Continuous variable, to time of relapse if applicable
Overall survival after surgery (months)	Continuous variable

APPENDIX 3

Summary of lower extremity Musculoskeletal Tumour Society Functional Evaluation [38]

Score	*Pain*	*Function*	*Emotional Acceptance*	*Supports*	*Walking*	*Gait*
5	None	No restriction	Enthused	None	Unlimited	Normal
4			*Intermediate*			
3	Modest	Recreational restriction	Satisfied	Brace	Limited	Minor cosmetic
2			*Intermediate*			
1	Moderate	Partial disability	Accepts	One cane/crutch	Inside only	Major cosmetic, minor handicap
0	Severe	Total Disability	Dislikes	Two canes/crutches	Unable/unaided	Major handicap

Items are added and a percentage score calculated.

APPENDIX 4

Toronto Extremity Salvage Score Patient Questionnaire for the lower extremity

TESS-LOWER EXTREMITY

Please answer the following questions.

1A) Please state your current work status:

1_____ Employed full-time 4_____ Retired

2_____ Employed part-time 5 _____ Student

3_____ Unemployed 6_____ Disabled

1B) If you are employed, please describe your current job activities (examples: desk job; truck driver):

_____

1C) If you are retired, unemployed, or disabled, please describe your former job activities:

_____

_____

1D) If you are a student, please describe your area of study:

_____

_____

1E) If you are not working do you receive financial assistance such as insurance, sick benefits or a pension?

1_____ Yes 2 _____ No

2) Briefly describe your leisure or recreational activities (examples: sports, gardening, reading):

_____

_____

3A) Pain medication

1_____ none
2_____ NSAIDS e.g. anti-inflammatory drugs
3_____ non-narcotics e.g. paracetamol
4_____ narcotics e.g. morphine, dihydrocodeine, DF118

3B) Frequency of pain medication:

1 _____ not applicable i.e. no medication
2 _____ intermittent
3 _____ once a day
4 _____ twice a day
5 _____ 3 times a day
6 _____ 4 times a day
7 _____ more than 4 times a day

4) Describe the mobility or walking aid you use:

1 _____ No aid
2 _____ One cane or crutch
3 _____ Two canes
4 _____ Two crutches
5 _____ Walker
6 _____ Wheelchair
7 _____ Motorised wheelchair or scooter

5) List the factors that limit your ability to perform your everyday activities:

1 _____ pain
2 _____ stiffness
3 _____ fatigue
4 _____ weakness
5 _____ ROM
6 _____ other _____
7 _____ none

The following questions are about activities commonly performed in daily life. Mark each item (as in the example below) opposite the description that best describes your ability to perform each task during the **past week.** Some activities will be extremely easy for you to do, others will be extremely difficult or impossible.

EXAMPLE

Riding a bicycle is:

1 _____ impossible to do.
2 _____ extremely difficult.
3 _____ moderately difficult.
4 _____ a little bit difficult.
5 _____ not at all difficult.

99 ____ This task is not applicable for me.

You should choose the response "impossible to do ...." If the activity is **something that you normally do** in your daily activities but are **now unable to do** because of physical limitations such as weakness, stiffness or pain.

If you do not perform an activity as part of your normal lifestyle you would choose the response "99" to indicate that the item is not applicable.

Mark all items ensuring that you choose the description that most accurately describes your abilities in the **past week.**

The following questions ask about your ability to perform activities that are common to every day life. Considering the amount of difficulty you have performing the activity due to the current problem you are having with your leg, answer the questions by choosing the answer that best describes your ability to do the activity **over the past week.**

1) Putting on a pair of pants is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99_____ This task is not applicable for me.

2) Putting on shoes is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99_____ This task is not applicable for me.

3) Putting on socks or stockings is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99_____ This task is not applicable for me.

4) Showering is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99_____ This task is not applicable for me.

5) **Light household jobs such as tidying and dusting are:**

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99_____ This task is not applicable for me.

6) **Gardening and yard work are:**

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99_____ This task is not applicable for me.

7) **Preparing meals is:**

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99_____ This task is not applicable for me.

8) **Going shopping is:**

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

9) **Heavy household jobs such as vacuuming and moving furniture is:**

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

10) Getting in and out of the bath tub is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

11) Getting out of bed is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

12) Rising from a chair is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

13) Kneeling is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

14) Bending to pick something up off the floor is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

15) **Walking upstairs is:**

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

16) **Walking downstairs is:**

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

17) **Driving is:**

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

17) **Walking in the house is:**

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

19) **Walking outdoors is:**

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficuit.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

20A) Sitting is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

21) Walking up or down hills or a ramp is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99_____ This task is not applicable for me.

22) Standing is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99_____ This task is not applicable for me.

23) Getting up from kneeling is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

24) Getting in and out of a car is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

25) Participating in sexual activities is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

26) Completing my usual duties at work is: (Work includes both a job outside the home and as a homemaker.)

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

27) Working my usual number of hours is: (Working includes both a job outside the home and as a homemaker,)

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

28) Participating in my usual leisure activities is:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

29) Socialising with friends and family is:

1_____ impossible to do.

2_____ extremely difficult.

3_____ moderately difficult.

4_____ a little bit difficult.

5_____ not at all difficult.

99 _____ This task is not applicable for me.

30) Participating in my usual sporting activities is:

1_____ impossible to do.

2_____ extremely difficult.

3_____ moderately difficult.

4_____ a little bit difficult.

5_____ not at all difficult.

99 _____ This task is not applicable for me.

1) Considering all the activities in which I participate in daily life, I would rate the ability to perform these activities during the past week as:

1_____ impossible to do.
2_____ extremely difficult.
3_____ moderately difficult.
4_____ a little bit difficult.
5_____ not at all difficult.
99 _____ This task is not applicable for me.

2) I would rate myself as being:

1_____ Completely disabled.
2_____ Severely disabled.
3_____ Moderately disabled.
4_____ Mildly disabled.
5_____ Not at all disabled.
99 _____ This task is not applicable for me.

Please make any additional comments about difficulties you experience below.

_____
_____
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Please check to make sure that you have answered all the questions.

Thank you for taking the time to answer these questions.

APPENDIX 5. PUBLICATIONS AND PRESENTATIONS

The following published papers derive from the work in this thesis and are reproduced with permission:

Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence
Gerrand CH, Wunder JS, Kandel RA, O'Sullivan B, Catton CN, Bell RS, Griffin AM, Davis AM
Journal of Bone and Joint Surgery (Br) 2001. Nov; 83B(8):1149-55

The influence of anatomical location on outcome in extremity soft tissue sarcoma
Gerrand CH, Bell RS, Wunder JS, Kandel RA, O'Sullivan B, Catton CN, Griffin AM, Davis AM
Cancer. 2003. 97 (2): p485-492

The influence of anatomic location on functional outcome in lower extremity soft tissue sarcoma
Gerrand CH, Wunder JS, Kandel RA, O'Sullivan B, Catton CN, Bell RS, Griffin AM, Davis AM
Annals of Surgical Oncology, 2004 May; 11(5): 476-82. [Editorial comment, p453-454]

The studies in this thesis have been presented at the following scientific meetings:

Classification of positive margins after resection of extremity soft tissue sarcoma predicts the risk of local recurrence

- Connective Tissue Oncology Society, Amsterdam, November 2000

The influence of anatomical location on outcome in extremity soft tissue sarcoma

- British Orthopaedic Association, Birmingham, September 2001
- International Symposium on Limb Salvage, Birmingham, October 2001
- Connective Tissue Oncology Society, Palm Beach (as poster), November 2001

Anatomical influences on functional outcome in lower extremity soft tissue sarcoma

- European Musculoskeletal Oncology Society, Budapest, March 2003
- British Orthopaedic Oncology Society, Stratford-Upon-Avon, June 2003

The anatomical basis of sarcoma surgery

- British Institute of Radiology, November 2003
- North East Plastic Surgery Annual Meeting, March 2004

Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence

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We considered whether a positive margin occurring after resection of a soft-tissue sarcoma of a limb would affect the incidence of local recurrence. Patients with low-grade liposarcomas were expected to be a low-risk group as were those who had positive margins planned before surgery to preserve critical structures. Two groups, however, were expected to be at a higher risk, namely, patients who had undergone unplanned excision elsewhere with a positive margin on re-excision and those with unplanned positive margins occurring during primary resection.

Of 566 patients in a prospective database, 87 with positive margins after limb-sparing surgery and adjuvant radiotherapy were grouped according to the clinical scenario by an observer blinded to the outcome. The rate of local recurrence differed significantly between the two low- (4.2% and 3.6%) and the two high-risk groups (31.6% and 37.5%). This classification therefore provides useful information about the incidence of local recurrence after positive-margin resection.

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After resection of a soft-tissue sarcoma the status of the surgical margin predicts the risk of local recurrence.[1-6] Enneking et al[6] described the margin as intralesional when resection was carried out within the (pseudo) capsule of the tumour, marginal when the tumour was shelled out within the surrounding reactive zone, wide when the resection passed through normal tissue outside the reactive zone but within the anatomical compartment which was involved, and radical when the entire compartment was resected. The rate of local recurrence was 50% after marginal, 25% after wide and 4% after radical excision.

Rydholm and Rooser[7] considered an intact muscle to be a distinct anatomical compartment and subclassified wide margins as wide-S (subcutaneous) when a subcutaneous tumour was excised with a cuff of subcutaneous tissue and deep fascia, wide-F (fascia) when a deep tumour was excised with an intact envelope of uninvolved fascia and wide-AM (areolar tissue and muscle) when a deep tumour was excised with a wide margin, some or all of which comprised muscle or areolar tissue. The five-year rate of local recurrence was 10% with wide-S and wide-F margins and 30% with a wide-AM margin.

Kawaguchi, Matumoto and Manabe[8] suggested a classification which abandoned the use of compartmental anatomy to describe the resection. Margins were classified as curative, adequate or inadequate depending on the width and quality of the tissue comprising the margin. Inadequate wide margins did not ensure local control even with adjuvant radiotherapy in high-grade sarcomas, but were sufficient for low-grade tumours.

Since the development of management which combines limb-sparing surgery and adjuvant treatment, the description of surgical margins as simply positive or negative has become more common.[1-5,9-11] A positive surgical margin in which there is tumour at the resection margin, implies that there is residual disease and is associated with an increased risk of local recurrence.[1-5] In this situation, the volume and biological activity of residual disease are presumably critical to the risk of recurrence. While recognising that a positive surgical margin may occur under different circumstances, we have examined how these may influence the risk of recurrence.

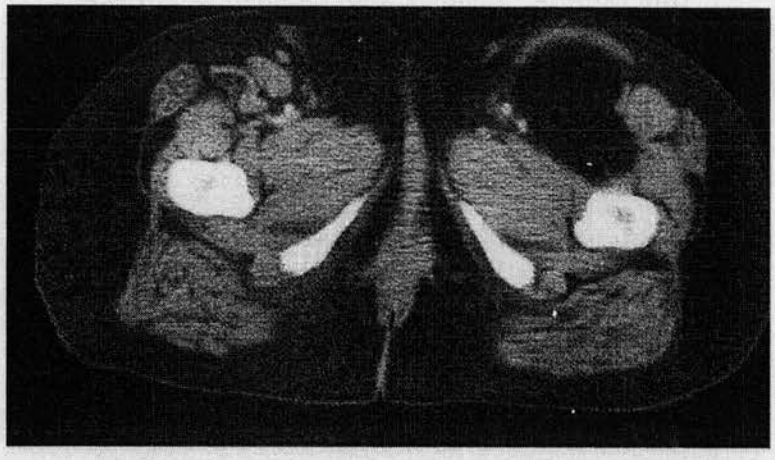

Fig. 1

Axial CT scan showing a homogeneous fat lesion in the proximal thigh which was treated by excision with positive margins. The final histological findings confirmed it to be low-grade liposarcoma.

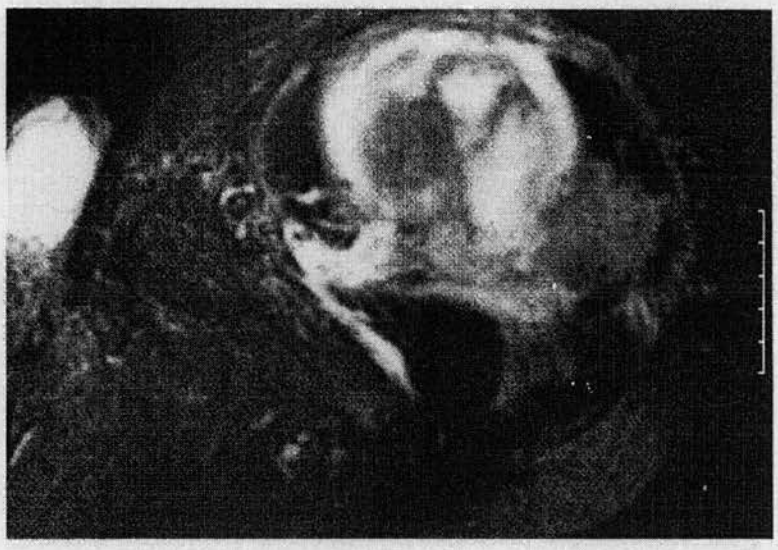

Fig. 2

T2-weighted axial MR image showing a myxoid liposarcoma in the proximal thigh which was excised with a planned positive margin along the femoral artery.

Patients and Methods

We agreed a classification of four mutually exclusive clinical groups representing the clinical scenario in which a positive surgical margin may occur after limb-sparing surgery for sarcoma of a limb. A positive margin was defined as the presence of tumour at the margin of resection or intraoperative exposure of the tumour, even if the margin was subsequently revised to 'negative'. We defined margins as grossly positive when the surgeon or the pathologist could identify tumour at the margin of resection. A microscopic positive margin occurred when inspection of the margin did not reveal tumour, which was identified at histological examination.

Low-grade liposarcomas (group 1). The first group included all patients with a low-grade, well-differentiated liposarcoma. In our experience, and that of others, low-grade liposarcoma arising in the limb seldom recurs locally after treatment and rarely metastasises.[12,13] These lesions are often extensive at the time of presentation and adjacent to critical structures such as nerves, vessels or bones. In this situation we frequently accept microscopically positive margins after resection to preserve critical structures. A positive margin in this situation reflects this treatment philosophy of deliberate marginal excision (Fig. 1).

Planned positive margins against critical structures (group 2). This group included patients who had positive surgical margins against one or more critical structures

(nerve, vessel or bone) which had been planned preoperatively as part of a primary resection. The decision to accept a positive margin was made in advance at a multidisciplinary team conference and confirmed at the time of resection by the surgeon and pathologist (Fig. 2).

Positive margin during re-excision after prior unplanned excision (group 3). Patients in this group had undergone unplanned excision of a sarcoma at another institution before referral, and subsequent re-excision at our centre with a positive surgical margin. An unplanned excision was defined as an excisional biopsy or resection carried out without adequate preoperative staging or consideration of the need to remove normal tissue around the tumour.[14] The extent and adequacy of the unplanned excision were assessed in discussion with the original surgeon and by review of the initial pathology report, the initial operative note, and imaging studies undertaken before re-excision in our centre. Further excision was done if there was gross residual tumour on clinical examination or imaging, or if the resection had been inadequate.

Unplanned positive margins (group 4). In this group, during primary resection in our centre, a positive margin occurred which had not been planned (Fig. 3). This usually followed an error in assessing the extent of the primary lesion despite review of the imaging of the local site. If the positive margin was recognised during or immediately after surgery, further tissue was excised if this did not compromise critical structures. If the positive margin was recognised after definitive histological evaluation, a further wide excision was always considered. No patients had grossly evident tumour left in the wound at the completion of surgery.

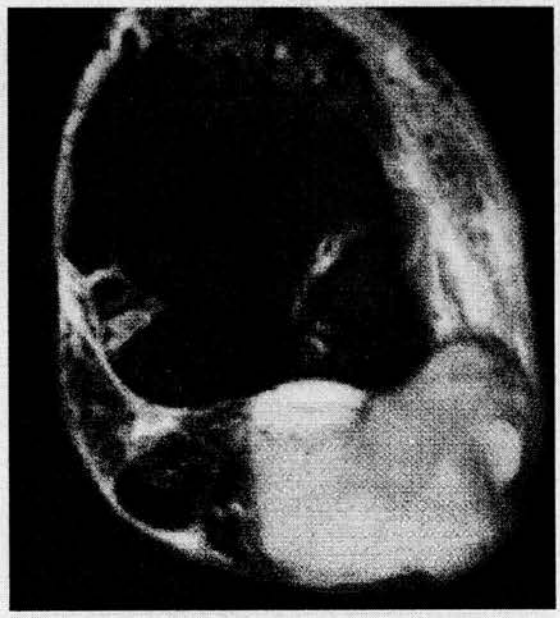

Fig. 3

T2-weighted axial MR image showing a myxoid liposarcoma in relation to the lateral aspect of the ankle, with considerable subcutaneous oedema. The anterior resection margin was positive in the subcutaneous tissues.

It was considered that groups 1 and 2 would be at low risk of local recurrence and that groups 3 and 4 would be at higher risk. To test this hypothesis, a prospectively collected database containing all patients undergoing surgery for soft-tissue sarcoma in our centre was used to identify suitable patients. The inclusion criteria were: 1) a diagnosis of sarcoma other than dermatofibrosarcoma protruberans; 2) location in a limb; 3) the undertaking of limb-sparing surgery with curative intent; 4) a positive surgical margin; and 5) the administration of neoadjuvant radiotherapy. All patients underwent surgery between January 1986 and April 1997 to allow a minimum follow-up period of three years.

Patients who received chemotherapy because of histological type or metastatic disease were excluded. Our standard protocol of adjuvant external-beam radiotherapy comprises either 50 Gy preoperatively, with a postoperative boost of 16 Gy if there is a positive margin, or 66 Gy postoperatively by a reducing-field technique.

The following data were extracted from the prospective database and verified against the clinical records: age at surgery, gender, presentation with a primary tumour or local recurrence, open or needle biopsy, histological type, grade, anatomical location (deep or superficial, extra- or intracompartmental), maximum diameter of the tumour, the presence of lung metastases at presentation (all patients were staged by chest CT) and grossly or microscopically positive margins. The further management of positive margins was assessed from the clinical records. A pathologist with expertise in sarcoma determined the histological type and graded the tumours as 1, 2 or 3.[15]

A reviewer (CHG), blinded to the clinical outcome, assigned each case to one of the four groups. All low-grade liposarcomas were assigned to group 1 and all patients who had had an unplanned excision before referral were assigned to group 3, regardless of further management. After the initial classification, the surgeons who undertook the operations reviewed the classification of each tumour to ensure a consensus. The number and timing of local recurrences were reviewed. Local recurrence was defined as the reappearance of the tumour, proven by biopsy, adjacent to or within the previously treated field at any time after treatment in our centre.

Statistical analysis. We consider that low-grade liposarcomas (group 1) differ in their biological behaviour and management from tumours of other histological types and therefore they were analysed separately. The remainder (groups 2 to 4) were compared for differences in the local recurrence-free rate and the disease-specific survival as well as variables which may account for differences in these outcomes.

Continuous variables were compared using one-way analysis of variance (ANOVA) and the Tukey *post-hoc* test. Differences in proportions were compared using the chi-

squared test. Curves for the local recurrence-free rate and disease-specific survival were constructed using the method of Kaplan and Meier and compared using the log-rank statistic. A p value of 0.05 or below was considered to be significant. Data were analysed using the SPSS version 10.0.5 (SPSS Inc, Chicago, Illinois).

Results

Between January 1986 and April 1997, 566 patients had been entered on the database, 112 of whom had positive surgical margins. We excluded 25 patients as follows: 12 who did not receive standard radiotherapy, seven who received chemotherapy, four with advanced metastatic disease who underwent palliative procedures, one with a positive margin after primary amputation and one who had exploration of an extensive sarcoma in the foot and was secondarily treated by amputation.

The remaining 87 patients, 42 men and 45 women, had a mean age of 60 years (21 to 95). A total of 24 patients died from metastatic disease at a mean of 1.8 years (0.3 to 6.6), and eight from unrelated causes at a mean of 2.1 years (0.2 to 7.7). The mean follow-up of the 55 surviving patients was 5.4 years (3.0 to 9.5).

The 24 patients with low-grade liposarcomas were placed in group 1. None had grossly positive margins. There was one local recurrence (4.2%, 95% CI 0 to 12.2) at four months, which was re-excised. All patients were alive and free from disease at a mean follow-up of 5.1 years (3.2 to 9.3).

Of the remaining patients, 28 were placed in group 2, 19 in group 3 and 16 in group 4 (Table I). When these groups were compared, group-3 tumours were significantly smaller than group-4 ($p = 0.04$), and group-4 tumours were smaller than group-2 ($p = 0.02$). There were more tumours in the proximal limb in group 2 than in group 3 (79% *v* 42%,

Table I. Details of the 87 patients who had resection of soft-tissue sarcoma of a limb

	Group*			
	1	2	3	4
Number of patients	24	28	19	16
Number of local recurrences (%)	1 (*4.2*)	1 (*3.6*)	6 (*31.6*)	6 (*37.5*)
Mean time to local recurrence (months)	4	2	35	25
Mean age (years)	54.8	62.5	66.7	57.5
Proportion male (%)	*54*	*54*	*37*	*44*
Presentation with local recurrence	4	3	2	1
Open biopsy	5	11	19	9
Grade of tumour				
1	24	1	–	2
2	–	8	9	6
3	–	19	10	8
Type of positive margin				
Microscopically positive	24	25	17	12
Grossly positive	0	3	2	4
Mean maximum diameter (cm)	14.4	14.7	4.8	9.6
Histological type				
MFH†	–	13	8	6
Liposarcoma	24	8	6	3
Other	–	7	5	7
Location				
Upper limb	6	6	5	6
Lower limb	18	22	14	10
Proximal limb	19	22	8	7
Distal limb	5	6	11	9
Superficial	–	–	2	–
Deep	24	28	17	16
Intracompartmental	10	6	1	3
Extracompartmental	14	22	18	13
Mean follow-up of surviving patients (years)	5.1	5.2	6.3	5.6
Presentation with metastases	–	1	–	1
Final status				
Alive, without disease	24	10	9	8
Alive with disease	–	2	1	1
Died from disease	–	11	6	7
Died from other causes	–	5	3	–

* see text

† malignant fibrous histiocytoma

$p = 0.01$) and group 4 (44%, $p = 0.02$). Groups 2, 3 and 4 did not differ significantly in regard to age, gender, local recurrence at presentation, grade and length of follow-up. There was no difference in the distribution of histological types across those groups, and no significant difference between the groups when deep and superficial, intra- and extracompartmental, and upper- and lower-limb tumours were compared.

In group 2, one of 28 patients developed a local recurrence (3.6%, 95% CI 0 to 10.4) at two months. This case was one of the 25 with microscopically positive margins. There were no local recurrences in the three patients with grossly positive margins. Twelve patients were alive at a mean of 5.2 years (3.0 to 7.4), 11 died from metastatic disease at a mean of 1.6 years (0.3 to 2.8) and five from other causes at a mean of 1.6 years (0.2 to 4.7).

In group 3, there were six local recurrences (31.6%, 95% CI 10.7 to 52.5). The mean time to local recurrence was 34.5 months (2.7 to 82.0). Clinical examination or imaging before re-excision identified 11 patients with a residual tumour mass. In five of these the positive margins were planned against critical structures adjacent to the residual mass and one had a further local recurrence. In comparison, an unplanned positive margin occurred during resection of the other six of the 11 patients with a residual tumour mass, and three of these had a local recurrence. In the eight patients without a residual tumour there were two local recurrences. Of all 19 patients, two had grossly positive margins and both had local recurrences, compared with four local recurrences in 17 patients with microscopically positive margins. In four patients, the positive margin was recognised intraoperatively, and the margin revised; two of these had a local recurrence. In two patients, the positive margin was recognised intraoperatively, but the margin could not be revised with acceptable morbidity. Neither of these developed a local recurrence. In 13 patients, the positive margin was recognised after histological examination; four of these developed a local recurrence. Of all 19 patients, ten were alive at a mean of 6.3 years (3.5 to 9.4), six died from metastatic disease at a mean of 1.7 years (0.7 to 3.2) and three died from other causes at a mean of 3.1 years (0.7 to 7.7).

In group 4, there were six local recurrences in 16 patients (37.5%, 95% CI 13.8 to 61.2). The mean time to the development of local recurrence was 24.9 months (5.9 to 68.1). One of four patients with grossly positive margins and five of 12 with microscopically positive margins developed a local recurrence. In nine patients, the positive margin was recognised intraoperatively, and the margin revised. Four of these developed a local recurrence. In three patients the positive margin was recognised intraoperatively, but the margin could not be revised with acceptable morbidity and none developed a local recurrence. In four patients, the positive margin was recognised after histological examination; three of these had no further surgery but two developed a local recurrence. In the fourth case, a second wide excision was carried out and there has not been local recurrence. Of the 16 patients in group 4, nine were alive at a mean of 5.6 years (3.0 to 8.9) and seven died from metastatic disease at a mean of 2.0 years (0.3 to 6.6).

The crude local recurrence rate in group 2 was significantly lower than that in group 3 ($p = 0.03$) and group 4 ($p = 0.01$), but that of group 3 and group 4 was not significantly different. The local recurrence-free survival was significantly different between groups 2 and 3 ($p = 0.01$) and groups 2 and 4 ($p = 0.02$), but not between groups 3 and 4 ($p = 0.64$; Fig. 4). The disease-specific survival in groups 2, 3 and 4 did not differ significantly ($p = 0.74$; Fig. 5).

Discussion

Our study shows that the significance of a positive surgical margin after resection of a soft-tissue sarcoma in a limb is determined by the clinical scenario, and that classifying patients into groups may predict the risk of the development of local recurrence. Low-grade liposarcomas are biologically different, with a low risk of local recurrence despite marginal excision. Planned positive margins during primary resection (with adjuvant radiotherapy) are associated with a low risk of local recurrence. Positive margins following unplanned excision before referral as well as unplanned positive margins are associated with a higher risk of local recurrence.

Positive margins are more likely after limb-sparing procedures, although amputation does not guarantee negative margins.[1,9] Trovik et al[16] reported that positive margins were more common in patients over 50 years of age, with either low-grade tumours, tumours the diameter of which was more than 7 cm, deep tumours or tumours involving the trunk. After excision of soft-tissue sarcomas of the trunk or limb the reported rates of positive margins vary from 1%[17] to 26%.[3] In a review of patients treated by an experienced multidisciplinary sarcoma group in Toronto, Wilson et al[18] reported nine positive margins in 62 patients, a rate of 14.5%. The higher rate of positive margins after resection of low-grade liposarcomas in our database (27 of 49 patients, 55%) reflects a management philosophy which accepts deliberate marginal excision in many patients. Our study confirms that this approach, when combined with adjuvant radiotherapy, is associated with a low rate of local recurrence at the medium-term follow-up. Our rate of positive margins for other histological types (85 of 518 patients, 16%) is within the range which has previously been described.

When a soft-tissue sarcoma is adjacent to critical structures, the multidisciplinary team has to weigh the benefits of wider excision against the morbidity. The low rate of local recurrence after a planned positive margin in this situation demonstrates that this is a safe approach for many tumours. The experience of the multidisciplinary team is

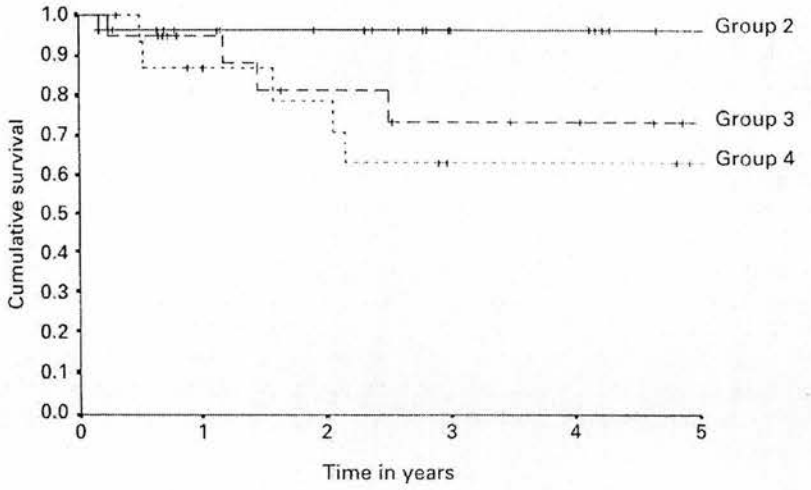

Fig. 4

Kaplan-Meier survival analysis for the rate of local recurrence. The upright marks represent censored cases.

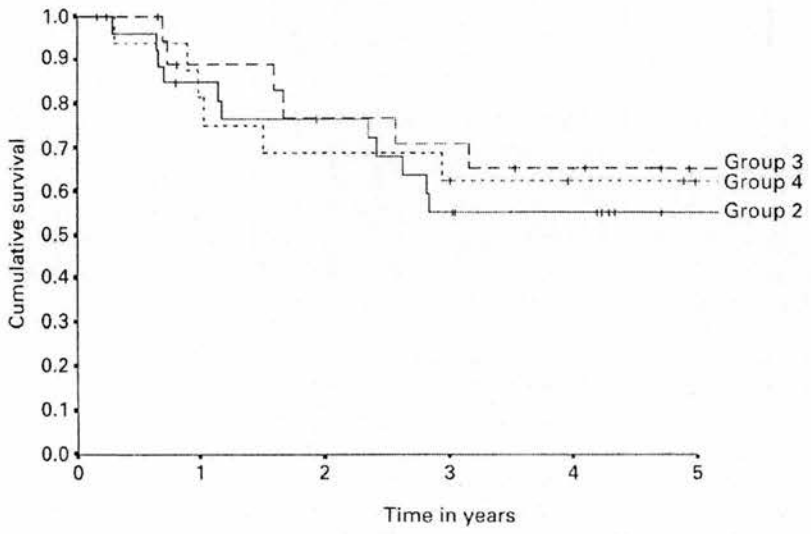

Fig. 5

Kaplan-Meier survival analysis for disease-specific survival. The upright marks represent censored cases.

critical in making the decision to approach treatment in this way and may contribute to better outcomes in specialised centres.

It is our practice to offer re-excision to all patients who have undergone an unplanned excision unless the margins can be reliably assessed as adequate.[19] If after unplanned excision there is a residual mass which lies adjacent to critical anatomical structures, a positive margin may be planned. If there is no residual mass, the extent of contamination by tumour cannot be accurately defined and re-excision has to be planned based on an estimate of the area at risk and the associated morbidity. A positive margin under these circumstances not only means that there is residual tumour, which may lead to local recurrence, but that the area involved with tumour has been underestimated.[14]

The exposure of tumour during primary resection because of surgical error is associated with a high risk of local recurrence.[20] There was one local recurrence in four such cases in group 4. Of 16 patients in whom an unplanned positive margin occurred, 12 had microscopically positive margins and five developed local recurrence, suggesting that microscopically positive margins are also associated with a high risk of local failure.

Our study was not designed to assess the effect of revision of a positive margin. In patients who were not able to undergo revision of the positive margin because of local anatomical constraints, there were no local recurrences. It may be that a positive margin against a structure such as muscle, which is readily revised, is associated with more residual disease than a positive margin against a critical structure such as bone, nerve or vessel, which may not readily be resected and which may be more resistant to invasion by tumour.

The experience which we have gained while treating this group of patients was used to generate hypotheses tested on the same group and this study thus remains exploratory. A prospective study on a different group of patients is

required to confirm the value of this classification. Classifying patients who have a positive resection margin in this way may provide useful information with regard to the development of local recurrence.

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No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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The Influence of Anatomic Location on Outcome in Patients with Soft Tissue Sarcoma of the Extremity

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BACKGROUND. The anatomic location of an extremity soft tissue sarcoma may influence the patient's presentation, management, and local and systemic recurrence rates. The objective of this study was to compare the presentation, management, and outcome of patients with soft tissue sarcomas of the upper extremity and the lower extremity.

METHODS. Prospectively collected data from patients who underwent limb-sparing surgery for extremity soft tissue sarcoma between January, 1986 and April, 1997 were analyzed. Local recurrence free rates and metastasis free rates were calculated using the method of Kaplan and Meier. Univariate and multivariate analyses of potential predictive factors were evaluated with the log-rank test and the Cox proportional hazards model.

RESULTS. Of 480 eligible patients, 48 patients (10.0%) had a local recurrence, and 131 patients (27.3%) developed distant metastasis. The median follow-up of survivors was 4.8 years (range, 0.1–12.9 years). Patients with upper extremity tumors had smaller lesions (6.0 cm vs. 9.3 cm; $P < 0.001$), more often underwent unplanned excision before referral (89 patients [64.0%] vs. 160 patients [46.9%]; $P < 0.001$), and less often received radiotherapy (98 patients [70.5%] vs. 289 patients [84.8%]; $P < 0.001$). The 5-year local recurrence free rate was 82% for patients with sarcomas of the upper extremity and 93% for patients with sarcomas of the lower extremity ($P = 0.002$). The 5-year metastasis free rate was 82% for patients with sarcomas of the upper extremity and 69% for patients with sarcomas of the lower extremity ($P = 0.013$).

CONCLUSIONS. Local recurrence was more frequent in patients who had sarcomas of the upper extremity compared with patients who had sarcomas of the lower extremity. Factors that contributed to this difference included histologic type, the use of radiotherapy, and local anatomy. Metastasis was more frequent among patients with sarcomas of the lower extremity, because those tumors tended to be large and deeper compared with upper extremity tumors. ***Cancer* 2003;97:485–92.**

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KEYWORDS: sarcoma, neoplasm, local recurrence, metastasis, surgical procedures, operative.

Factors known to influence local recurrence after treatment of an extremity soft tissue sarcoma include a positive surgical margin, presentation with a local recurrence, and age > 50 years.[1–3] The development of metastasis is associated with large, high-grade, deep tumors.[4–8] However, because tumor size, the width and quality of the surgical margin, and the use of adjuvant radiotherapy all may vary with anatomic location,[9] the site of a tumor may be an important determinant of oncologic outcome. A comparison of extremity and retroperitoneal soft tissue sarcomas illustrates this point. Compared

with extremity tumors, retroperitoneal soft tissue sarcomas tend to be large at presentation, difficult to excise with a wide margin, and difficult to irradiate because of adjacent vital structures. Proximity to vital structures also means that retroperitoneal sarcomas more often cause death by local recurrence, whereas extremity sarcomas are fatal through the development of pulmonary metastases.[10]

Clearly, there is wide variation in both the anatomic location of a soft tissue sarcoma and in the anatomy of the upper and lower extremities. The question of how this anatomic variation influences patient presentation, treatment, and outcome has not been addressed directly in the literature. However, some differences have been reported. Lower extremity tumors are more common,[11–15] larger,[9] and more likely to lead to metastasis[4,9,16] compared with tumors of the upper extremity. Conversely, patients with upper extremity tumors are more likely to have undergone unplanned excision before referral.[12,17] The purpose of this study was to determine whether there were differences in the presentation and management of patients upper extremity soft tissue sarcomas and lower extremity soft tissue sarcomas among our patient population and, subsequently, whether there were differences in the local recurrence free rate and the metastasis free rate.

MATERIALS AND METHODS

Since January, 1986, a record of all patients who underwent surgery in our center for an extremity soft tissue sarcoma has been kept in a password-protected, computerized data base. Data are collected prospectively in outpatient clinics and at a weekly multidisciplinary meeting. This data base was used to identify and retrieve information about patients who had an extremity soft tissue sarcoma and underwent limb-sparing surgery between January 1986 and April 1997 and, thus, had the potential for a minimum follow-up of 3 years. The upper extremity was defined as commencing at the medial border of the scapula, including the pectoral, periscapular, and latissimus dorsi muscles. The lower extremity was defined as commencing at the iliac crest. Patients with metastatic disease at the time of presentation or with the histologic types dermatofibrosarcoma protruberans, primitive neuroectodermal tumor, or rhabdomyosarcoma were excluded.

The following information was extracted from the data base: age at surgery, gender, unplanned excision before referral, presentation with a local recurrence, greatest tumor dimension (in centimeters), histologic type and grade, surgical margin status, adjuvant radiotherapy or chemotherapy, local recurrence, time to local recurrence after surgery, systemic recurrence, and time to systemic recurrence after surgery. An unplanned excision was defined as an excisional biopsy or unplanned resection that was performed without adequate preoperative staging or consideration of the need to remove normal tissue around the tumor.[18] A pathologist with an expertise in sarcoma determined the histologic type and graded tumors as 1, 2 or 3.[19] The status of the surgical margin was recorded as positive if the pathologist had identified tumor, viable or not, at the inked resection margin or if there had been intraoperative exposure of tumor. A local recurrence was defined as tumor within or at the edge of the previously treated field at any time after treatment. Metastatic disease was defined as tumor identified on chest X-ray or computed tomography scan during follow-up or the development of lymphadenopathy containing tumor. Wherever possible, after multidisciplinary discussion, patients were offered limb-sparing surgery. Amputation was performed when limb-sparing surgery would not have adequately resected the tumor or would have resulted in a limb without useful function. Adjuvant radiotherapy was given to patients with high-grade tumors who underwent resection with less than wide surgical margins or patients with low-grade tumors who underwent deliberately marginal surgical excision.

The following data relating to anatomic location were retrieved: extremity, location within the extremity, and depth. Location within the extremity was recorded in relation to the closest major joint as the shoulder, elbow, wrist/hand, hip, knee, and foot/ankle. Tumors above and that did not involve the investing fascia of the limb were considered superficial, and other tumors were considered deep.

Data were used first to define the characteristics of the whole group and the anatomic distribution of tumors. Next, differences in presenting features, tumor characteristics, and treatment between the extremities were determined. The local recurrence free rate in the extremities was compared using the methods of Kaplan and Meier and the log-rank statistic. Then, the Cox proportional hazards model was used to investigate first whether greatest tumor dimension was predictive of time to local recurrence and then whether surgical margin status, extremity, and unplanned excision before referral were predictive of time to local recurrence. Thereafter, exploratory analyses examined the influence of unplanned excision before referral, surgical margin status, and radiotherapy on the rate of local recurrence. The metastasis free rate was compared using the methods of Kaplan and Meier and the log-rank statistic. The Cox proportional hazards model was used to investigate whether histo-

logic grade, greatest tumor dimension, depth, and extremity were predictive of time to metastasis.

Differences in the mean values between groups were compared using one-way analyses of variance and the Tukey post-hoc test. Differences in proportions were compared using the Pearson chi-square test. When constructing Kaplan–Meier curves and in the Cox proportional hazards model, patients were censored at the time of last follow-up or death. In the Cox proportional hazards model, the hazard ratio for each covariate was plotted to ensure proportionality over time. Throughout, results with a P value < 0.05 were considered significant. Analyses were performed using SPSS software for Windows (release 10.0.5; SPSS Inc., Chicago, IL).

RESULTS

Five hundred sixty-six patients were entered into the data base between January 1986 and April 1997. There were 6 primary amputations in 168 patients with upper extremity tumors (3.6%) and 22 primary amputations in 398 patients with lower extremity tumors (5.5%). Another 58 patients were excluded: 34 patients who presented with metastatic disease, 12 patients who presented with a diagnosis of dermatofibrosarcoma protruberans, 7 patients who presented with primitive neuroectodermal tumors, and 5 patients who presented with rhabdomyosarcoma. Four hundred eighty patients remained in the study.

Characteristics of the Whole Group

There were 261 men (54.4%) and 219 women (45.6%) with a median age of 56 years (range, 15–96 years). Malignant fibrous histiocytoma (163 patients; 34.0%) and liposarcoma (107 patients; 22.3%) were the most common histologic types. Tumors were Grade 1 in 83 patients (17.3%), Grade 2 in 172 patients (35.8%), and Grade 3 in 225 patients (46.9%).

Forty-eight patients (10.0%) developed a local recurrence at a median of 1.4 years (range, 0.1–9.2 years). No patients died of local recurrence. One hundred thirty-one patients (27.3%) developed metastases at a median of 1.0 years (range, 0.1–12.8 years), and 86 of those 131 patients died of metastatic disease at a median of 1.5 years (range, 0.1–6.8 years). Nineteen patients died from causes other than metastatic disease at a median of 1.0 years (range, 0.0–7.7 years). Three of those 19 patients died in the immediate postoperative period after developing a pulmonary embolus. The median follow-up for the 375 surviving patients was 4.8 years (range, 0.1–12.9 years).

TABLE 1
Summary of Results by Extremity

Characteristic	Upper extremity	Lower extremity
No. of patients	139	341
Age at Surgery (yrs)		
Median	54	56
Range	17–86	15–96
Proportion of males (%)	84 (60.4)	177 (51.9%)
Greatest tumor dimension (cm)		
Mean	6.0	9.3
Range	1.0–26.0	1.0–40.0
Deep to or involving investing fascia	97 (69.8)	280 (82.1)
Histologic grade (%)		
1	30 (21.6)	53 (15.5)
2	44 (31.7)	128 (37.5)
3	65 (46.8)	160 (46.9)
Unplanned excision before referral (%)	89 (64.0)	160 (46.9)
Presentation with a local recurrence (%)	18 (12.9)	38 (11.1)
Positive surgical margins (%)	28 (20.1)	71 (20.8)
Adjuvant radiotherapy (%)	98 (70.5)	289 (84.8)
Follow-up of survivors (yrs)		
Median	4.9	4.7
Range	0.1–11.1	0.2–12.9
No. of patients with local recurrence	23	25
Time to local recurrence (yrs)		
Median	1.3	1.6
Range	0.2–9.2	0.1–6.6
Local recurrence free rate at 5 years (%)	82	93
No. of patients developing metastases	26	105
Time to metastasis (yrs)		
Median	1.0	1.0
Range	0.1–6.7	0.1–12.8
Metastasis free rate at 5 yrs (%)	82	69

Anatomic Distribution

There were 139 tumors (29.0%) of the upper extremity and 341 tumors (71.0%) of the lower extremity (Table 1). Seventy-four tumors (15.4%) were located around the shoulder, 41 tumors (8.5%) were located in the elbow, 24 tumors (5.0%) were located in the hand or wrist, 154 tumors (32.1%) were located in the hip, 148 tumors (30.8%) were located in the knee, and 39 tumors (8.1%) were located in the ankle or foot (Table 2). Three hundred seventy-seven tumors (78.5%) were deep to or involved the investing fascia of the extremity.

Differences between the Extremities

Presenting features

Patients with tumors of the upper extremity more often underwent unplanned excision before referral compared with patients who had tumors of the lower extremity (89 patients [64.0%] vs. 160 patients [46.9%]; $P < 0.001$). The proportion of patients presenting with a local recurrence was similar in each extremity (18 patients in the upper extremity [12.9%] vs. 38 patients in the lower extremity [11.1%]; $P = 0.576$).

TABLE 2
Summary of Results by Location Within Each Extremity

Location	No. of patients	Mean greatest tumor dimension (cm)	Unplanned excision before referral	Positive surgical margins	Adjuvant radiotherapy given	Local recurrences	No. of developing metastases
Shoulder	74	6.5	47	7	45	13	19
Elbow	41	6.3	26	16	34	5	6
Wrist/hand	24	3.9	16	5	19	5	1
Hip	154	10.6	65	28	125	11	45
Knee	148	9.0	73	35	128	10	49
Ankle/foot	39	5.3	22	8	36	4	11
Whole group	480	8.3	249	99	387	48	131

TABLE 3
Distribution of Histologic Types by Extremity

	Upper extremity			Lower extremity		
Histological type	No.	Percentage within extremity	Local recurrences	No.	Percentage within extremity	Local recurrences
Malignant fibrous histiocytoma	56	40.3	7	107	31.4	12
Liposarcoma, otherwise undesignated	21	15.1	3	86	25.2	6
Synovial sarcoma	14	10.1	0	18	5.3	1
Malignant peripheral nerve sheath tumor	10	7.2	3	22	6.5	2
Leiomyosarcoma	10	7.2	2	27	7.9	3
Fibrosarcoma	9	6.5	3	11	3.2	0
Epithelioid sarcoma	4	2.9	2	3	0.9	0
Angiosarcoma	2	1.4	1	3	0.9	0
Myxoid liposarcoma	1	0.7	0	29	8.5	1
Other	12	8.6	2	35	10.3	0
Total	139	100	23	341	100	25

Tumor characteristics

Upper extremity tumors were significantly smaller compared with lower extremity tumors (6.0 cm vs. 9.3 cm; $P < 0.001$) and less often were deep to or involved the investing fascia (97 patients [69.8%] vs. 280 patients [82.1%]; $P = 0.003$) (Table 1). The mean tumor dimension decreased from proximal to distal in both extremities (Table 2). There was a relative excess of synovial sarcomas, epithelioid sarcomas, and fibrosarcomas in upper extremity sites and of liposarcomas and myxoid liposarcomas in lower extremity sites (Table 3). Histologic grade did not differ significantly between upper extremities and lower extremities ($P = 0.219$) (Table 1).

Treatment factors

The proportion of patients with positive surgical margins did not differ significantly between the upper extremities and the lower extremities (28 patients [20.1%] vs. 71 patients [20.8%]; $P = 0.868$). However, within the group of patients with upper extremity tumors, positive surgical margins were more frequent around the elbow (16 of 41 patients; 39.0%) compared with the wrist and hand (5 of 24 patients; 20.8%) or the shoulder (7 of 74 patients; 9.5%; $P = 0.001$).

Overall, radiotherapy was given less often to patients with tumors of the upper extremity compared with its frequency among patients with tumors of the lower extremity (98 patients [70.5%] vs. 289 patients [84.8%]; $P < 0.001$). This was because patients with tumors around the shoulder were not treated with adjuvant radiotherapy (45 of 74 patients; 60.8%) as often as patients with tumors around the elbow (34 of 41 patients; 82.9%) or the wrist (19 of 24 patients; 79.2%; $P = 0.048$) (Table 2). The proportion of patients who received adjuvant chemotherapy did not differ significantly between those with tumors of the upper extremity or the lower extremity (2 of 139 patients [1.4%] vs. 8 of 341 patients [2.3%]; $P = 0.528$).

Follow-Up

The median follow-up for survivors was 4.9 years (range, 0.1–11.1 years) among patients with tumors of the upper extremity and 4.7 years (range, 0.2–12.9

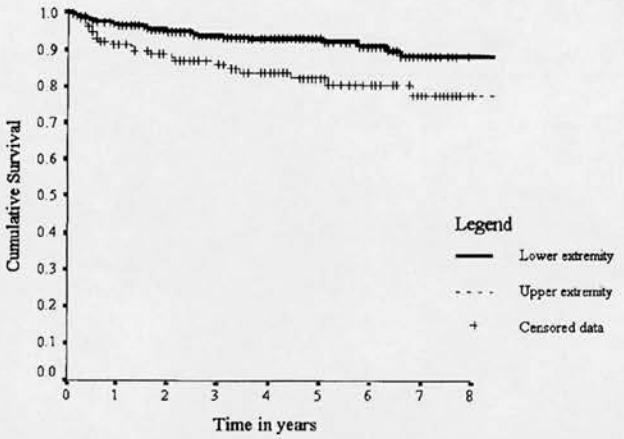

FIGURE 1. Kaplan–Meier curve for the local recurrence free rate. Tick marks represent censored patients.

years) among patients with tumors of the lower extremity.

Local recurrence

There were 23 patients (n = 139 tumors) who developed local recurrences in the upper extremity and 25 patients (n = 341 tumors) who developed local recurrences in the lower extremity. The median time to local recurrence was 1.3 years (range, 0.2–9.2 years) for patients with tumors of the upper extremity and 1.6 years (range, 0.1–6.6 years) for patients with tumors of the lower extremity. The local recurrence free rate at 5 years was 82% for patients with tumors of the upper extremity and 93% for patients with tumors of the lower extremity (log-rank test; P = 0.002) (Fig. 1).

The difference in the local recurrence free rate between the extremities was investigated with a Cox proportional hazards regression model. First, recognizing the difference in tumor size between the extremities, regression was performed using the greatest tumor dimension as a single, continuous variable. This did not reach significance (P = 0.074), confirming our belief that tumor size is not a determinant of local recurrence. A second model was constructed using (in the following order) categorical variables for surgical margin status (negative or positive), extremity (lower or upper), unplanned excision before referral (no or yes), and an interaction variable of extremity and unplanned excision before referral. Plots for each variable confirmed proportionality of the hazard ratio over time. Surgical margin status reached significance in the model ($P < 0.001$) with a hazard ratio of 3.16 (95% confidence interval, 1.76–5.69) associated with a positive margin. Extremity, unplanned excision before referral, and the interaction variable of extremity and unplanned excision before referral did not reach significance (P = 0.127, P = 0.056, and P = 0.868, respectively).

An exploratory analysis of the correlation between an unplanned excision before referral, surgical margin status, and local recurrence compared crude local recurrence rates in four groups (Table 4). Among patients who underwent primary excision of a tumor with positive surgical margins, patients who had tumors of the upper extremity were more likely to develop a local recurrence compared with patients who had tumors of the lower extremity (3 of 13 patients [23.1%] vs. 2 of 46 patients [4.3%]; P = 0.032).

A further exploratory analysis examined the effect of radiotherapy on local recurrence by calculating how many patients who developed local recurrences among these four groups had received radiotherapy (Table 4). Six of 11 patients with upper extremity tumors who underwent unplanned excision before referral and reexcision with negative margins and who developed a local recurrence had not received radiotherapy. In three patients, all with tumors located around the shoulder, this was because radiotherapy had been given on a previous occasion, precluding further radiotherapy. In two of the remaining patients, radiotherapy was not given, because no tumor was identified in the reexcision specimen. The sixth patient had a low-grade fibrosarcoma around the shoulder that was believed to have been completely excised.

Metastasis free survival

Twenty-six patients with upper extremity tumors (n = 139 tumors) developed a metastasis compared with 105 patients with lower extremity tumors (n = 341 tumors). The median time to metastasis was 1.0 years (range, 0.1–6.7 years) after surgery for patients with tumors of the upper extremity and 1.0 years (range, 0.1–12.8 years) after surgery for patients with tumors of the lower extremity. The metastasis free rate at 5 years was 82% for patients with tumors of the upper extremity and 69% for patients with tumors of the lower extremity (log-rank test; P = 0.013) (Fig. 2). There was a trend toward fewer metastases in patients with distal tumors (Table 2).

To investigate the difference in metastasis free rates between the extremities, a Cox proportional hazards model was constructed using, in the following order, histologic grade (low [Grade 1] or high [Grade 2 or 3]), greatest tumor dimension (in cm), depth (superficial or deep), and extremity (upper or lower). Proportionality over time was confirmed for each variable. There was an increased risk of metastasis with high histologic grade (hazard ratio, 17.28; 95% confidence interval, 4.26–70.10; $P < 0.001$), greatest tumor

TABLE 4
Exploratory Analysis of the Relation between Unplanned Excision Before Referral, Surgical Margin Status, and Local Recurrence

Group	Upper extremity			Lower extremity			*P* value for difference in local recurrence rates between extremities
	No. of patients	No. oflocal recurrences (%)	Local recurrences not given radiotherapy	No. of patients	No. of local recurrences (%)	Local recurrences not given radiotherapy	
Primary excision with negative surgical margins	37	2 (5.4)	1	135	7 (5.2)	0	0.957
Primary excision with positive surgical margins	13	3 (23.1)	1	46	2 (4.3)	0	0.032
Unplanned excision before referral, reexcision with negative margins	74	11 (14.9)	6	135	9 (6.7)	2	0.054
Unplanned excision before referral, reexcision with positive margins	15	7 (46.7)	0	25	7 (28.0)	1	0.231

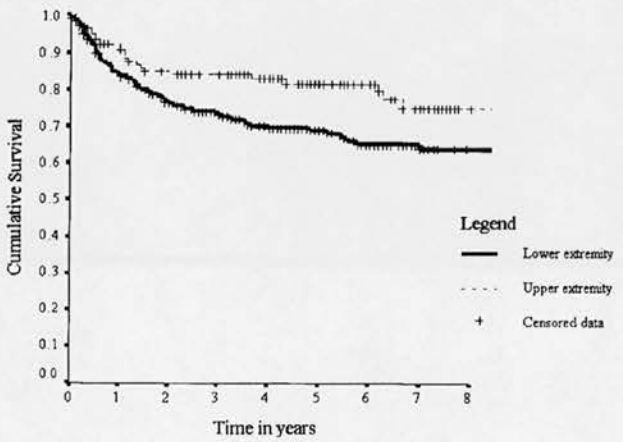

FIGURE 2. Kaplan–Meier curve for the metastasis free rate. Tick marks represent censored patients.

dimension (hazard ratio, 1.05; 95% confidence interval, 1.02–1.08; per cm increase, $P < 0.001$), and deep location (hazard ratio, 1.93; 95% confidence interval, 1.07–3.48; $P = 0.028$). The variable for extremity did not reach significance ($P = 0.211$).

DISCUSSION

This study compared the presentation, treatment, local recurrence free rate, and metastasis free rate of upper and lower extremity soft tissue sarcomas in our patient population. We showed that patients with upper extremity tumors have smaller lesions, more often undergo unplanned excision before referral, have tumors of different histologic types, and less often meet our criteria for adjuvant radiotherapy. We also showed that, after treatment for extremity soft tissue sarcoma, the local recurrence free rates and metastasis free rates vary with anatomic location. In particular, local recurrence is more frequent after treatment of an upper extremity sarcoma. Conversely, lower extremity sarcomas are associated with an increased metastatic rate.

A number of factors may contribute to the higher local recurrence rate among patients with tumors of the upper extremity. These include differences in tumor characteristics, such as histologic type, and differences in treatment, such as the effect of unplanned excision before referral and the use of radiotherapy. The strongest predictor of local recurrence in many studies is a positive surgical margin, which implies the presence of residual disease.[7,14,20,21] The Cox model confirmed this correlation in our series and showed that, after incorporating the effects of a positive surgical margin, an unplanned excision before referral, or the location of a soft tissue sarcoma in the upper extremity rather than the lower extremity, they did not reach significance. Sadoski et al. suggested that the relation between a positive surgical margin and local recurrence is stronger in the upper extremity compared with the lower extremity.[21] However, in our series, there was a higher local recurrence rate in the upper extremity in both patients with positive margins and patients with negative margins (Table 4).

The proportion of patients who had positive surgical margins was particularly high (16 of 41 patients) among those who had tumors around the elbow, which may reflect local anatomy. Despite this finding, the local recurrence rate in this group was not as high as it was among patients with tumors in other upper extremity sites (Table 2). The reason for this may be that four patients in this group had low-grade liposarcomas and, thus, were at low risk of local recurrence.

Although it was a subgroup analysis and, thus,

should be treated with caution, it is interesting to note that there was a significant difference in local recurrence rates between the extremities among patients who underwent primary excision with positive margins. There are a number of possible explanations for this. We showed previously that an unexpected positive margin after a surgical error is associated with a higher risk of local recurrence compared with a planned positive margin against a critical structure (such as nerve, vessel, or bone) or a planned marginal resection of a low-grade liposarcoma.[22] In 5 of 16 patients (31.3%) who underwent primary resection of an upper extremity sarcoma with a positive surgical margin, the positive margin was unexpected compared with 8 of 48 patients (16.7%) with lower extremity sarcomas, which may explain the higher local recurrence rates. This suggests that primary resection of a soft tissue sarcoma in the upper extremity is technically more demanding or that, to preserve function, the surgeon is prepared to operate closer to the tumor in the upper extremity. Another explanation for the difference in local recurrence rates is that there were more low grade liposarcomas in the lower extremity. These tumors are at low risk for local recurrence.[23]

The distribution of histologic types may have contributed to the difference in local recurrence rates between the extremities in another way. The histologic types angiosarcoma and malignant peripheral nerve sheath tumor have been associated with an increased risk of local recurrence.[12,24] Both of these types were relatively more frequent among tumors of the upper extremity compared with tumors of the lower extremity. Within the upper extremity, these histologic types were associated with 4 of 23 patients (17.4%) who developed local recurrences, compared with 2 of 25 patients (8.0%) who had tumors of the lower extremity (Table 3).

Variations in the use of radiotherapy also may have influenced the local recurrence rate. In particular, patients with tumors around the shoulder did not meet our criteria for radiotherapy as often as patients who had tumors in other upper extremity sites. This probably is because a proportion of soft tissue sarcomas around the shoulder occur in muscle (such as deltoid), where they can be excised with an adequate margin more readily compared with tumors located in other upper extremity sites. Therefore, it is more likely that an unplanned excision will be successful in removing all identifiable tumor, and adjuvant radiotherapy is not indicated after reexcision. It also was more common for the shoulder to have been treated with radiotherapy previously, both for the presenting tumor and for unrelated conditions, such as Hodgkin disease.

An unplanned excision complicates the further management of patients with soft tissue sarcoma by obscuring tissue planes and potentially contaminating a large volume of tissue. Patients with tumors of the upper extremity more frequently undergo unplanned excision before referral, possibly because the tumors are smaller and more often are superficial. However, whether unplanned excision increases the risk of recurrence remains controversial,[25] and we could not conclusively prove an adverse influence of unplanned excision on local recurrence in the Cox model.

The finding that lower extremity tumors are associated with a higher rate of metastasis confirms the reports of other authors.[4,9,16] The Cox model suggested that that most of this difference is accounted for by recognized risk factors for metastasis (i.e., grade, size, and depth[4,5,7,8,16]) rather than another hitherto unrecognized feature of lower extremity sarcomas. The analysis makes the assumption that, after the treatment of an extremity soft tissue sarcoma, local recurrence and metastases are independent events and are not competing events. The length of follow-up of survivors was similar among patients with tumors of the upper extremities and patients with tumors of the lower extremities; therefore, we do not believe that the higher local recurrence rate among patients with tumors of the upper extremity was caused by an increased death rate and shorter follow-up of patients with tumors of the lower extremity.

There were more tumors of the lower extremities than tumors of the upper extremities in our series, an experience shared by other authors.[11–15] This probably reflects the greater volume of mesenchymal tissue available to undergo malignant change in the lower extremity. Tumors in the upper extremity are smaller, probably because the smaller volume of the extremity allows the earlier detection of tumors or because the upper extremities are exposed, and abnormal swellings are identified readily. However, in common with others, we have shown that tumor size is not a strong predictor of local recurrence.[4,5,7] We agree with the suggestion that the threshold above which a mass should be treated as potentially malignant should be lower for patients with tumors of the upper extremity.[9] The larger size of lower extremity tumors probably explains why they more often involve the investing fascia of the limb and, thus, are classified as deep.

In conclusion, we have shown that, among our patient population, sarcomas of the upper extremity were associated with a higher local recurrence rate compared with sarcomas of the lower extremity because of differences in histologic type, the use of radiotherapy, and local anatomy. Although patients with upper extremity sarcomas more often underwent un-

planned excision before referral, we could not conclusively prove that this had an adverse effect on local tumor control. In contrast, lower extremity sarcomas tend to be larger and more often are deep to fascias compared with upper extremity sarcomas; therefore, patients with lower extremity sarcomas have an increased risk of metastasis. This study also shows that, in our patient population, the higher rate of local recurrence in the upper extremity was not matched by a higher rate of metastatic disease. This supports our philosophy of preserving function in the upper extremity when possible. We do not believe that there is an underlying difference in the biological behavior of upper extremity soft tissue sarcoma and lower extremity soft tissue sarcoma, although the clinical course differs depending on the anatomic location.

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The Influence of Anatomic Location on Functional Outcome in Lower-Extremity Soft-Tissue Sarcoma

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Background: The purpose of this study was to explore the relationship between the anatomical location of lower-extremity soft-tissue sarcoma and functional outcome.

Methods: Function was evaluated with the Musculoskeletal Tumor Society (MSTS 1993) score and Toronto Extremity Salvage Score (TESS); 207 patients (median age, 54 years) were eligible. The median maximum tumor diameter was 8.0 cm; 58 tumors were superficial and 149 were deep. Nine locations based on anatomical compartments were defined: 6 tumors were in the groin/femoral triangle; 8, the buttock; 52, the anterior thigh; 22, the medial thigh; 20, the posterior thigh; 10, the popliteal fossa; 13, the posterior calf; 11, the anterolateral leg; and 7, the foot or ankle.

Results: Treatment of superficial tumors did not lead to significant changes in MSTS score (mean, 90.6% preoperatively vs. 93.0% postoperatively; $P = .566$) or TESS (mean, 86.4% preoperatively vs. 90.9% postoperatively; $P = .059$). Treatment of deep tumors lead to significant reductions in MSTS score and TESS (mean MSTS, 86.9% preoperatively vs. 83.0% postoperatively; $P = .001$; and mean TESS, 83.0% preoperatively vs. 79.4% postoperatively; $P = .015$). Anatomical location was not a significant predictor of aggregated MSTS and TESS evaluations. Exploratory analysis showed variation in MSTS pain and gait handicap or limp items and TESS dressing, sitting, bending, and bathing items by anatomical location.

Conclusions: The treatment of superficial tumors does not lead to significant changes in MSTS score or TESS. Anatomical location is not a significant predictor of aggregated MSTS and TESS evaluations. However, there is variation in MSTS and TESS item scores across anatomical locations.

Key Words: Lower extremity—Soft-tissue sarcoma—Anatomical site—Functional outcome.

The function of patients after treatment is an important consideration in the management of extremity soft-tissue sarcoma. In this context, function has been conceptualized in a variety of ways. Some authors have used clinical measures such as range of motion and muscle strength[1,2] or activities of daily living.[1] The Musculoskeletal Tumor Society Rating Scale (MSTS 1987) combines symptoms and clinical measures,[3] and the revised MSTS (1993) includes scores for symptoms, mobility, and the use of assistive devices.[4] Other studies have used generic health measures, such as the Sickness Impact Profile.[5] We have previously used the World Health Organization definitions of impairment, disability, and handicap as a guide to the assessment of function.[6,7] The Toronto Extremity Salvage Score (TESS) was based upon the World Health Organization definition of disability as "any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being."[6] The TESS evaluation has demonstrated reliability, validity, and responsiveness in the extremity sarcoma population.[8,9] The MSTS scores are closest to the WHO definition of impairments as "any loss or abnormality of psychological, physiological, or anatomical structure or function."[6]

We have previously analyzed factors that predict functional outcome after treatment of lower-extremity soft-

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tissue sarcoma as measured by the MSTS and TESS rating systems.[7] We showed that large tumor size, resection of bone, resection of major motor nerves, and complications of surgery predicted lower MSTS 1987 and 1993 scores and that patients with large, high-grade tumors who required motor nerve resection had lower TESS values.[7] Although anatomical location as defined as proximity to the nearest major joint (hip, knee, ankle) was not a significant predictor of functional scores in this study, we hypothesized that the anatomical location of a tumor is nevertheless important in determining functional outcome. For example, function after treatment of a buttock tumor is likely to differ from function after treatment of a tumor in the foot or ankle by virtue of anatomical location alone. The purpose of this study therefore was to further examine the influence of anatomical location on functional scores in patients with lower-extremity soft-tissue sarcoma.

PATIENTS AND METHODS

Patients were eligible for this study if they underwent limb-sparing surgery in our center for lower-extremity soft-tissue sarcoma and had a minimum follow-up of 1 year for functional evaluation, at which point functional scores are known to plateau.[10] Two measures were used to assess function. The MSTS (1993) is completed by the clinician and consists of six items: pain, overall function, emotional acceptance, walking ability, walking aids, and gait handicap or limp.[4] Each item is rated on a scale of 1 to 5. The total score is calculated from a sum of the individual items and expressed as a percentage. The TESS questionnaire is completed by the patient and comprises 30 items in which the patient indicates the difficulty experienced in performing a range of everyday activities, such as dressing, grooming, mobility, work, sports, and leisure.[8] Each item is rated on a scale of 1 to 5 and the total is expressed as a percentage. The TESS was first used in April 1994, and therefore patients treated before this date were excluded. Patients were also excluded if they had metastases at presentation, had a local or systemic relapse before functional assessment at 1 year, or underwent chemotherapy. The lower extremity was defined as commencing at the pelvic brim.

We did not use the MSTS (1987) system because it is site-specific and therefore not suitable for this analysis. We did not use the generic general health status measure Short-Form 36 (SF-36) because we have shown that it is not sensitive to local treatment factors.[7]

A prospectively collected database was used to identify suitable patients and the following data were extracted from it: age, gender, type of surgery, metastases at presentation (yes/no [Y/N]), presentation with a local recurrence (Y/N), chemotherapy (Y/N), radiotherapy (Y/N), unplanned excision before referral (Y/N), histological type and grade, maximum tumor diameter in centimeters, resection of bone (Y/N), resection of major motor nerve (Y/N), and complications of surgery (Y/N). Complications of surgery were defined as major wound dehiscence, infection, or fracture.

Anatomical Definitions

The anatomical location of the tumor was determined by review of the operating note and imaging. One author (CG) assigned tumors to anatomical regions as described below. These regions were based upon the concept of anatomical compartments developed by Enneking because these were thought to have both oncological and functional significance.[11] A tumor involving more than one region was assigned to the region that was most involved. Tumors superficial to and not involving the deep investing fascia of the limb were classified as superficial and others as deep. To minimize errors, data relating to anatomical location were entered twice into a spreadsheet (Excel 97, Microsoft, Redmond, WA) and checked for compatibility with the preexisting anatomical classification, in which tumors were grouped by their proximity to the nearest major joint.

Groin/Femoral Triangle

This triangle comprises proximally the inguinal ligament, posteriorly the iliopsoas and anterior hip capsule, and laterally the tendon of rectus femoris, as well as the proximal extent of the femoral artery, vein, nerve, and inguinal nodes.

Buttock

The buttock comprises proximally the posterior brim of pelvis, medially the sacrum, anteriorly the posterior border of tensor fascia lata, the anterior border of gluteus medius, and as the deep boundary, the outer table of pelvis. It also contains the gluteus maximus, minimus, medius, quadratus femoris, and the proximal extent of the sciatic nerve.

Anterior Thigh

This comprises proximally the brim of pelvis, distally the patella, and laterally the intermuscular septum. It also contains the quadriceps, including patella and patellar tendon, sartorius, tensor fascia lata, femoral artery, vein, and nerve.

Medial Thigh

This comprises proximally the pubic rami and ischial tuberosity, anterolaterally the adductor canal and medial

intermuscular septum, posteriorly the posterior surface of adductor magnus, and distally the pes anserinus. It also contains the gracilis, adductors brevis, longus, magnus, pectineus, and profunda femoris vessels.

Posterior Thigh

This comprises laterally the intermuscular septum, medially the adductor magnus fascia, proximally the ischial tuberosity, distally the musculotendinous junctions of the hamstring muscles, anteriorly the linea aspera, and the posterior face of femur. It also contains the semimembranosus, semitendinosus, and biceps femoris.

Popliteal Fossa

This comprises superficially the deep fascia, anteriorly the posterior capsule of knee joint and the heads of gastrocnemius, distally the confluence of gastrocnemius, and proximally the musculotendinous junctions of hamstrings. It also contains the sciatic nerve, popliteal vessels, and lymph nodes.

Posterior Calf

This comprises anteriorly the posterior surface of the tibia, interosseous membrane, posterior aspect of fibula, and posterior intermuscular septum; posteriorly the deep fascia of the calf; superiorly the confluence of gastrocnemius; distally the commencement of the tendo Achilles. It also contains the gastrocnemius, plantaris, soleus, popliteus, flexor digitorum longus, flexor hallucis longus and tibialis posterior, and the posterior tibial vessels and nerve.

Anterolateral Leg

This comprises anteriorly the deep fascia of the leg; posteriorly the lateral surface of the tibia, the interosseous membrane, the fibula, and the posterior intermuscular septum; proximally the proximal extent of the insertion of tibialis anterior into the tibia; and distally the superior extensor retinaculum of the ankle. It also contains the peroneus longus and brevis, peroneus tertius, extensor digitorum longus, extensor hallucis longus, tibialis anterior, the anterior tibial vessels, and the deep peroneal nerve.

Foot and Ankle

Proximally this space in bounded by the superior extensor retinaculum anteriorly and the commencement of the tendo Achilles posteriorly.

Analysis

Initially, descriptive variables were calculated for the whole group of eligible patients. Recognizing that treatment of tumors located superficial to the investing fascia of the limb was likely to have little impact on the function of the underlying compartment, these superficial tumors were analyzed as a separate group. Next, variables for the anatomical location of deep tumors were added to factors already recognized to have an influence on MSTS (1993) score and TESS in multiple linear regression models. Finally, an exploratory analysis was performed in which individual MSTS and TESS items for deep tumors were compared by anatomical location.

Statistical Notes

Differences in mean values between two groups were compared with use of independent-samples *t*-tests and between multiple groups with one-way analysis of variance (ANOVA) and the Tukey post-test. Differences in proportions were compared with the Pearson χ^2 test. MSTS scores and TESS values are not normally distributed. Therefore, when comparing scores between two groups, we used the nonparametric Mann-Whitney test. When comparing scores before and after treatment, we used the Wilcoxon test for paired samples, and we used the Kruskal-Wallis test to compare scores across more than two groups. Results with a P value of $< .05$ were taken to be significant (SPSS software for Windows, release 10.0.5, 1999; SPSS, Chicago).

RESULTS

Between April 1994 and March 1999, data relating to 397 patients were collected. Ninety-seven patients had upper-extremity tumors and 17 had an amputation. The following patients were also excluded: 22 with metastases at presentation, 32 who developed metastases, 2 who died of other causes, 3 with a local recurrence in the first year, and 10 who received chemotherapy. For seven patients there were no functional data available. Therefore, 207 patients remained in the study.

Completeness of Function Data

Preoperative MSTS results were available for 203, and 1- or 2-year MSTS results were available for 189 patients. Preoperative TESS results were available for 172 and 1- or 2-year TESS results were available for 155 patients. Of the patients for whom 1- or 2-year TESS results were not available, 20 did not speak English, 11 were lost to follow-up, 7 were infirm and unable to complete the questionnaire, and 14 had no data available for other reasons.

TABLE 1. *Differences in characteristics and functional scores between deep and superficial tumours*

Site	No. of cases	Mean diameter in cm (SD)	Complications of surgery	Radiotherapy	MSTS		TESS	
					Mean preop score	Mean postop score	Mean preop score	Mean postop score
Superficial	58	4.6 (3.2)	10	35	90.6 (32.0–100.0, 17.2)[a]	93.0 (23.0–100.0, 14.0)	86.4 (29.2–100.0, 18.6)	90.9 (41.7–100.0, 14.0)
Deep	149	11.2 (6.6)	41	135	86.9 (16.0–100.0, 20.3)	83.0 (23.0–100.0, 19.9)	81.8 (15.0–100.0, 20.5)	79.5 (25.8–100.0, 18.0)
		$P < 0.0001$[b]	$P = 0.123$	$P < 0.0001$	$P = 0.271$	$P < 0.0001$	$P = 0.081$	$P < 0.0001$

[a] Range and standard deviation for functional scores shown in parentheses.
[b] P values are shown for comparison of values between superficial and deep tumours.
SD, standard deviation; MSTS, Musculoskeletal Tumor Society; TESS, Toronto Extremity Salvage Score.

Characteristics of the Whole Group

There were 106 females (51.2%) and 101 males (48.8%), of median age 54 (15 to 89) years. Twelve patients (5.8%) presented with a local recurrence after treatment elsewhere. Seventy-six patients (36.7%) had been treated by unplanned excision before referral. The distribution of histological types was similar to that in other series, with malignant fibrous histiocytoma in 48 (23.2%), liposarcoma otherwise undesignated in 49 (23.7%), and myxoid liposarcoma in 28 (13.5%). Tumors were grade 1 in 40 cases (19.3%), grade 2 in 76 (36.7%), and grade 3 in 91 (44.0%). The median maximum tumor diameter was 8.0 cm (0.3 to 36.0).

A tissue transfer or split-thickness skin graft was used for wound closure in 40 cases (19.3%), and 170 patients (82.1%) received adjuvant radiotherapy. Resection of bone was required in 12 cases (5.8%), and resection of a major motor nerve in 12 cases (5.8%). Forty-eight patients (23.2%) had a wound complication and 3 (1.4%) had a fracture.

After anatomical classification there were 58 superficial tumors (28.0%) and 149 deep tumors (72.0%). Superficial tumors were significantly smaller than deep tumors (4.6 vs. 11.2 cm; $P < .0001$). Of the deep tumors, 6 were located in the groin/femoral triangle, 8 in the buttock, 52 in the anterior thigh, 22 in the medial thigh, 20 in the posterior thigh, 10 in the popliteal fossa, 13 in the posterior calf, 11 in the anterolateral leg, and 7 in the foot and ankle (Table 2). Of the deep tumors, 119 (79.9%) involved one site only, 28 (18.8%) involved two sites, and 2 (1.3%) involved three sites.

The Differences Between Deep and Superficial Tumors

Functional scores grouped according to whether the tumor was superficial or deep are shown in Table 1. There was no significant difference in MSTS score or TESS at presentation when superficial and deep tumors were compared (mean MSTS score, 90.6% [superficial] vs. 86.9% [deep]; $P = .271$; and mean TESS, 86.4% [superficial] vs. 81.8% [deep]; $P = .081$). Treatment of superficial tumors was not associated with a significant change in MSTS score (mean, 90.6% preoperatively vs. 93.0% postoperatively; $P = .566$) or TESS (mean, 86.4% preoperatively vs. 90.9% postoperatively; $P = .059$). However, treatment of deep tumors was associated with a significant reduction in MSTS score and TESS (mean MSTS, 86.9% preoperatively vs. 83.0% postoperatively; $P = .001$; mean TESS, 83.0% preoperatively vs. 79.4% postoperatively; $P = .015$). MSTS and TESS results differed significantly between superficial and deep tumors after treatment (mean MSTS, 93.0% [superficial] vs. 83.0% [deep]; $P = .000$; mean TESS, 90.9% [superficial] vs. 79.4% [deep], $P = .000$).

Variation in Characteristics of Deep Tumors by Anatomical Location

Variation in tumor size, type, treatment, and functional scores among deep tumors by anatomical location is summarized in Table 2. Comparison of MSTS score and TESS by anatomical location revealed no significant differences in preoperative MSTS score ($P = .120$) or TESS ($P = .282$). The impact of anatomical location of deep tumors on postoperative MSTS score was assessed with a linear regression model in which variables previously shown to be significant in predicting postoperative MSTS score (tumor diameter, grade, motor nerve sacrifice, bone resection, complications of surgery) were used.[7] The only factor to reach significance was resection of a motor nerve ($P < .0001$).

A multiple regression model for postoperative TESS was constructed in the same fashion with use of variables previously identified as predictive (tumor diameter, grade, and motor nerve resection). Once more, resection of a motor nerve was the only variable to reach significance in this model ($P = .002$).

TABLE 2. *Characteristics of deep tumours, treatment and functional scores by anatomical location*

Anatomical location	No. of cases	Mean diameter in cm (SD)	Major motor nerve resection	Bone resection	Complications of surgery	Radiotherapy	MSTS		TESS	
							Mean preop score	Mean postop score	Mean preop score	Mean postop score
Groin/femoral triangle	6	8.8 (1.9)	2	1	4	6	58.6 (16–80, 28.1)[a]	64.3 (27–90, 24.1)	54.9 (15.0–89.2, 31.5)	63.8 (25.8–82.5, 20.9)
Buttock	8	8.1 (4.1)			2	8	86.8 (33–100, 22.3)	90.0 (77–100, 9.3)	79.2 (19.4–100, 31.9)	77.8 (54.2–99.1, 19.7)
Anterior thigh	52	11.8 (6.3)	4	1	12	47	89.8 (20–100, 18.6)	80.1 (23–100, 23.7)	80.7 (21.7–100, 17.6)	77.5 (25.8–100, 19.6)
Medial thigh	22	13.5 (8.5)			9	17	84.9 (27–100, 22.7)	88.0 (37–100, 18.1)	81.2 (24.1–100, 22.5)	83.1 (35.8–100, 18.7)
Posterior thigh	20	14.9 (6.5)	2		1	18	90.4 (67–100, 12.1)	80.5 (43–100, 17.3)	85.9 (54.4–100, 13.9)	75.7 (54.2–96.7, 12.6)
Popliteal fossa	10	9.5 (5.7)		1	3	10	93.8 (80–100, 8.3)	92.3 (67–100, 11.6)	90.6 (71.7–100, 11.3)	83.3 (43.5–100, 19.1)
Posterior calf	13	8.8 (4.8)	1	1	5	13	79.8 (24–100, 26.1)	87.0 (60–100, 14.7)	76.2 (15.0–100, 27.6)	88.3 (68.3–100, 11.5)
Anterolateral leg	11	8.7 (5.5)	1	6	2	10	91.8 (48–100, 16.8)	84.4 (50–100, 17.3)	90.6 (66.7–100, 10.8)	80.2 (39.2–97.5, 18.7)
Foot and ankle	7	4.6 (1.7)		2	3	6	77.7 (24–100, 28.0)	84.2 (57–100, 17.6)	90.4 (67.5–100, 13.3)	88.1 (73.3–100, 11.3)

[a] Range and standard deviation for functional scores shown in parentheses.
SD, standard deviation; MSTS, Musculoskeletal Tumor Society; TESS, Toronto Extremity Salvage Score.

Comparison of MSTS and TESS Items by Anatomical Location

An exploratory analysis of item variation by anatomical location was performed with use of the nonparametric Kruskal-Wallis test. Items in which there was significant variation by anatomical location were further examined. There was significant variation by anatomical location for the pain and gait handicap or limp items of the preoperative MSTS (Table 3). Tumors in the groin/femoral triangle were associated with more preoperative pain than those in other locations. Preoperatively all patients with tumors in the groin/femoral triangle required analgesia, with most requiring narcotic analgesia. The lowest preoperative mean score for the gait handicap or limp item was for tumors in the groin/femoral triangle, followed by the

TABLE 3. *MSTS subscales for pain and gait handicap or limp by anatomical location*

Anatomical location	MSTS preop, mean scores		MSTS postop, mean scores	
	Pain	Gait handicap or limp	Pain	Gait handicap or limp
Groin/femoral triangle	1.4	4.0	2.7	3.8
Buttock	3.5	5.0	3.8	4.7
Anterior thigh	4.2	4.8	4.0	4.6
Medial thigh	3.8	5.0	4.4	5.0
Posterior thigh	4.0	5.0	3.9	4.8
Popliteal fossa	4.6	4.9	4.4	5.0
Posterior calf	3.9	4.2	4.2	5.0
Anterolateral leg	4.3	4.7	4.2	4.6
Foot and ankle	3.7	4.3	4.0	5.0

MSTS, Musculoskeletal Tumor Society.

posterior calf, the foot and ankle, and the anterolateral leg (Table 3).

In the postoperative MSTS, significant variation was also seen in item scores for gait handicap or limp. Once more, the lowest postoperative scores were seen in tumors in the groin/femoral triangle. Patients with tumors in the medial thigh, popliteal fossa, posterior calf, and foot and ankle all walked normally (Table 3).

In the preoperative TESS, the exploratory statistical analysis did not identify any items with significant variation by anatomical location, although the item score for sitting approached significance. Patients with tumors in the groin/femoral triangle, buttock, and posterior thigh had the greatest difficulty with sitting (Table 4).

In the postoperative TESS significant variation was seen in the items for putting on pants, putting on socks or stockings, getting in and out of the bath, and bending to pick something up off the floor (Table 4). Once more, patients with tumors in the groin/femoral triangle had the greatest difficulty with these activities. Putting on socks and stockings also appeared to be difficult for those with posterior thigh or buttock tumors. Getting in and out of the bath was also difficult for those with posterior thigh or anterolateral leg tumors. Bending to pick something up off the floor was most difficult for patients with tumors in the groin/femoral triangle, buttock, and the posterior thigh (Table 4).

DISCUSSION

The purpose of this study was to examine the influence of anatomical factors on impairment as measured by MSTS (1993) score and disability as measured by TESS. We have shown a difference in MSTS and TESS when superficial and deep tumors are compared and that although there does not appear to be significant variation in the MSTS and TESS for deep tumors by anatomical location, some items do vary with anatomical location.

Our study shows that unlike deep tumors, the treatment of superficial tumors is not associated with a significant decrease in MSTS and TESS values. In fact, mean scores for superficial tumors increase slightly after treatment, whereas those for deep tumors decrease after treatment. Higher MSTS (1993) and TESS values for superficial tumors likely reflect their smaller size and the fact that surgery does not involve major muscle, motor nerve, or bone resection.

We could not demonstrate that the variables for anatomical location made a significant contribution to total postoperative MSTS score and TESS in the regression model, and it may be that our study was not sufficiently powered to detect this. However, the exploratory analysis suggests that most of the variability with anatomical location lies at the item level, rather than in aggregated scores. Although the number of patients in the group was small, it was of interest that tumors in the groin/femoral triangle were associated with more preoperative pain, as measured by the MSTS item for pain, than those in other locations. This may be related to the relatively high rate of major nerve involvement in this location (two of six patients required major motor nerve resection). Other than those in the groin, tumors located below the knee appeared to be associated with the lowest preoperative gait handicap or limp item scores. Postoperatively tumors in the groin/femoral triangle were associated with the lowest mean MSTS gait handicap or limp item scores. This may have been because one patient had a major femoral nerve resection and scored zero for the gait handicap or limp item postoperatively.

TABLE 4. *Selected TESS item scores by anatomical location*

	Preop TESS, mean item scores	TESS postop, mean item scores			
Anatomical location	Sitting	Putting on pants	Putting on socks or stockings	Getting in and out of the bath	Bending to pick something up off the floor
Groin/femoral triangle	3.8	3.5	3.0	3.2	3.2
Buttock	3.9	4.2	3.8	4.0	3.4
Anterior thigh	4.7	4.6	4.1	4.1	3.9
Medial thigh	4.4	4.4	3.9	4.2	4.0
Posterior thigh	4.2	4.1	3.1	3.5	3.8
Popliteal fossa	4.9	4.6	4.4	4.6	4.0
Posterior calf	4.6	4.9	4.8	4.6	4.7
Anterolateral leg	4.9	4.9	4.3	3.9	4.0
Foot and ankle	5.0	5.0	5.0	4.8	4.8

TESS, Toronto Extremity Salvage Score.

The TESS evaluation contains a greater number of items than the MSTS, and some items, such as the ability to sit, are likely to have a clear relationship with anatomical location. We found that tumors in the buttock and posterior thigh were associated with greater difficulty in sitting than those in other locations, which may reflect the discomfort experienced when sitting directly on the tumor. Patients with tumors in the groin/femoral triangle also have difficulty sitting normally, likely because of restriction of normal hip flexion. The postoperative TESS evaluation confirms that after treatment, patients with tumors in the groin/femoral triangle continue to score lower for the items putting on socks, getting out of the bath, and bending to pick up, all of which involve hip flexion.

To conclude, we have shown that when considering the function of a patient after treatment of lower-extremity soft-tissue sarcoma, anatomical location is important. The treatment of superficial tumors is not associated with a significant decrease in functional scores, whereas the treatment of deep tumors is. Although the contribution of the anatomical location of deep tumors to aggregated MSTS (1993) and TESS values does not appear to be significant, there is variation in score items with anatomical location. This information may be of value in counseling patients about their likely disability and impairment after treatment.

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