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AUTHOR:

ANDREW JOHN SPILLANE B.Med Sci, BM BS (Uni of Tas), FRACS

THE INADEQUACIES OF THE CURRENTLY AVAILABLE SOFT TISSUE SARCOMA STAGING SYSTEMS DEMONSTRATED BY THE CLINICOPATHOLOGICAL ASSESSMENT OF THREE SUBTYPES OF SOFT TISSUE SARCOMA - MYXOID LIPOSARCOMA, SYNOVIAL SARCOMA AND EPITHELIOID SARCOMA

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SUPERVISOR:
PROFESSOR P STANTON

ADVISORS:
MR JM THOMAS
DR C FISHER
DR R A'HERN

I, **Andrew John Spillane**, certify that this Thesis contains no material that has been accepted for a degree or diploma by the University of Tasmania or any other institution, except by way of background information and duly acknowledged in the Thesis. To the best of my knowledge and belief no material previously published or written by another person except where due acknowledgment is made in the text of the Thesis.

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ABSTRACT

Staging of tumours is important. A widely applied and reliable staging system can give important prognostic information for the patient and treating physicians. This information can be used to determine appropriate treatment, compare outcomes between centres and act as a structure for research into modifications to treatment that aim to improve outcomes.

Soft tissue sarcomas are a heterogeneous collection of tumours that are commonly grouped together because of similarities in mesenchymal origin and behaviour but partly because of their individual rarity. Unfortunately the common staging systems for soft tissue sarcoma, although prescribed for application to virtually all STS, have not been validated sufficiently for this application. The staging systems that will be discussed are the American Joint Committee for Cancer (AJCC), Union Internationale Cancer Committee (UICC) and the recently published Royal Marsden Hospital (RMH) Staging Systems.

This thesis demonstrates the weaknesses in the current commonly used staging systems for STS by assessing relatively large case series of three subtypes of STS (synovial sarcoma, myxoid liposarcoma and epithelioid sarcoma). Rigorous clinicopathological assessments of each subtype have been done. These data demonstrate the particular characteristics that

dominate the clinical behaviour for each subtype. By applying the AJCC / UICC and the RMH staging systems to each subtype I have then demonstrated how the individual characteristics reflect as inadequacies in the prognostic reliability of the staging systems for each of these subtypes.

After these individual assessments I present combination data which supports the arguments that the current staging systems for STS represent an averaging of the heterogeneous behaviour of the many subtypes of STS but this "averaging" is dominated by the more common subtypes. The results indicate that inappropriate information is most probably being given to many individual patients, particularly those with the less common and non-extremity lesions. This is because the current staging systems for STS are not taking into account the variability in clinical behaviour seen between the different subtypes of STS or sometimes the influence of the different sites of primary STS.

More research needs to be done to develop reliable disease patterns for all the subtypes of STS as well as assessment of specific site differences on possible STS prognostic factors. Most reliably the multi-institution pooling of prospectively collected case series with central review of all pathological material, could be used to then develop a staging system (or

individual staging systems / prognostic profiles) that take into account this variability between subtypes of STS.

In conclusion, the subtype analysis completed in this thesis indicates that in many individual cases the currently published staging systems for STS are not clinically relevant and should only be used as a guideline of essentially academic interest.

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LIST OF PUBLICATIONS RELATING TO THESIS

1. Spillane AJ, Fisher CF, Thomas JM. Myxoid Liposarcoma. The frequency and the natural history of soft tissue metastases. Ann Surg Oncol 1999;6;4:389-394.
2. Spillane AJ, Judson IR, A'Hern R, et al. Synovial Sarcoma - Experience with 150 cases in 11 years. Eur J Cancer 1999;35;Suppl4:abstract 1060.
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Other Publications on Soft Tissue Sarcoma During Period of Thesis Drafting (Indirectly Related to Central Theme)

1. Spillane AJ, Thomas J M. Retroperitoneal Sarcoma with Infected Necrosis: an unfavourble prognostic factor. Sarcoma 1998;2;3-4:179-81.
2. Spillane AJ, Thomas JM. Surgical Aspects of Iliopsoas Compartment Tumours. Eur J Surg Oncol 1999;25;4:389-391.
3. Spillane AJ, Thomas JM. Gynaecological Presentation of Retroperitoneal Tumours. Br J Obstet Gynaecol.2000;107;2:170-173.
4. Hughes TMD, Spillane AJ. Imaging of Soft Tissue Tumours.(Editorial) Br J Surg 2000;87:3:259-260.
5. Hoeber I, Spillane AJ, Fisher C, Thomas JM. The Accuracy of Biopsy Techniques for Limb and Limb Girdle Soft Tissue Tumours. Ann Surg Oncol.2001;8:80-87.

INTERNATIONAL PRESENTATIONS RELATING TO THESIS

1. Synovial Sarcoma - Experience with 150 cases in 11 years. European Cancer Conference Vienna Sept 1999 - full presentation.
2. Myxoid Liposarcoma. The frequency and the natural history of soft tissue metastases. European Cancer Conference Vienna Sept 1999 - Poster / Verbal presentation.

3. The Problem with Subtype Application to the Current AJCC Staging System for Soft Tissue Sarcoma. Accepted for Oral Presentation Society of Surgical Oncology Meeting – Washington DC March 2000.

OTHER PRESENTATIONS RELATING TO THESIS.

1. The inadequacies of the current staging systems for soft tissue sarcoma. Medical Officers Association Reunion Week Royal Prince Alfred Hospital, Sydney. June 2000

CHAPTER 1. BACKGROUND

1.1 - INTRODUCTION AND CONCEPT

The concept of this Thesis developed from several events that occurred around the time I commenced Post-Fellowship Surgical Training at the Royal Marsden NHS Trust in London in April 1998. One of my predecessors had recently published a proposed modification to the 1992 (4th Edition) version of the American Joint Committee of Cancer (AJCC) and Union Internationale Cancer Committee (UICC) Staging Systems on soft tissue sarcoma (STS) [1-3]. Unfortunately by the time this modification came to publication the 4th Edition versions of the AJCC / UICC STS Staging Systems had been superseded by the 1997 (5th Edition) versions.[4,5] The new Edition made several changes from the earlier version, principally to include depth of the tumour in relation to the body's investing fascia. To my mind this change was not a significant advancement from the 4th Edition version of the staging systems and this precipitated my further investigation of the current staging systems. The changes to the 5th edition versions of the AJCC / UICC Staging Systems did not incorporate the major concept from which the RMH Staging System was developed. This concept was that both size and grade are continuous variables when calculating the prognosis of many STS. This concept had been previously noted in the literature [6,7], but not strongly emphasized by the AJCC / UICC Committees.[4,5]

During the time of my review of the STS Staging Systems [8] I had been investigating Synovial Sarcoma, Myxoid Liposarcoma and Epithelioid Sarcoma because each of these subtypes has characteristic biological behaviour. They were chosen for evaluation because there were weaknesses in the existing literature regarding their clinicopathological behaviour and the RMH had considerable experience with each. It became obvious to me that one of the greatest limitations of an effective staging system for STS was indeed the heterogeneity of biological behaviour of STS which is largely overlooked by combining all STS together and applying the whole cohort to a STS Staging System. The reason this has been done in the past is because of the rarity of STS has necessitated combining data on subtypes to get large enough numbers for statistically significant separation of staging groups. Fortunately the RMH's large experience with STS has enabled me to gather excellent data with some of the largest cohorts of the three subtypes of STS in the literature. Rather than combining the subtypes to assess stage, each subtypes has been individually applied to try to validate the current AJCC / UICC Staging Systems and the RMH Staging System for each. This has been useful in demonstrating the limitations of the staging systems for each subtype and highlighting peculiarities of each subtype, which have not previously been documented or emphasised in the literature. Despite the large experience of the RMH, the number of cases particularly of Epithelioid Sarcoma has been a limiting factor in determining statistical

significance at a subgroup stage in particular. Nevertheless, the assessments conducted have allowed a thorough review of the problems with the currently available STS staging systems and has allowed me to make recommendations for future improvements.

The other aspect of this thesis will be a description of the significant findings of my assessment of the Synovial Sarcoma, Myxoid Liposarcoma and Epithelioid Sarcoma that have been recognised as significant contributions to the literature.[9-12]

A major limitation of this kind of investigation is that these patients have nearly all been referred to one consultant surgeon at one tertiary referral institution. This undoubtedly introduces a referral bias that is likely to be significant but is impossible to quantity without population-based data on the actual frequency and distribution of the various subtypes of STS. This would require uniformity of pathological diagnosis and management strategies, which does not occur in the United Kingdom.

1.2 - BACKGROUND INFORMATION ON STS

Adult STS are rare tumours with an annual incidence of approximately 1.35 per 100 000 individuals.[13] Adult STS are derived from mesenchymal cell lines or in some cases neuroectoderm. STS can arise in any soft tissue areas but most commonly involve the limb and limb girdles in 75 % of cases.[13] Childhood STS are much more frequently of primitive cell differentiation such as rhabdomyosarcoma or neuroblastoma, and have completely different biological behaviour. Childhood STSs are therefore managed differently and in specialist centres of paediatric oncology. They will not be discussed further in this thesis. Sarcomas arising from bone are excluded from this thesis, as they are not referred to the RMH.

Pathogenesis of STS

The pathogenesis of most STS is still unknown. There are a number of documented associations with development of STS.

- Genetic factors are involved in the development of cases of neurofibrosarcoma in Von Recklinghausen's Disease (neurofibromatosis). Similarly people with the Familial Adenomatous Polyposis gene have a higher rate of desmoid tumours. People with p53 abnormalities on the short arm of chromosome 17, which is associated with Li-Fraumeni Syndrome, have an increased incidence of STS, in particular, familial rhabdomyosarcoma. Increasingly differentiation

between subtypes of STS is made on the basis of chromosomal alterations. A good example would be the specific chromosomal translocation t(x;18)(p11.2;q11.2) in synovial sarcoma.[14] This allows poorly differentiated sarcomas to be subtyped specifically which can have management implications.

- Ionising radiation is also associated with an incidence of subsequent development of STS in approximately 0.1% of cases.
- Patients often report a recent or past injury to the area where STS occur. In most cases it is likely that the trauma often seems to draw attention to the lesion, however, occasionally there is reasonable evidence for a link. In rare types of tumours this is difficult to definitively prove.
- Environmental carcinogens such as asbestos in pulmonary mesotheliomas have a strong link. Dioxin exposure (particularly in Agent Orange in Vietnam veterans) has been implicated but causality remains unproven.
- Oncogenic viruses have been implicated in the development of animal model STS but not proven in humans aside from a possible role in Kaposi's sarcoma.[13]

Distribution

STS have a propensity for proximal limb sites but there is a wide range of locations with all mesenchymal tissues able to develop STS. A typical distribution of STS would be 46% lower extremity, 14% upper extremity, 8% head and neck, 19% trunk, and 13% retroperitoneum.[13]

Subtypes of STS

STS can be classified as (most commonly) spindle cell, round cell or pleomorphic sarcoma. This separation is morphologically convenient but prognostically often meaningless. The most often used method for classification of types of STS is the pattern of differentiation along specific cell lines that often reflect a mesenchymal tissue of origin. A typical distribution of subtypes is shown in Table 1.1.[15] The commonest subtypes of STS in most series are leiomyosarcoma, liposarcoma, and malignant fibrous histiocytoma and synovial sarcoma. Combined these subtypes represent approximately 70 % of the total. The remaining subtypes are relatively rare.

As the understanding of STS morphology has developed the classification of subtypes of STS has varied with differing percentages of each type being identified. For example before immunohistochemical staining became widespread larger percentages of cases were diagnosed as Malignant Fibrous Histiocytomas. These tumours are more often diagnosed as less well differentiated forms of other subtypes of STS nowadays. In the future, particularly as the genetic assessment of STS is more thoroughly undertaken, further refinement of subtyping of STS and indeed prognosis determination will no doubt occur.

Table 1.1 The Distribution of the Subtypes of Soft Tissue Sarcoma [15]

PATHOLOGY OF SOFT TISSUE SARCOMA	PERCENTAGE (nearest whole)
Malignant Fibrous Histiocytoma	21
Leiomyosarcoma	19
Liposarcoma	17
Synovial Sarcoma	12
Not otherwise specified	11
Malignant Peripheral Nerve Sheath Tumour	6
Dermatofibrosarcoma	3
Rhabdomyosarcoma	2
Soft Tissue Chondrosarcoma	2
Clear Cell Sarcoma	1
Alveolar Soft Part Sarcoma	1
Haemangiosarcoma or Lymphangiosarcoma	2
Soft Tissue Ewing's Sarcoma	1
Primitive Neuroectodermal Tumour	1
Haemangiopericytoma	1
Embryonal Rhabdomyosarcoma	1
Fibrosarcoma	0
Epithelioid Sarcoma	0

Heterogeneity of Behaviour

There are a number of subtypes of STS that have "non-typical" behaviour. Three good examples are the 3 subtypes (Synovial sarcoma, Epithelioid Sarcoma and Myxoid Liposarcoma) and these will be discussed in later chapters. I shall demonstrate that each subtype, respectively, can be characterised by unpredictable aggressive behaviour at a small size, propensity for frequent loco-regional recurrence, and an unusual metastatic site distribution. These three subtypes provide examples but many other subtypes of STS have clinical behaviour which distinguishes them as well as having defining histological characteristics.

Other indications of subtype heterogeneity include the frequency of the various subtypes differing with the location of the primary tumour. That is, some subtypes have a propensity for particular locations. For example in the distal extremity there is a higher proportion of synovial sarcoma and epithelioid sarcoma. This contrasts with more proximal limb sites where the more common subtypes predominate and the retroperitoneum where liposarcomas and leiomyosarcomas are relatively more frequent.(see Table 1.2)

The frequency of the various subtypes also varies with the age of the person. For example the peak incidence of MFH and leiomyosarcoma is approximately 65 - 70 years while synovial sarcoma and epithelioid

sarcoma cases have a median age of around 30 years. As mentioned above, the frequency of various subtypes of STS varies with time. This is due mostly to refinements in pathological diagnostic techniques as well as a better understanding of STS biology and genetics. Institutional variation is another factor. This is particularly when large American cancer centres dominate the literature on STS, referral biases and peculiarities in diagnostic criteria can have considerable impact. An example of this would be the frequency of diagnosis of extremity Fibrosarcoma noted from the RMH in Table 1.1 (0 %) compared to MSKCC in Table 1.2 (10 %).

The above confounding factors in diagnosis of the various subtypes of STS have the capacity to make comparisons of prognostic factors over time difficult and hazardous. This has obvious potential implications for multi-institutional validation of a staging system.

Table 1.2 Distribution of Subtypes of STS by Site.[7,16]

SUBTYPE OF STS	RETROPERITONEAL SARCOMA - % OF CASES BY SUBTYPE[16]	EXTREMITY LOCATIONS - % OF CASES BY SUBTYPE[7]
LIPOSARCOMA	42	29
LEIOMYOSARCOMA	23	8
OTHERS	17	24
FIBROSARCOMA	8	10
MFH	7	25
MPNST	3	5

MFH - malignant fibrous histiocytoma
MPNST – malignant peripheral nerve sheath tumour

1.3 DIAGNOSTIC EVALUATION OF STS

(The first part of this section 1.3a relates to the full text of the publication: Hoeber I, Spillane AJ, Fisher C, Thomas JM. The accuracy of biopsy techniques for limb and limb girdle soft tissue tumours. Ann Surg Oncol 2001;8:80-87.[17]
Also 1.3b is taken in part from: Hughes TMD, Spillane AJ. Imaging of Soft Tissue Tumours.(Editorial) Br J Surg 2000;87:3:259-260.[18])

1.3a ABSTRACT

Background: The biopsy method of choice for soft tissue sarcomas (STS) of the limb and limb girdle is controversial. There have been no randomised controlled trials comparing incision biopsy with Tru-cut biopsy. We present a large series, which includes an analysis of the effectiveness of Tru-cut core biopsy both in a tertiary referral centre as well as from many referring hospitals. This is compared to the other methods of biopsy of all soft tissue tumours (STT) referred to this institution.

Methods: A retrospective review of all patients who were referred to Royal Marsden Hospital NHS Trust (RMH) from 1989 to 1998.

Results: There were 570 patients (576 lesions) identified. Overall Tru-cut biopsy differentiated benign from malignant tumours with a sensitivity of 99.4 %, specificity 98.7 %, positive predictive value 99.4 % and negative predictive value 98.7 % with similar results for RMH and referral hospitals. Tru-cut identified both tumour subtype and grade in approximately 80 % of STS. Incision biopsy had similar sensitivity and specificity for differentiating benign from malignant STT as well as

subtype of STS but was less accurate for grade assessment. Tumours from patients referred following enucleation had a median maximum tumour diameter (MTD) of 4.9 cm while median MTD of tumours diagnosed at referring hospitals by Tru-cut biopsy was 10.6 cm. ($p< 0.001$)

Conclusion: Tru-cut biopsy is highly sensitive and specific in the diagnosis of STT as well as subtyping and grading of STS. It is equally effective as incision biopsy in all these parameters and has lesser morbidity. The failure to use Tru-cut biopsy is most likely because the possibility of STS is not suspected in patients with small tumours even when they are deep to the investing fascia.

INTRODUCTION

The diagnostic method of choice for soft tissue sarcomas (STS) is controversial. There has been much discussion in the sarcoma literature about the advantages and disadvantages of Tru-cut biopsy compared to incision biopsy.[17,19-29] Advocates of open incision biopsy claim that Tru-cut core biopsy does not give the histopathologist sufficient tissue to make a confident diagnosis [20] especially when the pathologist is inexperienced and that Tru-cut biopsy is unreliable in differentiating subtype and grade.[24,25,27] Those who favor Tru-cut biopsy would argue that at the initial point of diagnosis it is debatable whether information on grade and subtype is going to change management in the majority of cases (except in small round cell tumors) and the diagnosis of benign from malignant is by far the most important information to be achieved from the initial biopsy. Advocates of Tru-cut biopsy also point to its simplicity and lack of complications compared to the more invasive methods.[19,21,22,26,28] Most specialists in STS would agree that excision biopsy (enucleation) is the least advantageous method of biopsy [22,23,27,28,30,31] because microscopic residual disease is reported to remain in up to 50 % of cases [30-32] and further management is often compromised and complicated. Recently there has been a suggestion that enucleation followed by reresection may have a survival advantage over cases which had only one definitive operation.[33] This could be seen as having major implications for the correct diagnostic strategy for new STS

and may be seen as validating enucleation. We believe this conclusion should not be encouraged until the data are further assessed and validated by a randomised controlled trial.

In the past no reason has been suggested to explain why enucleation [22] is performed as initial management in such a high percentage of patients. It has always been our hypothesis that excision biopsy of STS is performed because the possibility of a STS diagnosis is not considered especially when the lesion is small and alarm bells are not sounded in the surgeon's or radiologist's mind. To assess this, patients who had biopsy performed before referral to RMH were analyzed to determine the maximum tumour diameter (MTD) and investigate any correlation between tumour size and biopsy technique employed.

Therefore this paper aims to give an appraisal of the effectiveness of Tru-cut core biopsy in a tertiary referral center as well as the referring hospitals. This is compared to the other methods of diagnosis of all soft tissue tumours (STT) referred to one institution. We also investigate possible reasons why excision biopsy is still used in more than half the cases diagnosed outside specialist centers [22] and discuss the problems with the problems with the recently published evidence that reresection after excision biopsy may have a survival advantage.[33]

METHODS

A retrospective review of all patients with previously untreated limb and limb girdle STT who were referred to Royal Marsden Hospital NHS Trust (RMH) from 1989 to 1998 was performed. Information was collected on the method of diagnosis and final histopathology. Unfortunately assessment of depth of the tumour in relationship to the investing fascia was not collected. All histopathology discussed has been reviewed at the time of referral by one histopathologist with a specialist interest in STS (CF). Patients who were referred following excision biopsy all underwent wide excision of the tumour bed unless there was a clear history of adequate wide resection from the referring surgeon, supported by histopathological evidence of clear margins. An assessment of the incidence of residual disease was made in these cases.

Statistical analysis for diagnostic methods used compared with the trend in MTD was made using the Mann Whitney Test. Significance was set at $p < .05$ and 95% confidence intervals (CI) are given for the results for incision biopsy as they are based on small numbers.

RESULTS

Final Histopathology

Diagnostic information on 570 patients (576 lesions) was available. Of these, 402 lesions were proven to be soft tissue sarcoma (STS), 159 lesions benign STT and 15 were non-STS malignancies. The tumour types are given in Table 1.3 The 576 lesions were analysed as two separate groups depending on whether the biopsies were performed at RMH or were referred after biopsy elsewhere (Table 1.4).

Diagnostic Methods Used

Table 1.5 gives the diagnostic methods used for STT and STS at RMH and the referring hospitals respectively. As can be seen in Table 1.5. eighteen lesions were definitively diagnosed on excision biopsy at RMH, 15 were proven to be benign and the 3 malignant tumours were widely excised.

Tru-cut Biopsy

To assess the accuracy of Tru-cut biopsy in the diagnosis of STT, the histology of the 314 cores (237 lesions available following resection at RMH as well as a further 77 cases performed outside RMH) was compared to the histology of the resected specimens. However 55 of these cases were excluded from the analysis. The reasons for exclusion are that the STS was treated by radiotherapy and / or chemotherapy only in 21

patients, 13 had a benign STT not resected, 11 were non-STS malignancies, 7 had non-diagnostic core biopsies (technical failure), 2 had neoadjuvant radiotherapy and 1 was a patient with an unresectable STS. Therefore the final assessment was made on 259 patients. The combined RMH and referral center accuracy of Tru-cut biopsy in differentiating STS from benign STT, the accuracy of Tru-cut in differentiating subtype and grade of tumours is demonstrated in Table 1.6. The one false negative was a well-differentiated liposarcoma diagnosed as a benign lipoma. The one false positive was an intramuscular lipoma diagnosed as low-grade myxofibrosarcoma. Analysis of Tru-Cut biopsies performed at RMH and elsewhere as two separate groups lead to similar results for differentiating STS from benign STT and for differentiating grade and subtype after review of the histopathology at RMH.

Tru-cut biopsy accurately diagnosed all non-STS malignancies that presented as soft tissue masses initially (Table 1.3). The commonest non-STS malignancy was lymphoma (10 out of 15).

Incision Biopsy

To assess the accuracy of incision biopsy in the diagnosis of STT, the histology of the incision biopsy specimens from 8 lesions at RMH and from 48 tumours outside RMH was compared to the histology of the specimen resected. However from that total of 56 cases (Table 1.5) 12

were excluded from this analysis because the STT were not resected in 6 patients, 2 were non-STS malignancies, 2 were STS treated by neoadjuvant chemotherapy, 1 patient was treated with neoadjuvant chemoradiotherapy and 1 was an unresectable STS. Therefore the final assessment was made on 44 patients. The assessment of the ability of incision biopsy to differentiate STS from STT is demonstrated in Table 1.7. The one false negative was a well-differentiated liposarcoma diagnosed as a benign lipoma. There were 3 wound breakdowns identified in the 56 patients (5.4%) who had incision biopsy.

Mean Tumor Diameter and Biopsy Method

Assessing the patients with STT who had biopsy performed before referral to RMH we determined the MTD of 162 cases following excision biopsy and 77 who had Tru-cut biopsy (Table 1.5). However 31 of the 162 excision biopsies and 4 of the 77 Tru-cut biopsies were excluded because the MTD could not be ascertained (for excision biopsy this is usually because the tumour had been removed piecemeal!). The median MTD of 131 STT biopsied by excision was 4.9 cm (range 0.5 to 20 cm) in contrast to a median of 10.6 cm (range 2.5 to 30 cm) of 73 STT biopsied by Tru-cut biopsy. The trend in distribution of methods of diagnosis is statistically significant ($p < 0.001$). (Table 1.8)

Residual Disease after Excision Biopsy

Of the 140 cases of STS diagnosed by excision biopsy before referral to RMH (Table 1.5), tumour bed resection was performed in 107 patients and residual disease was found in 60 cases (42.9 %). There were 47 resection specimens (33.6 %) free of tumour. No tumour bed excision was performed in 33 patients (23.6 %) following discussion of resection technique with the referring surgeon and histopathological verification of clear margins.

Table 1.3: Tumour Histopathological Description and Subtypes

SOFT TISSUE SARCOMA n = 402		
Malignant fibrous hisiocytoma	98	24.4%
Leiomyosarcoma	90	22.4%
Liposarcoma	58	14.4%
Not otherwise specified	38	9.5%
Synovial sarcoma	36	9.0%
Malignant peripheral nerve sheath tumour	15	3.7%
Soft tissue Ewing's sarcoma	11	2.7%
Soft tissue chondrosarcoma	8	2.0%
Rhabdomyosarcoma	7	1.7%
Fibrosarcoma	7	1.7%
Clear cell sarcoma	6	1.5%
Epithelioid sarcoma	6	1.5%
Alveolar soft part sarcoma	5	1.2%
Malignant mesenchymoma	4	1.0%
Primitive neuroectodermal tumour	3	0.7%
Malignant schwannoma	3	0.7%
Dermatofibrosarcoma	2	0.5%
Osteosarcoma	1	0.2%
Angiosarcoma	1	0.2%
Haemangiopericytoma	1	0.2%
Follicular dendritic cell sarcoma	1	0.2%
Malignant solitary fibrous tumour	1	0.2%
BENIGN NEOPLASTIC, INFLAMMATORY & OTHER n = 159		
Lipoma (deep to the deep fascia)	58	36.5%
Fibromatosis	20	12.6%
Myxoma	12	7.5%
Unspecified benign tumour	15	10.1%
Neurilemoma	8	5.0%
Neurifibroma	5	3.1%
Benign cellular fibrous histiocytoma	3	1.9%
Dermatofibroma	2	1.3%
Arteriovenous malformation (AVM)	10	6.3%
Unspecified cystic lesion	6	3.8%
Non-specific inflammation	4	2.5%
Proliferative myositis	3	1.9%
Myositis ossificans	2	1.3%
Synovitis	2	1.3%
Ganglion	2	1.3%
Other not otherwise specific	6	3.8%
NON-STS MALIGNANCY n = 15		
Lymphoma	10	66.7%
Carcinoma	2	13.3%
Bony chondrosarcoma	1	6.7%
Bony Ewing's sarcoma	1	6.7%
Malignant pilomatrixoma	1	6.7%

Table 1.4: Distribution of Histopathological Diagnostic Groups in Patients Referred to RMH With and Without Prior Biopsy Proven Diagnosis

Primary limb & limb girdle STT	Patients referred to RMH on suspicion	with previous diagnosis	Total
STS	148 (36.8%) [54.4%]	254 (63.2%) [83.6%]	**402** (100%) [69.8%]
Benign STT	111 (69.8%) [40.8%]	48 (30.2%) [15.8%]	**159** (100%) [27.6%]
Non-STS malignancy	13 (86.7%) [4.8%]	2 (13.3%) [0.7%]	**15** (100%) [2.6%]
Total	**272** (47.2%)	**304** (52.8%)	**576** (100%)

Table 1.5: Methods of Diagnosis Performed on Primary Limb and Limb Girdle STT & STS at RMH

SOFT TISSUE TUMOURS						
Method of diagnosis	Tru-cut biopsy	Excision biopsy	Incision biopsy	Fine needle aspiration biopsy	CT, others	Total
At RMH	**237 (87.1%)**	18 (6.6%)	8 (2.9%)	2 (0.7%)	7 (2.6%)	**272** (100%)
And elsewhere	77 (25.3%)	**162 (53.3%)**	48 (15.8%)	7 (2.3%)	10 (3.3%)	**304** (100%)
Total	**314**	**180**	**56**	**9**	**17**	**576**
SOFT TISSUE SARCOMA						
At RMH	**144 (97.3%)**	2 (1.4%)	1 (0.7%)	0 (0%)	1 (0.7%)	**148** (100%)
And elsewhere	65 (25.6%)	**140 (55.1%)**	42 (16.5%)	4 (1.6%)	3 (1.2%)	**254** (100%)
Total	**209**	**142**	**43**	**4**	**4**	**402**

Table 1.6: Accuracy of TRU-CUT Biopsy in the Diagnosis of STS from Benign STT and Subtype of STT

TRU-CUT RESULT	**Final Histology STS**	**Final Histology STT (Benign)**	
MALIGNANT	179	1	PPV 99.4%
BENIGN	1	78	NPV 98.7%
	Sensitivity 99.4%	Specificity 98.7%	
TRU-CUT SUBTYPE RESULT*			
	Correct	**Incorrect**	**Indeterminable**
STS n = 179	143 (79.9%)	11 (6.1%)	25 (14.0%)
STT (benign) n = 78	63 (80.8%)	6 (7.7%)	9 (11.5%)
TRU-CUT GRADE RESULT			
	Correct	**Incorrect (Lower in all cases)**	**Indeterminable**
STS n = 179	152 (84.9 %)	12 (6.7%)	15 (8.4%)

* 2 core-needle biopsies excluded because wrong diagnosis given

PPV = positive predictive value

NPV = negative predictive value

Table 1.7: Accuracy of Incision Biopsy in the Diagnosis of STS from Benign STT, Diagnosis of Subtype of STS and Subtype of Benign STT, and Diagnosis of Grade of STS

INCISION BIOPSY RESULT	**Final Histology STS**	**Final Histology STT (Benign)#**	
MALIGNANT	37	0	PPV 100%
BENIGN	1	6	NPV 85.7%
	Sensitivity 97.4%	Specificity 100%	
INCISION BIOPSY SUBTYPE RESULT*			
	Correct	**Incorrect**	**Indeterminable**
STS n = 37	30 (81.1%)	5 (13.5%)	2 (5.4%)
STT (benign) n = 6	6 (100%)	0 (0%)	0 (0%)
INCISION BIOPSY GRADE RESULT			
	Correct	**Incorrect (Lower in all cases)**	**Indeterminable**
STS n = 37	24 (64.9%)	6 (16.2%)	5 (13.5%)

11 benign STT, 2 lymphomas excluded

*1 incision biopsies excluded because wrong diagnosis given

Table 1.8: Correlation Between MTD and Method of Diagnosis at Referring Hospital

MTD (cm)	Excision biopsy frequency (%)	Tru-cut biopsy frequency (%)
0 to 5	87 (**66.4%**)	10 (**13.7%**)
5.1 to 10	38 (29.0%)	35 (47.9%)
10.1 to 15	4 (3.1%)	17 (23.3%)
15.1 to 20	2 (1.5%)	6 (8.2%)
20.1 to 25	0 (0%)	3 (4.1%)
25.1 to 30	0 (0%)	2 (2.7%)
Total	**131** (100%)	**73** (100%)

DISCUSSION

Soft tissue tumours have a benign to malignant ratio in a hospital population of 100:1 with the majority of lesions representing benign lipomas.[34] Tumours deep to the investing fascia are much more frequently malignant and should be assumed to be so until proven otherwise by representative histology. The biopsy method of choice in STT is strongly contested.[19,21,22,24-28,33] This paper is different from other series on the topic in that it assesses the performance of our specialist unit and contrasts this to the referring hospitals. We have demonstrated the effectiveness of both incision biopsy and Tru-cut biopsy in both settings, hopefully answering some of the major criticisms of the Tru-cut technique, which undoubtedly has lower morbidity.[19]

Tru-cut biopsy can be performed under local anesthesia at the time of initial consultation. The technique has been criticized because the volume of the tumour offered to the pathologist is too small for full histological evaluation.[20,24,25,27] However this series and others [21,22,26,28] have shown that Tru-cut biopsy can reliably differentiate benign from malignant STS. In addition this paper shows that in patients with STS, tumour subtype and grade can be accurately predicted in 80% of patients. This paper and earlier work from this institution also demonstrates that the histopathological results from Tru-cut biopsy are reliable even if the mass turns out to be a non-STS malignancy.[35] The quality of the Tru-

cut cores obtained was equal at the RMH to the referring hospitals suggesting that the technique's successful performance may not be dependent on the volume of the specialist's experience. It may be possible that in a retrospective study such as this that the referring hospitals did not admit to a failed Tru-cut attempt in their referral, however we have made every attempt to exclude this possibility by reviewing all histopathology concerning each referral. The argument that non-specialist pathologists can't reliably diagnose STS on small samples [27] is flawed because even small samples can be sent to a second (specialist) opinion! The false negative Tru-cuts for malignancy in this series and others [26] are due to well-differentiated liposarcoma being misdiagnosed as lipoma. However this distinction can be difficult even with the whole specimen. We often do a Tru-cut biopsy but base management on CT Scan findings and tend to be conservative in this subtype of STS with virtually no metastatic potential. We believe that to reflect negative predictive values as low (79 %) for Tru-cut biopsy based on this subtype of STS is misleading.[26]

Incision biopsy has been stated to be the favored option for the diagnosis of STT. This is to give a volume of tissue for reasons of "adequate" assessment by inexperienced pathologists. Incision biopsy is also said to be better for subtyping and grading the tumor preoperatively. Other than being able to be more confident about the need for postoperative

radiotherapy we have found that taken in conjunction with radiological findings, as long as the tumour is accurately determined to be malignant, information on grade has little potential to alter the subsequent steps in management. Similarly information on subtype is rarely useful preoperatively other than in the case of small round cell tumours, which are easily identified on Tru-cut biopsy. When the evidence to support the assertion of better sensitivity and specificity for incision biopsy compared to Tru-cut for determining subtype and grade is investigated the most frequently quoted studies are flawed in that they either do not have final resection histopathology in all cases [24], they group FNA and Tru-cut together for assessment of "needle biopsy" [25] or they are based on relatively small numbers [24-26]. In this large series, which may be biased by our preference for Tru-cut biopsy, we have accumulated similar numbers of cases with incision biopsy to most of the series that are quoted as demonstrating these factors. All those cases that did not have definitive tumour resection for comparison with the Tru-cut and incision biopsy were excluded. In doing this we have found similar sensitivity for both techniques for diagnosing benign from malignant STT, similar accuracy for subtyping and somewhat surprisingly the results for grade were slightly worse for incision biopsy. A possible reason for this finding include that the majority of the incision biopsies were performed at referring centers and as explained below they are often taken from the dome of the tumour which is likely to have the poorest blood supply and

most chance of necrosis and unrepresentative sample. Tru-cut biopsy can be taken in a number of directions through the same small stab incision and this may in fact give more reliable sampling for grade according to this data. We believe that the frequency of inadequate sample with Tru-cut biopsy can be lessened by following a simple principle. If the specimen sinks in formalin the specimen is usually representative. If the specimen floats we take more cores.

Despite the recent counter-intuitive evidence suggesting that reresection of extremity STS improves patient survival by an unexplained mechanism [33], we still believe that excision biopsy is an undesirable and avoidable error in the initial management of patients with STS. Enucleation usually takes place in the plane of the false capsule and it is known from this series and others that following subsequent tumour bed excision residual disease remains in about half the cases.[30-32] Furthermore the anatomy returns rapidly to near normal after enucleation and it is difficult to identify the site of the tumour bed on imaging due to the disturbance caused by surgery. Consequently at tumour bed excision it frequently happens that more unaffected tissue is removed than would have been necessary had wide surgical resection been performed with the tumour in situ. The only way to avoid this error is to raise awareness and to encourage appropriate biopsy of all tumours deep to the deep fascia.

Open incision biopsy and enucleation require at least day case admission and often a general anaesthetic. The disadvantages of enucleation and (occasionally) incision biopsy are that the scar may be inappropriately placed with reference to the incision required for wide surgical clearance. The incision is often done in a cosmetically pleasing transverse skin crease incision that makes it very difficult to make an appropriate longitudinal incision for a wide or compartmental resection. Furthermore the incision is usually placed over the dome of the tumour where skin vascularity is most likely to be impaired and consequently the incision may fail to heal or become infected.[19] Subsequent tumour fungation through the wound from the incision biopsy (or occasionally an enucleation) is unfortunately not a rare occurrence in our experience. One of the consequences of enucleation, and a common source of referral to this institution with recurrent disease, is the situation where patients have been assessed (or assumed) to have clear margins by the treating physicians, and they are not appropriately referred. This may not only result in inadequate surgery, with close margins or microscopic foci of disease remaining, but also may result in failure to receive appropriate adjuvant radiotherapy with its proven advantages for local control in high grade STS.[36-38] These events result in higher rates of local failure with the associated psychological stress, increased morbidity from further

treatment and there is increasing evidence that local recurrence events have an impact on survival.[38]

STS are uncommon tumours and it has been our hypothesis that they are inappropriately excised because the diagnosis was not considered. Patients are frequently referred with letters that state that the preoperative diagnosis was intramuscular lipoma. We therefore looked at the MTD of tumours biopsied outside RMH by excision and Tru-cut biopsy. The results demonstrated that the median MTD of excised tumours was 4.9 cm and that of tumours biopsied by core was 10.6 cm. Stated differently 66.4 % of tumours undergoing excision biopsy were smaller than 5 cm and 86.3 % of tumours diagnosed by Tru-cut biopsy were greater than 5 cm. This data suggests it is the smaller STS that are at greatest risk of enucleation and inappropriate management, when it is this group of patients who have the best prognosis.[1,4] The larger STT are more often suspected of being malignant and are more often biopsied appropriately. The recent data presented by Lewis et al. support this contention with 60 % of the cases that were reresected being smaller than 5 cm.[33] It could be argued that the reason why more tumours were enucleated when they were small was because they were small and superficial. The work of Heslin et al. and Lewis et al. support this argument to some extent.[26,33] Superficial tumours were first recognized to have a better prognosis than those deep to the investing fascia by Hajdu.[39] More recently this

parameter has been included in the 5th Edition AJCC and UICC Staging Systems.[4,5] When the impact of the changes to these staging systems is assessed only 5 % of cases fall into the new AJCC / UICC stages 1B and 2C and therefore in practice do not have a significant impact.[8,40] The presentation of a STS with a superficial location rarely alters our preference for biopsy before definitive management.

Fine needle aspiration biopsy (FNAB) has not featured in this discussion as it is generally agreed that there is no place for FNAB in the diagnosis of primary STS.[41,42] It can be a useful confirmation of recurrence.

The recently published study by Lewis et al. has major implications for the diagnostic strategy that should be encouraged for STS.[33] The authors conclude that there is a survival advantage for reresection of STS over those cases that have a single definitive operation (which implies a suitable preoperative biopsy in the majority of cases).[33] The authors can not explain their result but believe they have eliminated all the obvious biases in their analysis. However all the important data has not been presented in their paper and the authors have not discussed some inconsistencies in their data before reaching their conclusions. Firstly in the AJCC Stage analysis (data not presented, only discussed in the text) the authors state "In all stages there was a trend toward improved survival for the reresection group, and this was most apparent and statistically

significant (P=.005) for stage III (> 5cm, high grade, and deep) disease." [33] In a study where there was a heavy weighting towards the small, superficial STS this appears to state that the only stage group that reached statistical significance is stage III which may have had the fewest cases. Secondly, there is a discrepancy between the 2 groups in the study as far as subtype distribution is concerned. This is particularly noticeable for fibrosarcoma where 85 % of cases were in the one operation group. Different subtypes of STS behave in a different biological manner and this can influence the validity of the AJCC Staging System in relationship to them.[8] Thirdly, the discrepancy in microscopic margin positivity rate between the 2 groups has not been adequately explained. Positive microscopic margins are a predictor for decreased survival in some studies of extremity STS [7] but this variable is not taken into account in the AJCC Staging System.[4] There are only three possible explanations for the margin positivity discrepancy. Either the surgeons were different (obviously not), the tumours were different (this could relate to subtype discrepancies) or the sites of the tumours were different with patients with the more difficult sites being more likely to be referred for specialist opinion. Following this logic one would assume more cases in the one operation group to be very distal, very proximal in the limb or around neurovascular structures, however, this data has not been presented. Some studies have identified extracompartmental site versus compartmental site of STS as an independent prognostic factor for STS.[43,44] This concept

has been refuted by Gaynor et al. from the multivariate assessment of a retrospective series of 423 patients and has not been further assessed since.[45] Therefore we conclude that the counter-intuitive conclusions of Lewis et al. have a number of questions which remain unanswered regarding their validity. In the mean time these conclusions should not be accepted and definitive preoperative biopsy should be the standard of practice until a randomised controlled trial that could eliminate these biases is undertaken.

In conclusion every mass deep to the deep fascia is a sarcoma until proven otherwise. The possibility of malignancy tends not to be considered when the tumour is small. Tru-cut biopsy at the time of initial consultation will not only differentiate benign from malignant STT but will also define tumour subtype and grade in a high proportion of patients. Incision biopsy is equally effective in differentiating STS from benign STT and it has similar ability to identify subtype and grade of STS, however, it has a higher morbidity than Tru-cut biopsy. Therefore failure to get adequate sample or adequate information with the initial Tru-cut can be followed by repeat Tru-cut or if there are specific indications, incision biopsy. Even though recent evidence suggests excision biopsy may be associated with an unexplained improvement in survival there are unexplained sources of bias in the data used to reach

this conclusion. Certainly, in terms of functional outcome the best results are achieved following planned surgical excision with the tumour *in situ*.

Summary – Diagnosis of Soft Tissue Tumours

A new presentation with an undiagnosed soft tissue tumour is best assessed clinically to determine location, involvement of neurovascular structures, as well as clinical evidence of regional and distant metastases. A lesion which is small and superficial consistent clinically with a lipoma should have excision biopsy with no further investigation. Larger lesions and all deep tumours should have radiological assessment and pre-operative biopsy performed to give definitive histological confirmation of the diagnosis.

1.3b Imaging:

At the RMH the standard practice if the lesion was likely to be malignant was for the lesion and the thorax to be assessed with Computerised Tomography scan (CT Scan) with intravenous contrast. As far as assessment of the primary tumour site we found the dogma of Magnetic Resonance Imaging's (MRI) superiority over CT Scan to be unjustified on current best available evidence. Indeed we warned against the over-reliance on MRI or CT Scan with both having high false positive and false negative rates for neurovascular involvement in a recent editorial.[18]

1.4 PROGNOSTIC FACTORS IN STS

STS tend to be grouped together for describing their biological behaviour, determining prognostic factors and planning management strategies. This convenience has been driven by the clinical rarity of the individual subtypes, the relative inexperience of all but the most specialised of treatment centres, and publication of large series from specialist referral centres where these management groupings have been encouraged.[7,43-45,47] I have hypothesized that this tendency for grouping together tends to result in an averaging of individual subtype behaviour, or more accurately, a weighting towards the more common subtypes behaviour characteristics. The more recent staging systems for STS have been developed from cohorts of extremity lesions but applied more widely. I have hypothesized that this must weaken the validity of the staging systems in the sites not tested specifically. It would be very interesting to see the outcome when tumours that occur in the retroperitoneum were assessed for prognosis according to the staging system. To my knowledge this has never been done. The large studies on retroperitoneal sarcoma do not assess the validity of the AJCC / UICC Staging Systems as a prognostic indicator as most STS at this location present as > 5 cm and deep (by definition). Therefore grade is the only discriminator relevant to the staging system. The recent series by Lewis et al. with 500 cases from a single institution would have been an excellent opportunity to assess the

validity of the staging systems in retroperitoneal sarcoma but this was not done.[16]

Prognostic factors for STS can be assessed for their relevance to various end points. Generally speaking the most important end points is overall survival. However other points of relevance to the patient and physicians are disease free survival, local recurrence free survival, and distant disease free survival.

The important primary tumour factors in determining overall survival for STS have been shown to be the grade, size and depth of the tumour in relation to the deep fascia. Therefore higher grade, larger size and deep location indicate the worst prognosis. The presence of regional or distant metastases are known to be indicative of a very poor prognosis.[7,10,11] Other factors have been suggested to have prognostic significance. These include patient age (with younger patients doing better), recurrent disease at presentation (to a major sarcoma centre) and positive microscopic resection margins.[7] Some reports focus on the subtype of STS as being relevant with malignant peripheral nerve sheath tumours and leiomyosarcomas having a worse prognosis.[7]

Some of the prognostic factors for local recurrence free survival are different to those for overall survival.[7] Pisters et al. demonstrated that

local recurrence is predicted for by the size and grade of the primary tumour, age greater than 50 years, presentation (to a referral centre) with local recurrence, histological subtypes fibrosarcoma and malignant peripheral nerve sheath tumour, and most significantly equivocal or microscopically positive surgical margins.[7] These factors are not all integrated into the current staging systems but are important in specific situations.

There have been several studies that have identified compartmental versus extra-compartmental STS as being an independent prognostic factor for extremity STS.[48,49] This has been disputed by Gaynor et al. in a retrospective study of 432 patients.[45] The explanation given was that extra compartmental tumours tend to have a higher incidence of margin positivity and that may independently influence survival. The significance of compartmental versus extra-compartmental disease has not been further assessed in the larger prospective series published since the time that Gaynor et al. made their assessment.

1.4a GRADING STS

Histological grade has been shown to be the most important prognostic factor in STS in virtually all studies. This is despite of the various grading systems in use.[7,49-63] One of the greatest problems with the development of universally cohesive management strategies in STS is the

failure to develop a consensus grading system for all STS. This is reflected by the EORTC grading system having 3 grades [50] whereas the UICC Staging System now recognises 4 grades [5] that are effectively grouped as high and low grade (i.e. grade 1 / 2 and grade 3 / 4 are always grouped together in the staging system).

The factors that are generally important in the determination of grade include degree of cellularity, mitotic rate (frequency and abnormality of mitotic figures), the presence of necrosis and haemorrhagic changes, cellular pleomorphism and anaplasia, and an expansive or infiltrative, invasive growth pattern. All these factors are often closely related but the 2 most important factors are considered to be mitotic count and extent of necrosis.[65] The relative importance of each component to grade determination can vary in the different subtypes of STS and this is one basis for the difficulty in obtaining uniformity in grading between different pathology centres.

Certain subtypes of STS have their grade determined by their very nature. Alveolar and embryonal rhabdomyosarcomas, neuroblastoma, extraskeletal Ewing's sarcoma, peripheral neuroepithelioma, and osteosarcoma, for example, are always high grade.[13] Fibromatosis is always seen as a low grade STS. In relation to this thesis epithelioid sarcoma is always considered high grade, synovial sarcoma has generally

been determined to be high grade (although this is increasingly controversial) whereas myxoid liposarcoma is usually low grade but the presence of a significant round cell component indicates a higher grade.

Intuitively grade has been recognised as a continuous variable and this has formed the basis of the staging and grading systems for STS.[1,2,4,5,51,52,60-64] Recent changes to the AJCC / UICC Staging Systems [4,5] from a 3 grade system to an effectively 2 grade system (grade 1&2 and 3&4 are always grouped together) intuitively lessen the potential for prognostic separation based on grade by obvious mechanisms of allowing less couplings of prognostic factors to form less stage groups. This initially may seem undesirable but the practical issues involved in management of STS dictate many adjuvant radiotherapy or even chemotherapy trial decisions simply require separation of high and low grade STS for determining their use. Therefore these practical considerations have driven the change rather than the desire to have more nicely distributed stage groups.

Other factors such as Ki-67 reactivity, argyrophilic stain for nucleolar organiser regions (AgNOR counts), and mast cell counts have been investigated as potential histological markers for assessment of proliferative activity and prognostic implications in STS but to date has not impacted on the commonly used grading systems.[13] To date

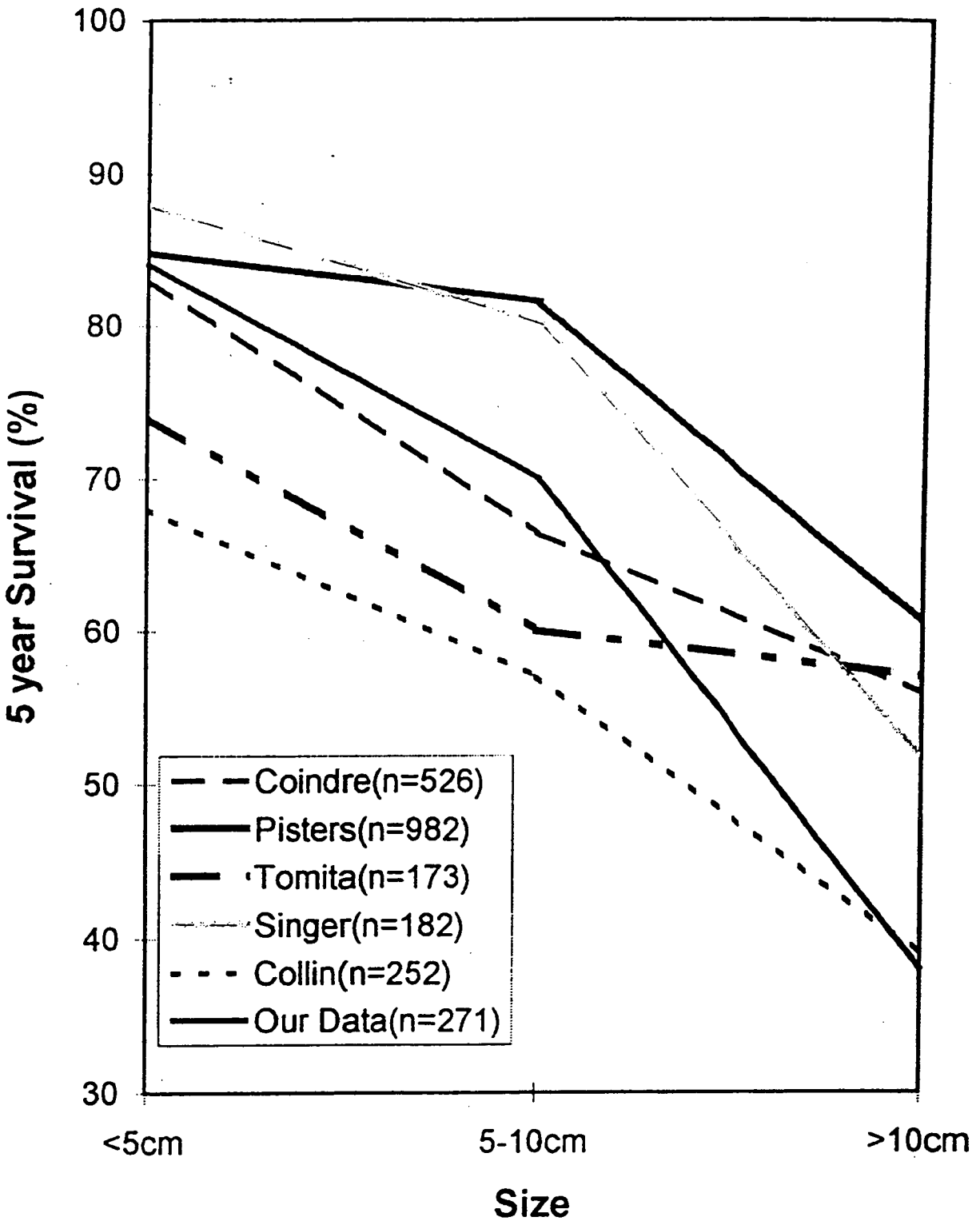
chromosomal alterations have not made an impact of grade differentiation. With the development of a better understanding of carcinogenesis and metastatic potential, one would expect these factors would have an impact as they have already with subtype determination.

1.4b SIZE

The prognostic significance of STS tumour size will be discussed in more detail in Chapter 2, which discusses problems with the current staging systems in STS. Size has been known to be of prognostic significance in STS for many years. However it has traditionally been allocated lesser significance than the grade of the STS.(Table 1.9) Size is generally considered either < 5 cm or > 5 cm but in certain subtypes of STS such as epithelioid sarcoma many tumours are smaller that 2 cm at presentation. Similarly most retroperitoneal sarcomas and many thigh STS for instance are much larger than 5 cm. In Chapter 2. I argue that the currently accepted size brackets in the staging systems do not reasonably represent this common range of size of STS, when there is excellent evidence from the work at the RMH as well as other institutions that size is a continuous variable. There are at least 6 studies that have demonstrated separation in prognosis based on size brackets < 5, 5 – 10 cm and > 10 cm. Figure 1.1 demonstrates the association between size and 5 year survival as summarised in Ramanathan et al.[1,7,47,66-68]

Pathological assessment is the most accurate measurement of size of a STS but occasionally it is necessary to rely on pre-operative radiological parameters or even clinical assessment.

Figure 1.1 Published literature demonstrating significant association between size and 5 year survival.[1]



Comparison between 5-year survival of different tumor size categories (< 5, 5-10, and > 10 cm) reported in other studies and our results.

1.4c DEPTH OF TUMOUR

Hajdu first recognised that tumours deep to the investing fascia have a worse prognosis than those more superficial and that this was otherwise independent of tumour location and size.[64] Previously it had been assumed that superficial lesions were found at a smaller size and were often lower grade.[47,67,69] Depth has been incorporated into the latest edition of the AJCC and UICC Staging Systems for STS as will be critically discussed in Chapter 2.

The parameter of tumour depth is readily applicable to extremity and body wall truncal STS. At other sites, such as the retroperitoneum and in the thorax, where all tumours are deep, depth does not discriminate. It would have to be questioned whether a staging system should be applied to these sites when the staging system had been developed from data on extremity lesions. Despite the current AJCC / UICC Staging Manuals stating that the staging systems are applicable to a number of non-extremity sites, I am not aware of any studies validating their use in these sites.[4,5]

1.5 DEVELOPMENT OF STAGING SYSTEMS FOR SOFT TISSUE SARCOMA

Enzinger and Weiss state that "the histological type of sarcoma does not always provide sufficient information for predicting the clinical course, and grading and staging of soft tissue sarcoma are essential for accurate prognosis, planning and evaluation of therapy, and comparison and exchange of data." This concept has driven the development of staging systems for STS.

During the last 20 years various clinicopathological staging schemes have been described for STS.[13,51,52,60-63] The staging of soft tissue sarcoma has developed principally from large American or European centres who have made assessments from their pooled data including all subtypes of STS, with the qualification that in some series under-represented subtypes of STS were excluded. Only the largest studies have made an assessment of subtype in relation to prognosis.[7]

Early on in the development of the staging systems grade was identified as the principle determinant of outcome. Size was seen as secondary importance and therefore the earliest proposed staging system from multi-institutional data related this.(see Table 1.9) The attractive simplicity of this staging system has been hard to escape since that time and has blinded the responsible staging committees to data that has been known

about for some time regarding size being a continuous variable in STS [6,7], the importance of depth of the tumour in relation to the body's investing fascia [7,39,45,47], and specific biologic behaviour of subtypes of STS [7,10-12]. Nevertheless, further refinement of the staging of STS has occurred principally derived from work published from Memorial Sloan-Kettering Cancer Center (MSKCC) regarding the significance of depth and that small, high grade STS had a better prognosis than identified by the earlier versions of the AJCC Staging System.[45,51] Therefore the 5th Edition version of the AJCC Staging System was the first time that major adjustments were made to this original structure based on assessment of large numbers of cases with prospectively collected data.[4,5]

Table 1.9 The Earliest AJC Staging System for STS [51]

AJC STAGE	PARAMETERS
STAGE1A	Grade 1 < 5 cm
STAGE 1B	Grade 1 ≥ 5 cm
STAGE 2A	Grade 2 < 5 cm
STAGE 2B	Grade 2 ≥ 5 cm
STAGE 3A	Grade 3 < 5 cm
STAGE 3B	Grade 3 ≥ 5 cm
STAGE 4A	Any Grade, Any Size, Lymph Node +ve
STAGE 4B	Any Grade, Any Size, Distant Metastasis

1.6 CURRENT STAGING SYSTEMS FOR STS

The current widely accepted staging systems in use are the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer Staging Systems (UICC). These 2 staging systems are the same in their 5th Edition. They are demonstrated in Table 1.10. Table 1.11 summarises the recently published RMH Staging System that will be used to compare and contrast the staging assessment for the three subtypes of STS examined in this Thesis. It is useful to note that the AJCC document references a number of publications as to be the source of the information from which they derived their staging system.[51,53,67,70-79] The AJCC document quotes survival and disease free percentages directly (from otherwise not referenced) MSKCC data. The UICC – TNM Classification of Malignant Tumours (5th Edition) does not quote references and therefore I assume, in this thesis, that the data from which the staging systems are derived is from the AJCC publication.

Table 1.10 The 5th Edition AJCC / UICC Staging Systems [4,5]

STAGE	AJCC / UICC (5th Edition) STAGING SYSTEM [4,5]	AJCC PREDICTED % 5 YEAR SURVIVAL
1A	G1-2 T1a / b N0 M0	All Stage 1 98.8
1B	G1-2 T2a N0 M0	
2A	G1-2 T2b N0 M0	All Stage 2 81.8
2B	G3-4 T1a-b N0 M0	
2C	G3-4 T2a N0 M0	
3	G3-4 T2b N0 M0	All Stage 3 51.6
4	G1-4 T1-2 N0-1 M1	

Note:
AJCC / UICC 5th Edition Version T1 ≤ 5 cm, T2 > 5 cm, a = superficial*, b = deep, G = grade, N0 = no nodal metastases, N1 = nodal metastases, M0 = no distant metastases, M1 = distant metastases

* Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumours.

The following histological types of malignant tumour are included:
Alveolar soft part sarcoma
Epithelioid sarcoma
Extraskeletal chondrosarcoma
Extraskeletal osteosarcoma
Fibrosarcoma
Leiomyosarcoma
Liposarcoma
Malignant fibrous histiocytoma
Malignant hemangiopericytoma
Malignant mesenchymoma
Malignant schwannoma
Rhabdomyosarcoma
Synovial sarcoma
Sarcoma NOS (not otherwise specified)

The following histological types of tumour are not included in the staging system's assessment: Kaposi sarcoma, dermatofibrosarcoma (protuberans), fibrosarcoma grade I (desmoid tumour), and sarcoma arising from the dura mater, brain, parenchymatous organs, or hollow viscera.

The T N M categories can be clinical / radiological or pathological.

Table 1.11 The proposed RMH Staging System [1]

STAGE	MODIFIED RMH STAGING SYSTEM [1]	% 5 YEAR SURVIVAL
1A	G1 T1	100
1B	G1 T2 G2 T1	83
2A	G1 T3 G2 T2 G3 T1	74
2B	G1 T4 G2 T3 G3T2	61
3A	G2 T4 G3T3	39
3B	G3, T4	18
4A	G 1-3, T 1-4, N1	6
4B	G 1-3;T 1-4, N0-1, M1	

Note:

T1 < 5 cm, T2 ≥ 5cm - < 10 cm, T3 ≥ 10 cm-< 15 cm, T4 ≥ 15 cm
G = grade, N0 = no nodal metastases, N1 = nodal metastases
M0 = no distant metastases, M1 = distant metastases

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CHAPTER 2.

2.1 PROBLEMS WITH THE CURRENT STAGING SYSTEMS IN SOFT TISSUE SARCOMA.

(Modified from: Spillane AJ, Thomas JM. Staging of Soft Tissue Sarcomas.(Editorial) Eur J Surg Oncol 1999;25;6:559-561. Also incorporating components of: Spillane AJ, Thomas JM. Misconceptions with Staging of Soft Tissue Sarcoma.(Letter) J Clin Oncol. 2000;18;8:1800-1801.)

Staging systems for many types of tumours change occasionally. Usually the change is the result of new information about the disease process or more sensitive diagnostic technologies and the modification should aim to give the most useful available prognostic information for the clinician and patient alike. If widely adopted a staging system allows comparison between centres which in turn may result in therapy being modified to achieve the best current results. The establishment of a universally acceptable staging system for soft tissue sarcoma (STS) has been hampered by their low incidence and heterogeneity, disagreement regarding the histogenesis and grading, and lack of consensus regarding the value of various prognostic factors.[1]

The AJCC and UICC Staging Systems (5th Edition) for STS were changed in 1997 [2,3] having been last modified in 1992.[4,5] The 5th Edition AJCC / UICC Staging Systems[2,3] for STS are currently being challenged for their deficiencies in offering adequate prognostic differentiation for individual patients.[1,6-8] Recently a suggested modified staging system from the RMH [1] elegantly demonstrated that

size and grade are equally important factors in determining prognosis of STS (Figure 2.1 & 2.2). The authors suggested modifications to the 4th Edition version of the AJCC / UICC Staging Systems[4,5] and despite this Edition subsequently being superseded the principle arguments still apply. Table 2.1 demonstrates a comparison between the RMH Staging System[1], current AJCC / UICC[2,3] and previous AJCC / UICC[4,5] Staging Systems with an indication of prognosis for each stage for the first two staging systems. Put simply 5 years after diagnosis AJCC Stage 1 disease has virtually no disease related deaths, Stage 2 disease has an 80 % survival, Stage 3 has a 50 % survival and Stage 4 disease having very few survivors.[2] To those who see large numbers of cases of STS it would seem optimistic to say the least to tell a person with a 15 cm high grade extremity STS that they had a 50 % 5 year survival. This contrast with the RMH Staging System which gives a more gradual and even spread deterioration in prognosis therefore giving both clinician and patient more realistic information about the likely outcome. It should be noted that the RMH Staging System has not been validated against any other dataset. Hence, the assumption of its reliability may not be widely accepted. Nevertheless, it provides an insightful alternative to the current staging system.

Fig.2.1 Plot of hazard ratios for disease-specific survival (log scale) of each histological grade within each RMH size bracket.

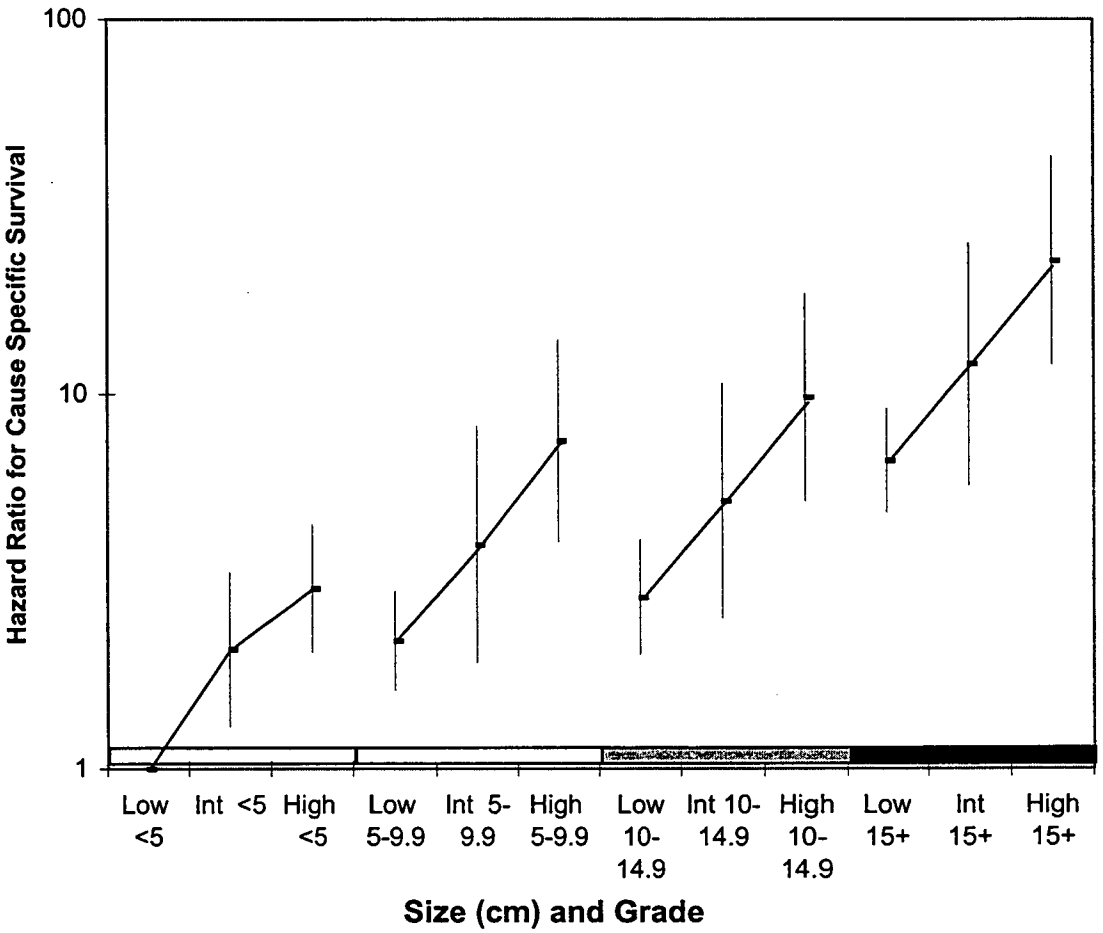

Fig. 2.2. Plot of hazard ratios for disease-specific survival (log scale) of each RMH size category within each histological grade.
[Reproduced with permission Ann Surg Oncol 1999;6;1:57-69]

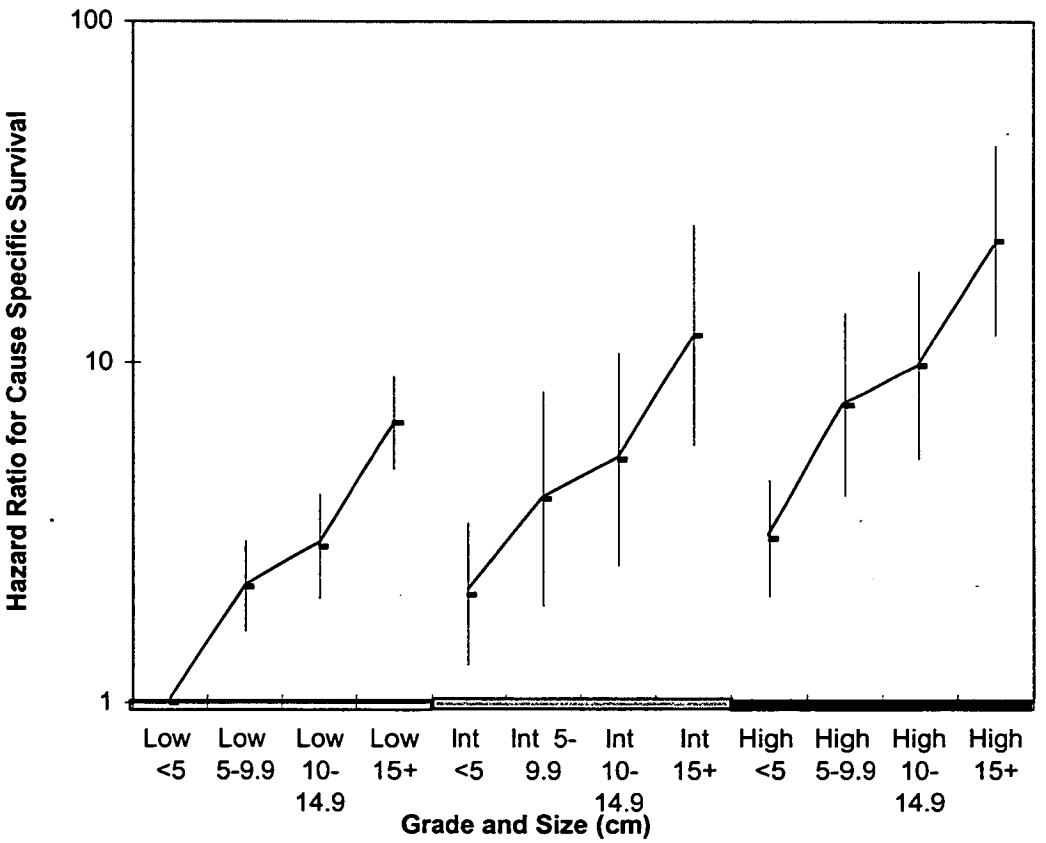

Table 2.1 Comparison of Staging Systems discussed.

STAGE	RMH STAGING SYSTEM [1]	% 5 YEAR SURVIVAL	AJCC / UICC (5th EDN) STAGING SYSTEM [2,3]	% 5 YEAR SURVIVAL	AJCC / UICC (4th EDN) STAGING SYSTEM [4,5]
1A	G1 T1	100	G1-2 T1a / b		G1 T1
1B	G1 T2 G2 T1	83	G1-2 T2a	98.8	G1 T2
2A	G1 T3 G2T2 G3 T1	74	G1-2 T2b		G2 T1
2B	G1 T4 G2 T3 G3T2	61	G3-4 T1a-b	81.8	G2 T2
2C			G3-4 T2a		
3A	G2 T4 G3T3	39	G3-4 T2b	51.6	G3 T1
3B	G3, T4	18			G3 T2
4A	G 1-3, T 1-4, N1	6	G1-4 T1-2 N0-1		G 1-3, T1-2, N1
4B	G1-3;T1-4, N0-1, M1		M1		G1-3, T1-2,N0-1,M1

n/a = not applicable

The RMH Staging System did not incorporate the variable of depth of the tumour in relation to the investing fascia of the body. This is partly because this variable had not been collected in the database from which the RMH Staging System was derived. Depth has been identified as being an independent predictor of prognosis and is not just related to the site of the tumour. The earlier explanation having been that superficial extremity lesions presented earlier, at a smaller size, and hence had a better prognosis.[1] The introduction of this previously recognised factor [9] has had the single most significant impact on the changes to the latest 5th Edition AJCC / UICC Staging Systems [2,3] being responsible for the creation of Stage 1B (low grade > 5cm superficial STS) and Stage 2C (high grade > 5 cm superficial STS). In Brennan's editorial [6] these two subgroups combined represented 5 % of 1059 extremity STSs. The reliability of a survival curve constructed on less than 50 cases has wide 95 % confidence intervals and predicably would not definitively discriminate from the surrounding substages. Thus this change would seem pointless and very much less relevant than the impact of introduction of a graduated size range as demonstrated by the RMH Staging System.[1] From the data presented by Ramanathan et al. there were 90 patients in the size groupings 5 – 10 cm, 50 in the group 10 – 15 cm and 52 in the > 15 cm group. This represents 102/271 (38 % of the caseload compared to < 5 % impacted on by depth.[1] Despite this depth should not be disregarded and any database on STS should include this

field for ongoing assessment of its value. Whether or not it remains important in the common staging systems for STS remains to be seen.

The latest AJCC / UICC Staging Systems [2,3] have also changed their grading method from grades 1 to 3 to 1 to 4. In effect this has lessened the impact of grade on the staging systems' ability to differentiate prognosis. With the 5th Edition version grade 1-2 and 3-4 are always grouped together therefore identifying tumours as high and low grade. In clinical practice the distinction between high and low grade is all that is critically important. Indeed at the RMH we tend to manage intermediate grade tumours as high grade from the point of view of adjuvant radiotherapy for instance. However if intermediate grade is included in the staging system, because grade is also a continuous variable, it facilitates a gradual separation between stages.(Figure 2.1 & 2.2, Table 2.1)

This work from the RMH, closer assessment of the MSKCC database [10] and previous work by Suit et al. [11] confirms that both grade and size are continuous prognostic variables in STS. Furthermore, after a period of 30 months follow up, size of the primary tumour becomes more important than grade in determining future prognosis.[6,10] Other biological variables such as histological type of STS, local recurrence events at presentation (to MSKCC) and involved surgical margins also have a significant influence on prognosis.[10,12]

The 5th Edition AJCC / UICC Staging System have also had an adjustment following the recognition that small high grade STS have a better prognosis [13] than identified by the 4th edition versions of the AJCC / UICC Staging Systems.[4,5] Geer et al. suggested a 91 % 5 year survival for this subgroup. [13] The 5th Edition AJCC Staging System suggests around 82 % 5-year survival however this includes those tumours that are exactly 5cm. This is because the 5th Edition AJCC / UICC definition of T1 is ≤ 5 cm rather than the original < 5 cm. This change in definition of T1 from the earlier editions, has recently been erroneously reported by a major cancer centre in the USA.[14] Such mis-interpretations have the potential to significantly impact, as there is a natural tendency for pathologists, radiologist and clinicians to rounding off around 5 cm or other size brackets. At the very least this sort of confusion is a potential source of staging bias particularly if it is not widely appreciated.[6,14] This subgroup of small high grade STS patients is classified Stage 2A by the RMH Staging System and has a 74 % 5 year disease specific survival.[1] The explanation for the discrepancy with the work of Geer et al.[13] is not entirely clear as both sets of data are prospectively collected with a similar median follow up. Undoubtedly the 3 grade staging system used at RMH and in the previous AJCC / UICC Staging Systems [1,4,5] as opposed to the (effectively) 2 grade divisions used by the current AJCC / UICC committees [2,3] would have an impact

and tend to result in an apparent worse prognosis in the RMH small high grade group. The RMH data demonstrating an unexpectedly poor prognosis for this subgroup is supported by unrelated retrospective data from this institution for synovial sarcoma.[8] Clearly this is an important area where more detailed study is required.

The significance of nodal metastases in the RMH staging system was not specifically tested but to maintain reference to the AJCC / UICC 4th Edition Version, to which it was compared, Stage 4 was divided into stage 4A (lymph node metastasis) and stage 4B for those with distant metastases. This distinction is not necessary as regional lymph node metastases have the same dire prognostic implications as distant metastases in STS.[6,16] However, the substage separation can be useful when defining differences between groups of patients where there is a comparison between 2 groups of patients at different institutions (not comparing apples with apples).

The most recent version of the UICC and AJCC Staging Systems and the proposed RMH Staging System are based primarily on prospectively collected databases of extremity STS.[1,2,3] The previous edition of the UICC / AJCC Staging System was based primarily on retrospective, multi-institutional data on 1215 cases who were extremity origin in 53 %. However only 702 cases had adequate information to use for the

development of the staging system from which the original AJCC was derived and the site distribution of these 702 cases was not documented.[17] Despite this, all of these staging systems have been prescribed for wider site application with various qualifications such as defining retroperitoneal and visceral lesions as deep and excluding application to brain, parenchymatous organs and hollow viscera.[2-5] This wider application is largely untested and the associated problems are exemplified when the staging systems are applied to the special sites such as the retroperitoneum and head and neck. Both of these sites have particular biological behaviour with patients dying of transperitoneal spread / local recurrence and local recurrence respectively, which is otherwise unusual for STS.[18,19] There is also evidence that the risk factors for local recurrence are different (for extremity sites at least) to those for disease specific survival, which is the most important endpoint for a staging system.[10] I have recently reported that retroperitoneal sarcoma can also become infected presumably by direct communication with the bowel or haematogenous seeding of necrotic tumour and that this is another potential prognostic factor related to the site of the STS.[20]

The wider application of staging systems is also largely untested against the various histological subtypes of STS. To demonstrate this, synovial sarcoma is an almost exclusively high grade, deep STS that favours extremity sites in at least 75 % of cases. By applying a cohort of cases to

the current AJCC / UICC Staging Systems, as we have recently done, there are really only 2 assessable groups Stage 2B and 3 (high grade tumours smaller or equal to 5 cm and high grade tumours larger than 5 cm). Even though the predicted survival for SS analysed using the AJCC Staging System matched reasonably closely the predicted survival, a staging system based more evenly on size and grade such as the proposed RMH System, gives a more differentiating prognostic indication with more prognostic groups.[8] This is not to say that individual subtypes of STS need have their own staging system. Rather, a further limitation of the current staging system is demonstrated.

Another subtype of STS that can be contrasted against synovial sarcoma is myxoid liposarcoma. The contrast is due to the generally indolent behaviour but unusually frequent soft tissue metastases of myxoid liposarcoma.[21] This subtype of liposarcoma represents half of the cases of the second most common STS in most series. Because of its particular biological behaviour ML represents another subtype of STS that has a prognosis not well described by the current staging systems.

Other problems with the wider application of a staging system to all STS include the rarity of certain subtypes of STS with specific biological behaviour. For instance, epithelioid sarcoma typically involves the extremity of young adults and metastases to lymph nodes

frequently.[22,23] It is often both less than 5 cm maximum size dimension but multifocal at presentation. However at this size the tumour metastases unusually frequently with poor outcome.[22] This specific biological behaviour is hidden within the large numbers of more common STS that make up the cohorts from which staging systems for STS are developed. This undoubtedly results in limited ability to give useful information for the patients involved.

In conclusion, the staging of STS is still evolving. This is necessary because of the above problems and the ongoing development of the understanding of the complexities of STS biology. Unfortunately the opportunity to take a major step forward was lost in 1997 when the UICC / AJCC staging systems were altered, principally to allow for depth despite this affecting only 5 % of cases. Size is a continuous variable in for prognosis of STS. The RMH Staging System identifies the previously unrecognised concept that size and grade are equally important continuous variables in the determination of prognosis of STS. Other biological variable are important in STS [10,12] but none identified to date have the potential impact of giving equally representative importance to grade and size. If a truly effective staging system is to be developed to encompass all STS, it has to be developed from prospectively collected databases, compared to equal quality data from other sources, and assessed for specific sites and subtypes of STS before being accepted.

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CHAPTER 3.

SYNOVIAL SARCOMA: A CLINICOPATHOLOGICAL, STAGING AND PROGNOSTIC ASSESSMENT

(Spillane AJ, Judson I, A'Hern R, Fisher C, Thomas JM. Synovial Sarcoma - A clinicopathological, staging and prognostic assessment. J Clin Oncol 2000;18:3794-3803.
Presented at the European Cancer Conference{ECCO 10}Vienna 1999)

3.1 SUMMARY

PURPOSE: Synovial sarcoma (SS) is a common soft tissue sarcoma with a propensity for young adults and notable sensitivity to chemotherapy (CT). No large reviews include a sizeable number of cases treated with ifosfamide-based CT. Recent demonstration of a worse than expected outcome of patients with small, high grade STS has also been our anecdotal experience with a number of small SS. We also wanted to assess our data with focus on survival of smaller SS because of this recent controversy. The usefulness of the current staging systems for STS in SS is further assessed in light of this evidence and the applicability of the AJCC / UICC Staging Systems is compared to that of the Royal Marsden NHS Trust's recently proposed staging system for this subtype of STS. Therefore this study also provides a current clinicopathological correlation, staging and prognostic assessment for SS.

METHODS: Review of the prospective database from 1987 to 1998 with retrospective data added.

RESULTS: 150 patients were assessed; median age at diagnosis was 30 years and median follow up was 52 months. Site distribution was

widespread favoring extremity locations. Overall actuarial 5 year survival rate was 57 %. Size trend, but not a cut-off of <5 cm vs ≥5 cm, was a prognostic indicator ($p < 0.001$). The current AJCC / UICC Staging System differentiated prognosis less well than the recently proposed Royal Marsden Hospital Staging System. The RMH Staging System also gave more useful subgroups for analysis and more separation of substages, therefore providing more discriminating prognostic information. Age greater than 20 years at diagnosis implied worse prognosis. Local recurrence (LR) rate with clear margins was 18 % compared to 61 % for involved margins ($p < 0.001$). Overall radiotherapy significantly reduced LR ($p = 0.03$). Patients with LR had a worse survival than those with no LR ($p < 0.001$). 80 patients had CT (55 therapeutic). For therapeutic treatment 11 of 19 patients had an objective response to a combination of ifosfamide and doxorubicin. Four cases had complete response after CT. Twenty-one patients had pulmonary metastasectomy with an actuarial 5 year survival of 23 %.
CONCLUSIONS: SS tends to affect young people but has no specific relationship to large joints. In this subtype of STS size trend is the most significant influence on stage and hence survival however many SS smaller than 5 cm also have poor prognosis. Currently the AJCC / UICC Staging System is not particularly discriminating for this subtype of STS. Adequate surgical margins and RT gives the best local control and may affect survival. SS is often chemosensitive and given its poor prognosis

multi-centre trials of adjuvant therapy are warranted. Improved survival should occur from better initial management and with development of better chemotherapy treatments.

3.2 INTRODUCTION

Synovial sarcoma (SS) is a rare but distinctive soft tissue sarcoma (STS) that displays epithelial differentiation. It represents between 5 -10 % of STS [1,2,3] with perhaps 200 new cases a year occurring in the UK and 800 cases per year in the USA.[1] SS has been described as "a clinically and morphologically well-defined entity that has been extensively described in the literature".[2] However, even in more recent publications the misconception that synovial sarcoma is somehow related to synovial tissues and hence arises in the vicinity of large joints is perpetuated.[4] Recently the chemo sensitivity of SS has been confirmed [5] and in the last 10 years the sensitivity of SS to ifosfamide-based chemotherapy has been documented with encouraging results especially from high dose ifosfamide therapy.[6,7] No large reviews of SS have included a significant number of cases with ifosfamide-based chemotherapy.

There has recently been a proposed revised staging system for extremity STS published from the Royal Marsden NHS Trust (RMH).[8] The authors recommended testing it against large series of STS including non-extremity tumours. We have therefore assessed this case series with the proposed RMH Staging System [8] and the American Joint Committee on Cancer (AJCC) / International Union Against Cancer (UICC) 5th Edition Staging Systems [9,10] to evaluate their predictive value in this subtype of STS.

Recently a worse than predicted 5 year survival has been demonstrated for a group of small, high grade STS.[11] We have had similar anecdotal experience and as SS are often small and high grade this aspect of our analysis became increasingly pertinent.

Thus, the intention of this paper was to perform a clinicopathological correlation, staging assessment and determine prognostic factors important for SS.

3.3 METHODS

Information was gathered from the Royal Marsden NHS Trust Hospital's (RMH) prospectively collected database. The period of assessment started with all patients registered at RMH from April 1987 until May 1998. Information was supplemented by review of the hospital records, liaison with referring physicians and by reviewing the original pathology reports from the referring hospitals when the patient presented having already had excision biopsy, local recurrence or metastatic disease. In nearly all cases one anatomical pathologist reviewed original histopathology at the time of referral with a specialised interest in this disease (CF). The other 5 cases were reviewed prior to inclusion in the study (2 by another expert second opinion). Detailed information was recorded on tumour characteristics including immunohistochemistry. Follow up information

was obtained from regular outpatient visits in the majority of cases or by correspondence with the referring physician in the case of distant referrals. Nine patients were seen for a second opinion only but complete data and pathological review was provided at the time of referral and has been updated in all cases. Up to 33 patients from this study may have been included in the 271 cases from which the proposed RMH Staging System [8] was developed. Nine patients were excluded from analysis on the basis of inadequate information being available.

Definitions:

- Proximal lower limb = buttock, thigh and groin area; Distal lower limb = knee and below
- Proximal upper limb = axilla, shoulder area, arm; Distal lower limb = elbow and below
- Persistent disease despite the primary therapy regimen is defined as local recurrence or metastatic disease (or both) at 0 months for the purpose of calculation of the first disease free interval (DFI) but the subgroup local recurrence at 0 months was excluded from analysis of time to local recurrence when relating it to surgical clearance.
- Survival figures were calculated from the time of the earliest histological verification of the diagnosis of synovial sarcoma to the date of death, last RMH review or other medical contact.
- Poorly differentiated synovial sarcoma is a recently described subtype of SS that has some typical morphological features of monophasic or

biphasic SS but also poorly differentiated areas characterized by high cellularity, numerous mitoses, and often necrosis. In each cases there is however compelling evidence of the diagnosis of synovial sarcoma made by immunohistochemical, ultra structural findings and demonstration of the specific chromosomal translocation t(x;18)(p11.2;q11.2).[12,13]

- Grading was assessed using the Trojani Classification.[14] Unless stated otherwise in the RMH pathology report all cases were assumed to be of high grade.
- Partial response to chemotherapy is defined as an objective decrease in tumour dimensions. Complete response is complete pathological or radiological response.

Survival, local recurrence free survival, metastasis free survival and disease free survival were compared between different groups using the logrank test, a test for trend being employed for ordered categories. Life-table curves were calculated using the Kaplan-Meier method.[15] Analysis of the effect of prognostic factors on cause specific survival was undertaken using Cox's regression.[16] The effect of local recurrence on survival was assessed by using local recurrence as a time dependent covariate in Cox's regression. Ninety five percent confidence intervals have been added to lifetable curves at 5 years (5 and 10 years for overall survival).

3.4 RESULTS

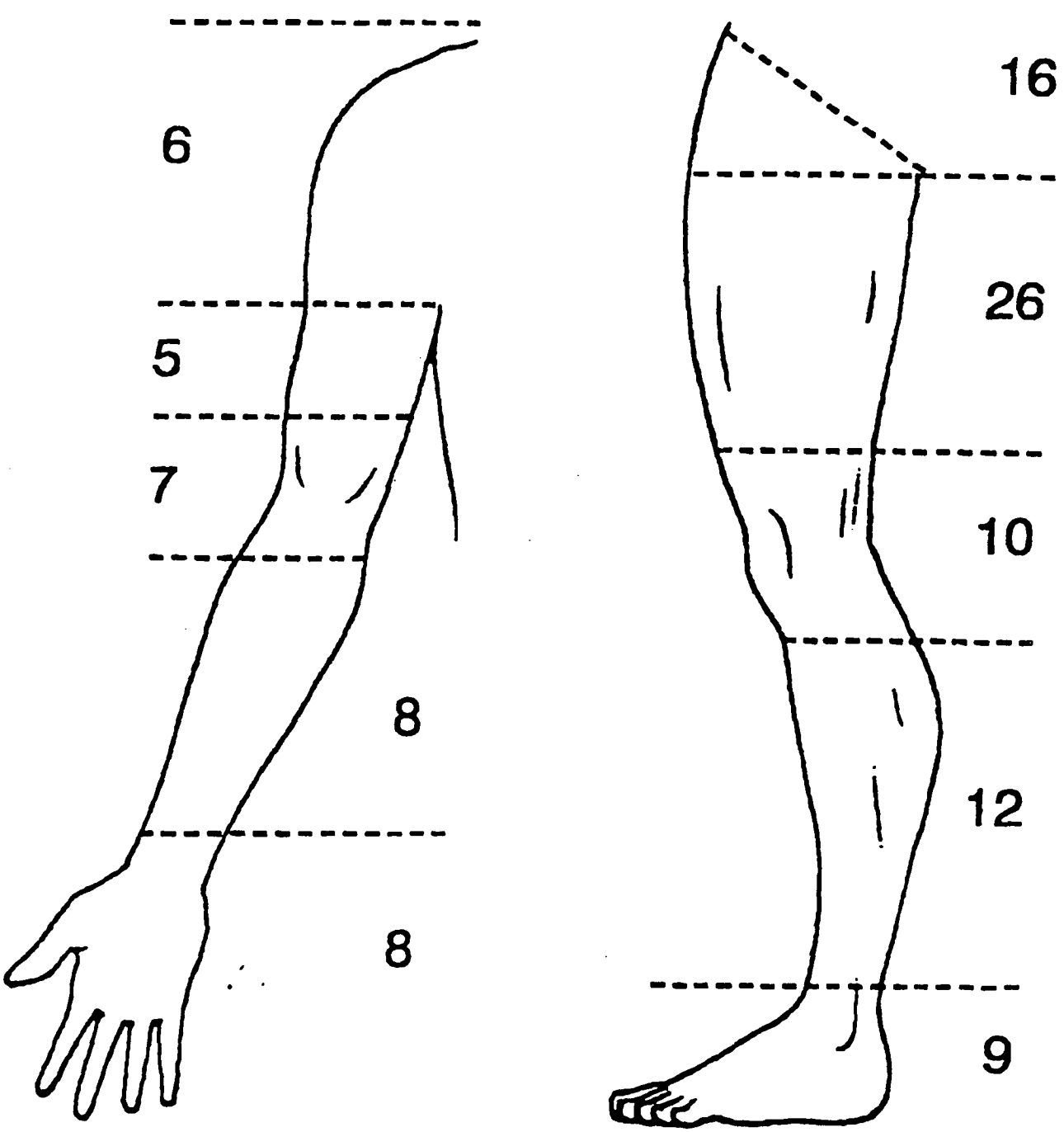
Patient Characteristics

There were 159 patients identified with 9 excluded from analysis. The median age at diagnosis was 30 years (range 3 - 85 years) with a median age of registration at RMH of 32 years (range 5 -76 years). There was a male / female ratio was 1.08:1. The distribution of tumour locations is detailed in Table 3.1. The most common site was the proximal lower limb but there was a broad spectrum of locations including 2 intracardiac primaries, 4 primary thoracic (mediastinal, pleural or pulmonary tumours), a supraglottic laryngeal tumour, a hypopharyngeal tumour and a maxillary antrum tumour. The site distribution of the 107 extremity SS (excluding 5 buttock tumours) is further assessed in Figure 3.1. to test the reported relationship to large joints. There were 3 cases with an intra-articular component. There were 96 patients who presented to RMH during the management of their primary tumour; 26 presented to the RMH with local recurrence (LR); 21 with metastatic disease (MD); and 7 with MD as well as LR. Assessing the 96 patients who presented with localised primary disease there were 63 patients whose presenting symptom was a mass, 26 had a painful mass, 5 had pain only and 2 had other symptoms. Duration of symptoms ranged from 1 month to 15 years. Two cases occurred in radiotherapy fields 9 and 19 years after radiotherapy.

Table 3.1 Sites of Primary Synovial Sarcoma.

SITE	NUMBER CASES (%)
Proximal Lower Limb	43 (28.7)
Distal Lower Limb	30 (20)
Proximal Upper Limb	12 (8)
Distal Upper Limb	22 (14.7)
Buttock	5 (3.3)
Trunk Abdomen	14 (9.3)
Trunk Chest	10 (6.7)
Retroperitoneal	5 (3.3)
Head & Neck	9 (6)
TOTAL	150

Fig 3.1 The distribution of 107 extremity synovial sarcomas (excluding 5 buttock tumours).



Pathology

The histological subtypes of synovial sarcoma were monophasic in 64 cases, 69 biphasic, and 17 poorly differentiated synovial sarcomas.[12,13] Three cases were categorised as being situated superficial to the deep fascia. There were 4 cases classified as low grade (who had histories of a mass for between 4 - 19 years before diagnosis), 12 cases of intermediate grade and the remainder were stated to be or assumed to be high grade. In 28 patients original size was obtained from clinical assessment or radiological size as no histopathological measurement was made. The immunohistochemical profiles of the cases included in this study are summarised in Table 3.2.

Diagnosis / Treatment

The method of first histological diagnosis was core biopsy in 38 patients (25.3 %) of which 26 were at the RMH, incision biopsy in 28 patients (18.7 %) none of which were at the RMH, and excision biopsy in 84 cases (56.0 %) of which 3 were performed at the RMH. The first treatment modality used was surgery in 113 patients (75.3 %), radiotherapy in 21 (14 %), chemotherapy in 10 (6.7 %), combined chemo-radiotherapy in 4 and isolated limb perfusion in 2 cases. The distribution of the surgical interventions performed at first referral to the RMH, categorised according to the Enneking Classification [17], are listed in

Table 3.3. There were 61 patients who had adjuvant postoperative radiotherapy for treatment of their primary tumour.

Table 3.2 Immunohistochemical (IHC) and Chromosomal Profile of Synovial Sarcoma Cases.

IHC MARKER	NUMBER POSITIVE (% *)
MNF 116	36 (65)
Cam 5.2	44 (65)
Cytokeratin	38 (72)
Keratin 903	95 (71)
EMA	108 (84)
bcl-2	21 (91)
MIC 2	20 (67)
Desmin	2 (2.5)
CEA	3 (33)
Actin / HMF 35	9 (28)
Vimentin	21 (100)
CD 34	1 (3)
S100	41 (41)
SMA	16 (30)
IHC Not Available (or not done)	8
TRANSLOCATION	13 (100)

* Percentage of those tested for that marker.

Table 3.3 Initial Surgical Interventions at RMH

SURGICAL INTERVENTION	**SURGICAL INTERVENTION AFTER FIRST REGISTRATION AT RMH ***
RADICAL (AMPUTATION)	9 (2)
WIDE LOCAL EXCISION (re-excision tumour bed) MARGINAL	58 (20) 14
INTRACAPSULAR	7

*17 of these cases were registered at RMH with local recurrence events

Chemotherapy

There were 80 patients who received neoadjuvant (n=14), adjuvant (n=11) or therapeutic (n=55) chemotherapy. The different types of chemotherapy given and an indication of response are listed in Table 3.4. Doses of chemotherapy were mostly dictated by the EORTC protocol for the trial in which the patient was enrolled. For example, ifosfamide $5g/m^2$ + doxorubicin 50 mg/m^2 was frequently employed, while as a single agent doxorubicin 75 mg/m^2 was used with dose adjustments based on toxicity. When given alone ifosfamide was given at higher doses typically $9g / m^2$. The therapeutic doxorubicin / ifosfamide combination was most successful with 11/19 having an objective decrease in size, compared to 8/22 in the doxorubicin alone group and 4/11 in the ifosfamide alone group.(see Table 3.4) Complete response (CR) to chemotherapy occurred in only 1 patient after neoadjuvant chemotherapy but there were another 3 patients who had good partial responses to their first line therapeutic chemotherapy and subsequently went on to have CR after high dose chemotherapy with melphalan or melphalan and etoposide combinations and peripheral blood stem cell rescue. Chemotherapy was not given at any stage in the treatment of 69 cases. I was unable to establish whether 1 of the patients had any chemotherapy. Following the doxorubicin and ifosfamide combination 14 patients had died at a median of 13 months (range 3 - 44 months) while 5 were alive between 10 - 89 months, one of

whom was disease free. Median survival was 15 months for this subgroup.

Table 3.4 Response of Synovial Sarcoma to Therapeutic and Neoadjuvant Chemotherapy

TYPE OF CHEMOTHERAPY	THERA-PEUTIC	RESPONSE	NEOADJ-UVANT	RESPONSE
Doxorubicin + Ifosfamide + /- others	19	PD 4, SD 4 PR 11**	8	PD 3, SD 2 PR 2, CR 1
Doxorubicin (epirubicin) +/- others	22 (1)	PD 8, SD 6 PR 8	5	PD 2, SD 1 PR 2
Ifosfamide +/- others	11	PD 4, SD 3 PR 4*		
Etoposide + Cyclophosphamide	1	PR 1		
Not Known	2	PR 1, 1?	1	PR 1
TOTAL	55	PD 16, SD 13 PR 25, 1?	14	PD 5, SD 3 PR 5, CR 1

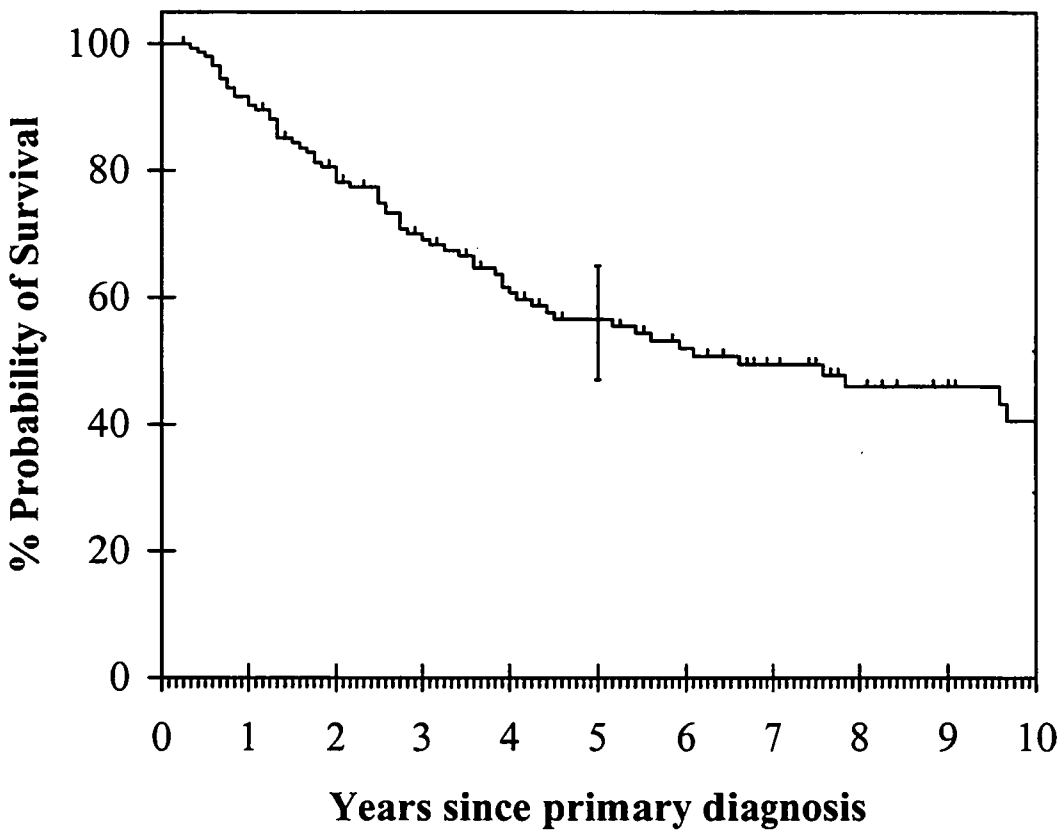
PD = progressive disease, SD = no response, PR = partial response, CR = complete response

*denotes individuals with later CR after second line chemotherapy

Outcome

The median follow up in patients still alive was 52 months (range 3 - 216 months). The overall 5 year survival was 57 %. (Figure 3.2) At final analysis there were 66 patients alive and disease free (9 had not been seen in the last 12 months including 8 who returned overseas). There were 16 people alive with disease - all except 3 had been seen in the last 3 months and were under frequent review at RMH. The other 3 patients were lost to follow up having returned to their country of origin for palliation, probably having died but we have been unable to confirm this. At final analysis there were 67 patients who died from synovial sarcoma. Another patient died of an unrelated cause but he had residual disease at that time.

Fig 3.2 The overall survival plot for 150 cases of synovial sarcoma. Short vertical bars indicate censored follow up events. The 5 year confidence limits are also included.



Prognostic Factors

The AJCC / UICC (5^{th} edition) [9,10] and the recently proposed Royal Marsden Hospital Staging System [8] groupings of these patients are shown in Table 3.5. Analysis of the actuarial 5 year overall survival, disease free survival and freedom from local recurrence for each stage assessable from the AJCC and RMH Staging Systems is shown in Table 3.5. Table 3.5 also documents the predicted rates for survival where available. Survival plots for AJCC and RMH Stages are shown in Figures 3.3 and 3.4. The other prognostic factors examined and their significance were sex, age, size < 5cm versus ≥ 5 cm, size trend through the groups < 5 cm, ≥ 5 - < 10 cm, ≥ 10 - < 15 cm and ≥ 15 cm , site, histological subtype and surgical margin after primary surgery. The univariate analysis of these factors appears in Table 3.6.

Table 3.5 Analysis of AJCC and RMH Staging System 5 year rates for freedom from local recurrence, metastasis free survival and overall survival.

AJCC STAGING SYSTEM [9]	No. CASES	Freedom from LocalRecurrence % (CI)	Metastasis Free Survival % (CI)	Overall Survival % (CI) [Predicted OS]
1A + B	1			
2A	3			
2B	43	50 (31-67)	49 (32-65)	75 (55-86) [2A+B+C = 81.8 %]
2C	1			
3	86	56 (42-68)	50 (38-61)	53 (40-64) [51.65 %]
4	13	81 (41-95)	0	0
Significance of Trend		NS	$\chi^2 = 19.6$ $p<0.005$	$\chi^2 = 24.5$ $p<0.001$
RMH STAGING SYSTEM [8]	**No. CASES**	**Identified Freedom from Local Recurrence**	**Metastasis Free Survival**	**Overall Survival (CI) [Predicted OS]**
1A + B	4			
2A	37	55 (32-72)	48 (28-65)	71 (50-84) [74 %]
2B	58	52 (34-67)	66 (51-77)	68 (52-80) [61 %]
3A	24	54 (28-74)	21 (7-41)	43 (21-62) [39 %]
3B	11	48 (14-76)	40 (7-74)	25 (4-55) [18 %]
4A+B	13	81 (41-95)	0	0 [6%]
Significance of Trend		NS	$\chi^2 = 33.2$ $p < 0.001$	$\chi^2 = 32.0$ $p < 0.001$

In 3 cases the original size was unknown; CI = 95 % confidence interval; NS not significant.

Table 3.6. Analysis of Potential Prognostic Factors for Synovial Sarcoma.

	Number Cases	Freedom Local Recurrence (CI)	Level Signifi-cance	Metastasis Free Survival (CI)	Level Signifi-cance	Overall Survival (CI)	Level Signifi-cance
Sex:							
MALE	78	59 (44-72)	NS	54 (40-65)	NS	54 (41-66)	NS
FEMALE	72	48 (32-61)		40 (27-52)		59 (45-70)	
Age:							
≤ 20	31	73 (28-87)	NS	57 (37-73)	NS	76 (54-89)	p=0.05
>20	119	49 (36-60)		43 (33-53)		51 (41-61)	
Size:							
< 5CM	37	53 (32-71)	NS	44 (26-60)	NS	67 (46-81)	NS
≥ 5 CM	110	55 (42-66)		48 (38-58)		52 (41-62)	
Size Trend:							
<5 cm	37	53 (32-71)		44 (26-60)		67 (46-81)	χ^2
≥5 - <10cm	61	59 (41-73)	NS	67 (53-78)	χ^2	70 (54-81)	=17.5
≥10 - <15 cm	30	48 (24-69)		22 (8-40)	=11.3	38 (20-56)	p
≥ 15 cm	19	57 (29-78)		30 (9-55)	p	21 (5-43)	<0.001
					<0.001		
Site:							
Extremity	112	54 (42-65)	NS	44 (34-54)	NS	59 (48-68)	NS
Trunk	38	52 (31-70)		55 (33-72)		50 (31-67)	
Histology:							
Biphasic	69	57 (41-70)		50 (36-63)		54 (40-66)	
Monophasic	64	53 (36-67)	NS	47 (32-60)	NS	62 (47-74)	NS
Poorly Diff.	17	60 (31-81)		33 (12-56)		50 (22-73)	
Surgical Margin							
CLEAR	72	80 (64-89)	p<	52 (39-64)	NS	66 (52-77)	NS
INVOLVED	65	34 (20-49)	0.001	47 (33-60)		60 (45-72)	

CI = 95 % confidence interval; NS = not significant.

Fig 3.3 The overall survival plot by AJCC Stages. Short vertical bars indicate censored follow up events. The 5 year confidence limits are also included.

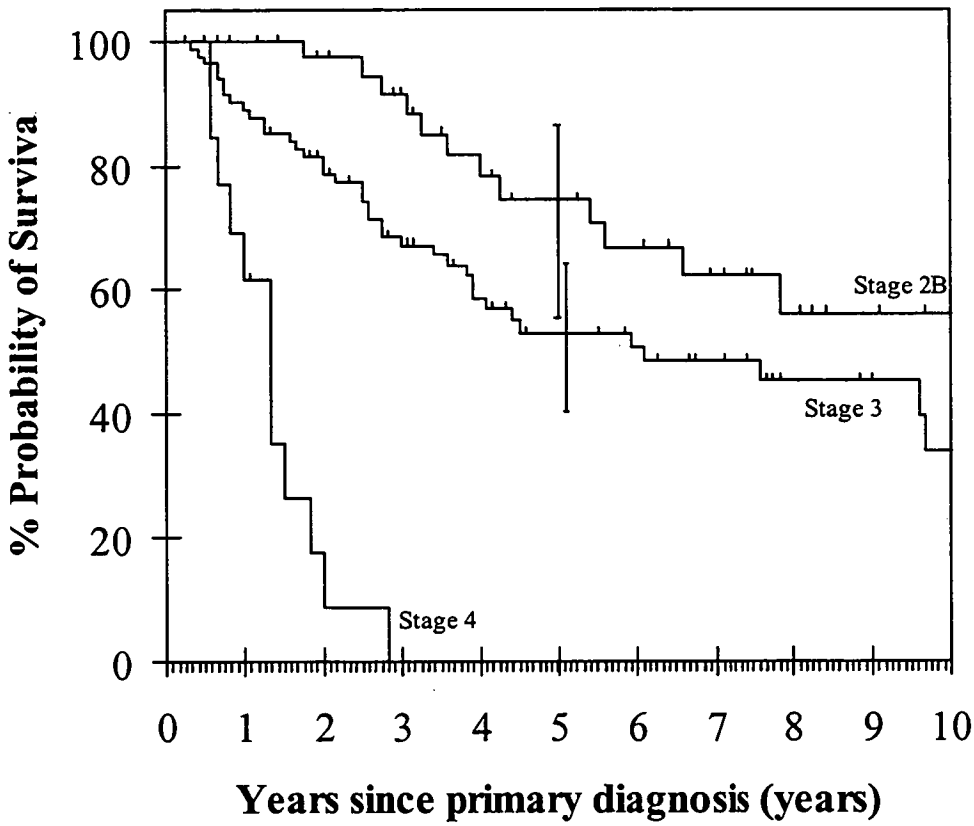
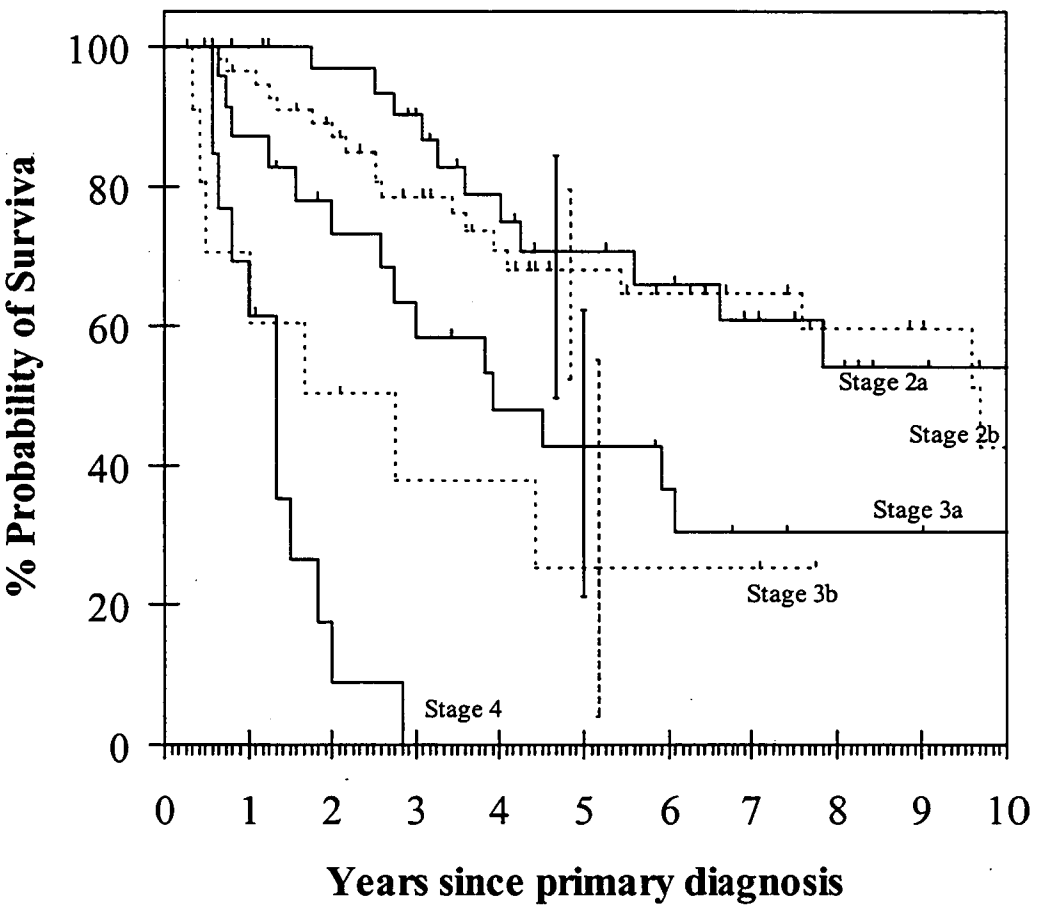


Fig 3.4 The overall survival plot by proposed RMH Stages. Short vertical bars indicate censored follow up events. The 5 year confidence limits are also included.



First Disease Free Interval

Five year disease free survival was 33 % (CI: 24 - 41 %). Median first disease free interval in the 103 patients who developed recurrent disease was 14 months (range of 0 -170). When LR was the first site of recurrent disease median time to LR in the 50 cases (including 9 with synchronous MD) was 23 months with a range 0 -168 months (of which 6 had persistent local disease i.e. LR at 0 months); median time to metastatic disease in the 62 cases (including the same 9 patients with synchronous LR) was 11 months (range of 0-170 months) with 14 of these having MD at presentation. There were 12 other later cases of LR in the 53 patients who developed MD as a first site of disease relapse. There were a further 20 later cases of MD in the 41 patients who developed LR as a first site of disease relapse.

Local Recurrence

In 72 patients, from all sites, microscopic margins were reported as free of tumour with an overall local recurrence rate of 13/72 (18.0 %) and an actuarial 5 year local recurrence rate of 20 %. There were 23 known marginal excisions / enucleations, with no microscopic description of margin, with a LR rate of 17/23 and 42 were shown to have microscopically involved margins with a LR rate of 23/42. Five other patients had debulking / non-resectional surgery and there were 8 patients who had no surgery. If the 2 groups of probable incomplete excision are

combined (65 cases) the reasons for acceptance of incomplete margins at RMH are - referral to RMH with LR or MD in 34 cases; referral after local therapy including radiotherapy completed in 6 cases; acceptance of microscopically involved margins with radiotherapy because of anatomical constraints in 14 cases; early on in the series marginal excision with radiotherapy was accepted in 9 cases; 2 cases had microscopically focally involved margins despite re-excision of tumour bed. Combining the 2 groups with probable incomplete excision 40/65 had LR vs 13/72 with clear margins, which is statistically significant ($p < 0.001$ by log rank test). The influence of radiotherapy on the relationship between excision margin and LR rate is shown in Table 3.7. In this non-randomised series the effect of radiotherapy on LR rates if margins were clear demonstrated 5/43 recurred after radiotherapy vs 8/29 without ($p = 0.12$, ns). When margins were involved LR rates was 18/36 in those receiving radiotherapy vs 22/29 without adjuvant radiotherapy ($p = 0.20$, ns). However overall radiotherapy had a significant effect on decreasing LR rate ($p = 0.03$).

Table 3.7 Influence of Surgical Margin and Radiotherapy on Local Recurrence.

MARGINS	*RADIO THERAPY*		*NO RADIO THERAPY*		TOTAL
	CLEAR	INVOLVED	CLEAR	INVOLVED	
LOCAL RECURRENCE	5	18	8	22	53
NO LOCAL RECURRENCE	38	18	21	7	84
TOTAL	43	36	29	29	137

5 people had non-resectional surgery, 8 had no surgical intervention other than biopsy.

Metastatic Disease

The overall metastatic rate was 39 % with an actuarial 5-year metastatic rate of 53 %. The first sites of MD were lung in 61, lung and soft tissue or bone in 8, bone alone in 4, soft tissue alone in 4, bone and soft tissue in 1 and 5 cases with lymph node metastases (2 synchronous with lung metastases). The actuarial 5-year survival rate after first metastasis was 6 %, with a median survival of 11 months. Pulmonary metastasectomy was undertaken in 21 patients, 12 had died at a median of 12.5 months (range 0 - 38 months) and 9 patients were still alive at a median of 25 months (range 2 - 106 months). Five patients had multiple pulmonary metastasectomy. Median post-pulmonary metastasectomy survival was 38 months. Actuarial 5-year survival rate following pulmonary metastasectomy was 23 %. When comparing the 6 cases < 20 years old to those ≥ 20 there was an improved survival in the younger group but this did not reach significance.

Death

Median time to disease related death was 30 months after diagnosis (range 4 - 248 months) at a median time of 16 months after first disease relapse (range 0 - 176 months). In this group of 67 patients with disease related death there were 23 LR as first site of relapse (of these 2 were never cleared of local disease and 8 had synchronous MD). All but 4 cases with LR as the first site of disease relapse subsequently developed

metastatic disease, which was responsible for their death. However a LR event was predictive of worse survival compared to patients with no LR ($p < 0.001$, OR 3.6, CI = 2.1- 6.1).

3.5 DISCUSSION

Large case series of this nature are published by specialist referral centres and tend to be biased by the number of cases with recurrent and metastatic disease at presentation to the institution. This can bias the clinical impression of the disease with the worst cases self-selecting for referral to centres with higher levels of expertise. There are perhaps 200 cases of synovial sarcoma in the United Kingdom each year [1] with a rate of accrual in this series of only 14 per year. However, the rate of accrual in this series is more rapid than the other large series published.[4,18-21] Acknowledging this case-mix bias, in an attempt to give an accurate picture of the disease, we have collected data from the earliest definitive diagnosis. Synovial sarcoma remains a disease with poor prognosis having an overall 5-year survival rate of 57 % in this series. This is despite taking into account the sensitivity to chemotherapy which is reported in this study as well as in the literature over the last decade.[5,6,7] The published 5 year survival figures have tended to improve slowly in the last 20 years with Hadju et al. reporting a 40 % 5 year survival in 1977 [22], Wright et al. reporting 55 % 5 year survival in 1982 [19], Brodsky et al. reporting 56 % 5 years survival in 1992 [18] and Singer et al. reporting 60 % 5 year survival in 1996.[4] However if the inclusion dates of each study are taken into account the trend is even less convincing.

Size (≤ 5 cm versus > 5 cm), grade and depth are the important prognostic factors considered in the current AJCC / UICC staging systems for STS.[9,10] Depth in relation to the investing fascia layer was initially identified as important in determining prognosis by Hajdu.[23] In this series there were only 3 cases of SS superficial to the deep fascia (2 %) which is not dissimilar to rates of superficial SS in the literature of 3 - 5.3 %.[18,19] Thus the influence of depth is minimal in this disease. Depth was not included in the previous UICC / AJCC 4th Edition versions [24,25] nor is it included in the recently proposed RMH staging system [8] (see Table 5) which is also a 4 stage system (with substages) but gives more weight to size than the current AJCC / UICC Staging Systems.[9,10] The editorial which accompanied the publication of the proposed RMH staging system accepted that the value of depth was limited in STS and that size was a continuous variable which becomes a more important consideration than grade with longer duration of follow up.[26] Traditionally SS have all been considered high grade [1] but more often lower grade variants are recognised [27] and certainly the clinical behaviour in a subset of patients, with clinical history of a lump for up to 15 years before presentation, is not typical of high grade sarcoma. As SS is mostly high grade it is not surprising that a staging system that favours differentiation based on size will give more meaningful prognostic information (if the staging system is accurate). Clearly the RMH Staging System needs to be validated against another dataset.

Effectively the AJCC / UICC Staging Systems have only 2 assessable groups in this disease so they provide limited information for the clinician and the patient. This contrasts with the proposed RMH System which gives 4 groups with a stepped deterioration in prognosis with increasing stage and close approximation to the predicted survival figures.(see Table 3.5) The most significant thing for the patients with this disease is that instead of being told that they have either and 80 % or a 50 % chance of survival at 5 years they can be given a more staggered estimate of prognosis. This in theory should be more useful when deciding on adjuvant therapy where one may be willing to accept the morbidity of chemotherapy if their risk of recurrent disease crosses a threshold seen by the patient and his carers as being significant.

Other factors suggested previously to worsen prognosis in SS include male sex [19], patient age >20 years [19,28], size of the tumour ≥ 5cm [18-20,29], monophasic subtype [29,30], microscopically positive margins of resection [4] and mitotic activity >10 / 10 high power fields.[4] Most of these factors are examined in Table 3.6 which demonstrates that age > 20 years and the trend in size were associated with a significantly worse prognosis whereas the other factors assessed were not. Of these factors most noteworthy was the size bracket < 5 cm versus ≥ 5 cm which, was not an independent predictor of survival. This

is at odds with other publications [18-20,28] but in agreement with the multivariate analysis of Oda et al.[31] Recent evidence suggests that high grade extremity STS smaller than 5 cm have a worse event free outcome than previously reported.[11] Our data certainly adds weight to this implication and in this subtype of deep small STS the 5 year survival of 67 % is less surprising than it would initially appear. In the study by Fleming et al. 50 % of the cases were superficial to the deep fascia making comparison of their 22 cases of SS [11] to the 37 less than 5 cm in our series difficult. We do not have complete data on mitotic rate or percentage of necrosis both of which are to be assessed in a future pathological review of this data intended to examine the factors important in establishing a reliable grading system for SS.

Adjuvant chemotherapy for localised resectable STS of adults has been shown on meta-analysis to improve the time to local and distant recurrence and overall recurrence-free survival, but only a trend towards improved overall survival.[32] The role of adjuvant chemotherapy in SS is difficult to assess in this series given that only 11 patients received it. Certainly our demonstrated sensitivity to ifosfamide and doxorubicin in combination for both therapeutic and neoadjuvant therapy, the work of Rosen et al. [7] and more recently the EORTC analysis [5] suggest SS is usually chemo sensitive. Given the overall poor prognosis in a

predominantly young age group, multi-centre trials of adjuvant therapy in this histological subtype of high risk STS patients are warranted.

Therapeutic chemotherapy for STS has a documented overall response rate of approximately 24 %, including doxorubicin / ifosfamide in combination, and even though quality-of-life measures may demonstrate an advantage to chemotherapy no overall survival advantage is proven.[33] The role of therapeutic chemotherapy in SS is similar with no evidence of overall survival advantage in the literature.[18] We have not tried to validate this statement in this series by comparing patients who did and did not receive chemotherapy because of the non-randomised nature of the data. However, in this series there was a median survival of 11 months following first diagnosis of metastatic disease for all patients, whereas the 19 cases who received ifosfamide / doxorubicin in combination had an overall median survival of 15 months. From these 19 cases there were 5 patients still alive between 10 and 89 months including one who was disease free. Van Glabbeke et al. reported a median survival less than 12 months after randomisation (or registration) for anthracycline-containing first-line regimens of chemotherapy for metastatic STS with no significant differences between regimens including ifosfamide and doxorubicin (+ /- GM-CSF).[5] Pisters et al. reported a 14.8 month post-metastasis survival for SS [34] while Rosen et al. reported a median survival of over 2 years for patients with diffusely

metastatic SS after high dose ifosfamide (14 - 18 g/m2).[7] Van Glabbeke et al. noted a higher than average STS post-metastatic survival after chemotherapy for SS on subset univariate analysis, however, when the influence of the low rate of hepatic metastases and younger age of the patients was taken into account in the multivariate analysis the significance of the SS subtype dropped out.[5]

The tendency of SS to arise in the vicinity of large joints, especially the knee, may have been overstated in the past. In our series 75 % of cases primary tumours were in the extremity. This compares to the more frequently reported distribution of 90% from the extremities with 30 % around the knee joint.[1,18,19] The distribution of locations in the extremities was random and bore no obvious relationship to large joints.(Figure 3.1) Only 3 cases (2 %) had intra-articular involvement which has been reported in up to 5 % of cases, among which the knee [35,36] and temporomandibular joint [37] are favoured sites. There have also been several reports of a high rate (12 - 27 %) of lymph node involvement in SS [22,28] but in this series there were only 5 cases of lymph node metastases (3.3 %) which is a similar rate to the 3 % reported by Brodsky et al.[18]

This series confirms that the commonest error in the initial management of STS is excision biopsy (enucleation).[38] Excision biopsy happens

because clinicians fail to suspect the diagnosis and then fail to undertake an appropriate next step of either core biopsy or incision biopsy or alternatively referring to a specialist centre on suspicion. Microscopic disease as a minimum remains after enucleation and the treatment options are either re-excise the tumour bed as we prefer to do or to irradiate and widely excise the tumour if / when it recurs. The first option presents difficulties because the exact site of the primary tumour is usually unknown. Imaging is of limited value because on computerised tomography the anatomy can return rapidly to normal and on magnetic resonance imaging the signals from haematoma and oedema are confusing and usually exaggerate the extent of disease. (JM Thomas personal comm.)

In this series, including all sites, surgical excision with clear resection margins gave a recurrence rate of 18.0 %. This is similar to the series by Mullen et al. who reported that 13.4 % of cases with clear margins had local recurrence despite all cases having received radiotherapy [20] and Brodsky et al. who reported a 14 % local recurrence rate for extremity lesions.[18] In patients operated on at the RMH the aim was to get a wide local excision or functional compartmental excision of the tumour if at all possible.[39] The high frequency of involved margins in this series (48 %) reflects the pattern of referral to the RMH where even though 96 cases were referred during the course of their primary tumour management only

28 of these patients had their first operation at the RMH. Earlier on in the series (during the late 1980s) marginal resection and radiotherapy was occasionally accepted as adequate treatment whereas in the later part of the series microscopically involved margins were occasionally accepted with addition of radiotherapy if anatomical constraints made re-excision of the tumour bed limb threatening. There were also 54 patients who were referred to the RMH with local recurrence or metastatic disease (or both) and these cases represent over half of the inadequate margin after primary surgery group. The high frequency of involved margins may also be a reflection of the aggressive biological nature of many SS and demonstrates the tendency for inexperienced surgeons to under-estimate local extent, which is a frequent problem with all STS.[40]

Radiotherapy was associated with a significant overall decrease in local recurrence but when clear margins were compared to those with involved margins separately the reduction in LR did not reach significance. The interpretation of this data is difficult given the non-random allocation of cases for radiotherapy. Patients with higher risk tumours (obvious biological aggressiveness) and closer margins would tend to get radiotherapy whereas a lower grade tumour with a wide resection margin may not always do so. Certainly the literature demonstrates a benefit in terms of local control from either external beam radiotherapy or brachytherapy in high grade STS.[41-43] The beneficial effect of

radiotherapy on local control has not translated into an increase in disease-specific survival in previous reports.[41,44] However a LR event was at least a predictor of poorer outcome in this series, which indirectly suggests radiotherapy may have an influence on survival. Several other authors have found microscopic involvement of surgical margins to be associated with worse survival.[34,45] In Pisters et al. study of 1041 STS of the extremities, the authors found positive resection margins and presentation with local recurrence were both predictive of inferior survival [34] supporting our results. Whatever the significance of this finding, local control from the time of primary tumour presentation certainly improves the quality of life for patients.

In conclusion, synovial sarcoma is a characteristic subtype of STS with a predilection for young people but has no specific relationship to large joints in this series. Size is the most useful staging discriminator, as grade and depth have little differentiating impact in this disease, and hence more useful prognostic information comes from the proposed RMH Staging System [8] than the AJCC / UICC Staging Systems [9,10]. Adequate surgical margins with the addition of radiotherapy give the best chance for local control and may improve overall survival. SS is usually chemo sensitive and given the overall poor prognosis multi-centre trials of adjuvant therapy in this histological subtype of high risk, younger age group patients are warranted. Future improvements in survival from this

disease will require better chemotherapy and better initial management preferably by specialist centres.

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CHAPTER 4.
MYXOID LIPOSARCOMA

(Spillane AJ, Fisher CF, Thomas JM. Myxoid Liposarcoma. The frequency and the natural history of soft tissue metastases. Ann Surg Oncol 1999;6;4:389-394. Modified to include increased follow up and data on staging system application from the publication.
Short Presentation / Poster ECCO 10, Vienna 1999)

4.1 SUMMARY

BACKGROUND: Myxoid liposarcomas (ML) comprise the major subset of liposarcoma, which in most series represent the 2nd or 3rd most common type of soft tissue sarcoma (STS). The tendency for ML to metastasise to other soft tissues (STM) in preference to lung parenchyma has been previously described however a natural history of this tumour's behaviour is poorly documented. The applicability of the current staging systems in this subtype of STS has not been previously discussed in the literature.

AIM: To analyze the natural history of ML and further quantify the incidence of STM concentrating on their significance in terms of survival. From this data observations regarding the usefulness of the current staging systems in the context of this unusual behaviour will be made.

METHODS: Review of the Royal Marsden Hospital's experience over a 10-year period, documenting the clinico-pathological behaviour of ML including the frequency of STM.

RESULTS: There were 50 patients with a median follow-up of 49 months. The actuarial 5 year distant metastasis rate was 30 %. Twelve of

13 cases with distant metastases had STM and only 1 case had isolated pulmonary metastases. Four others had pulmonary metastases (1 before STM, 1 synchronous with STM and 2 after STM). The commonest sites of STM were the retroperitoneum, abdominal wall and abdominal cavity. In those 12 patients who had STM there was a median interval of 23 months after original diagnosis to the time the first metastasis became apparent (range 0 - 142 months). Median survival following first distant metastasis was 41 months. 4 patients who had STM remain disease free at 30 - 67 months after the first STM. Any round cell component (RCC) of the ML was associated with significantly greater chance of metastatic disease ($p = 0.01$). In this series the overall 5 year and 7 year survival rates were 85 % and 68 %. Patients with STM had 4.5 times greater chance of dying than those who did not. The current staging systems for STS are poor predictors of outcome in this subtype of STS especially the AJCC Staging System that separates cases into only 2 assessable subgroups with similar survival.

CONCLUSIONS: Generally ML is an indolent disease but there is a subset of patients, principally those with a RCC, who develop STM and have a significantly worse prognosis.

STM can occur years after the initial diagnosis and can be associated with good medium-long term survival after they occur. STM should be managed aggressively because of this. The current staging systems for

STS do not give a reliable prediction for prognosis in this subtype of STS because of this unusual behaviour.

4.2 INTRODUCTION

Soft tissue sarcomas (STS) most commonly metastasise to the lungs.[1] Follow-up in patients with STS therefore primarily involves surveillance for local recurrence and pulmonary metastases. Liposarcomas are the 2nd or 3rd most common histological type of STS representing between 8 - 17.8 % in most series.[1,2,4] Myxoid liposarcoma with or without a round cell component (ML) compromises the major subtype of liposarcomas representing 45 - 55 % of cases.[2] Well-differentiated, pleomorphic and de-differentiated liposarcoma make up the other subtypes.[3,5]

ML and less commonly other subtypes of liposarcoma have been reported to demonstrate the phenomenon of non-pulmonary soft tissue metastases (STM) which has also been described as multicentric involvement of the retroperitoneum or opposite limb.[1,2,5,6,7,8] It has been the Royal Marsden NHS Hospital's (RMH's) experience that only ML has a propensity to STM compared to other STS and the natural history of this unusual sarcoma's behaviour is not obvious from the literature. Given this atypical behaviour for a STS I aim to give a chronological overview and to verify the incidence and prognostic significance of STM in a large series. I have also investigated the validity of the currently utilised STS staging systems for determining the prognosis in this subtype of STS.

4.3 METHODS

A retrospective review of the RMH records and private patient notes was conducted covering the period starting January 1988 and ending March 1998. The list of patients was obtained from the prospective Department of Anatomical Pathology database. The patients were all primarily managed by one surgeon (JM Thomas). Some of the patients were referred to the RMH with recurrent disease but in all cases the histology of the primary tumour was reviewed by one pathologist (C Fisher). Follow-up information was added to the database up to 1/6/99. Exclusions from analysis were made on the basis of inadequate information being available.

Definitions

- survival data were calculated from date of first histological diagnosis of ML to the date of last review or death. In the metastatic group survival was calculated from either the date of first histological proven metastatic disease or date of compelling radiological evidence of metastatic disease.
- disease at knee or elbow level was included in the distal limb group.
- myxoid liposarcoma was defined as that variant of liposarcoma with lipoblasts which are often signet-ring type, plexiform capillary pattern and pools of myxoid material or myxoid matrix with hyaluronidase-sensitive acid mucopolysaccarides. If present areas of round cell differentiation were noted.

- soft tissue metastases include all non-pulmonary parenchymal soft tissue and visceral metastases but exclude lymph node and bone metastases that were to be separately identified.
- the 5th edition version of the AJCC / UICC Staging Systems [9,10] and the recently proposed RMH Staging System [11] were utilised to assess the reliability of the currently available staging systems to this subtype of STS.

Survival data have been calculated using Kaplan Meier Method and survival curves were compared using Cox's Regression using the log rank test and a time dependent covariate was used to assess the prognostic importance of STM.[12,13]

4.4 RESULTS

Demographics

There were 55 patients identified who had a pathological diagnosis of myxoid liposarcoma (ML) during this period of time. There were 5 exclusions from the analysis, 3 patients who were lost to follow-up and 2 who were referred for a second opinion only. The median age at diagnosis was 44 years (range 21 - 77 years). Male to female ratio was 0.93.

Presentation and Pathology

The sites of primary ML are documented in Table 4.1. In one case there were 2 lesions at presentation (left thigh and right shoulder) and we were unable to state which was the primary. It is conceivable but less likely they were synchronous primaries.

Thirty-one patients presented with a painless lump. Twelve patients were referred to RMH with recurrent disease - 10 with local recurrence, 1 with a locally recurrent STM and a liver metastasis, and 1 had a supraclavicular STM. The pathological characteristics of the primary tumours were typical ML in 34 cases and ML with areas of round cell differentiation in 16 cases (32 %). There were 32 cases that were low grade, 8 intermediate and 10 high grade. Data on depth was not traditionally reported at the RMH, however using a combination of

clinical data and pathology reports it was possible to identify 4 cases that were almost certainly superficial to the investing fascia. Otherwise all cases were assumed to be deep. Table 4.2 demonstrates the distribution of the cases according to the AJCC / UICC 5th Edition Staging Systems [9,10] and the proposed RMH Staging System [11].

TABLE 4.1 Primary sites of myxoid liposarcoma

SITE OF PRIMARY	NUMBER OF CASES
PROXIMAL UPPER LIMB	2*
DISTAL UPPER LIMB	1
PROXIMAL LOWER LIMB	27*
DISTAL LOWER LIMB	7
BUTTOCK	5
RETROPERITONEUM	5
POSTERIOR CHEST WALL	1
SOFT PALATE	1
ABDOMINAL WALL	2

* 1 patient had 2 synchronously detected tumours

Table 4.2 Distribution of Cases of Myxoid Liposarcoma According to AJCC / UICC Stages.

AJCC / UICC STAGE	NUMBER OF CASES	RMH STAGE	NUMBER OF CASES
1A	5	1A	5
1B		1B	5
2A	25	2A	11
2B		2B	18
2C	2		
3	14	3A	4
		3B	3
4	1	4	1
UNKNOWN	3	UNKNOWN	3

Treatment

Overall surgery was the primary therapy used in 48 of the patients and radiotherapy in 2 cases. Primary surgical intervention was performed at the RMH in 27 cases and at other institutions in 23 cases. Eleven of these 23 cases required further local surgery to achieve adequate clearance. Adjuvant radiotherapy was given after surgery for the primary tumour in 20 cases. None of the patients received chemotherapy as a part of their primary therapy.

Disease Status

Follow-up ranged from 12 - 125 months with a median of 49 months in the 40 patients still alive. At the time of analysis there were 36 patients alive and disease free, 4 patients alive with clinically or radiologically apparent residual disease (2 of these were from the group with STM) and 10 patients had died of myxoid liposarcoma.

First Disease Free Interval

There were 17 cases with recurrent disease after initial therapy was complete and another 2 cases with persistent unresectable local disease. From the 17 recurrent cases, there were 5 cases with local recurrence as the first site of disease recurrence (one of whom later developed STM), 1 case with local recurrence and a STM, and 11 cases that had metastatic

disease as a first site of recurrent disease. The median first disease free interval was 23 months with a range 0 - 142 months.

Local Recurrence

Following management at the RMH there were 7 cases of local recurrence ranging from 11 - 40 months after diagnosis with a median of 26 months. There were another 2 cases never cleared of local disease. Three local recurrences occurred in the STM group, one of who had multiple local recurrences before referral. At assessment 3 of these patients who had a LR event were disease free, 2 were dead and 1 was alive with residual disease. The actuarial 5 and 7-year local recurrence rate after treatment at the RMH was 18 %.

Regional Recurrence

There were no regional nodal metastases in this series.

Metastatic Events

Overall there were 13 cases with distant metastases and these are summarised in Table 4.3 including the chronological history of their disease events and therapies. Twelve of the 13 cases had STM. The actuarial 5 year distant metastasis rate was 30 %. The presence of a round cell component on histopathology was predictive of a 5-year distant

metastasis rate of 58 % compared to those without a round cell component who had a 5-year metastasis rate of 15 %. ($p = 0.01$) In the group who had any metastatic events there was a median interval of 23 months after the primary being diagnosed to the time the first metastasis became apparent (range 0 - 142 months). Median survival following first metastasis was 41 months.

Four patients in this series had both pulmonary and soft tissue metastatic disease. In Case 7 lung parenchyma was the first site of metastatic disease and in Case 12 the lung metastasis was synchronously detected with a STM. The other 2 parenchymal lung metastases occurred after STM. There was only 1 case with isolated parenchymal lung metastases (Case 13) without any STM. Only 1 case had a liver metastasis (Case 5) and 1 patient had a presumed bone metastasis (Case 7).

TABLE 4.3 Case Descriptions of the patients with soft tissue metastases.

PRIMARY SITE PRIMARY THERAPY	METASTATIC SITE(S)	TREATMENT	Outcome at 9/98 from Diagnosis (Time since 1st Metastasis)
1. 12/92 R Posterolat Chest Wall Surgery	6/94 axillary + retroperitoneal mass 1/98 adductor compartment + intra-abdominal + abdominal wall 6/98 intra-abdominal + lung mets + pleural effusions	7/94 Ifosfamide 9g/m^2 X5, Doxorubicin 75mg/m^2 X4 -> SD 2/95 Axillary Surgery 2/96 Abdominal Surgery 5/97 Radiotherapy Abdomen 2/98 Debulked abdomen	DOD 8/98 68 months (50 months)
2. 6/93 R Quadriceps Surgery + RT	1/95 retroperitoneal mass 10/96 supraclavicular mass 1/97 lower posterior chest wall lesion 6/97 recurrent retroperitoneal mass with several transperitoneal sites 4/98 progression chest wall mass	1/95 Surgery + RT 1/97 Surgery + (supraclavicular) RT 6/97 Surgery 7/97 Doxorubicin 75 mg/m^2 X3 -> PD 9/97 Ifosfamide 9g/m^2 X6 -> PR 4/98 RT to post chest wall 8/98 Gemcitabine 1250 mg/m^2 X4	AWD 63 months (44 months)
3. 9/91 R Knee area Surgery	12/93 perineal + sigmoid mesocolon mets 8/94 paraspinal mass 4/95 abdominal wall metastases 9/95 adrenal metastases 5/96 further retroperitoneal disease	12/93 Surgery (both sites) 9/94 Surgery + RT 6/95 Debulking surgery 7/95 ifosfamide 9g/m^2 X2 ->PD 9/95 Doxorubicin 75 mg/m^2 X7 ->GPR 5/96 debulking surgery	DOD 9/96 60 months (33 months)
4. 8/96 L Thigh and R Shoulder Surgery	6/97 rectus sheath + L elbow + R thigh + L gluteus max. 10/97 R lung metastasis 12/97 R thigh	6/97 ifosfamide 12 g/m^2 X2 -> SD 8/97 Surgery 10/97 Pulmonary metastasectomy 12/97 Surgery	ADF 25 months (25 months)
5. 11/94 R Hamstring Surgery + RT	5/96 L flank + R lobe liver 1/97 disease progression flank 8/97 R supraclavicular + R infrascapular mets 9/97 L flank, R pleural apex (STM) 2/98 local recurrence R thigh	6/96 ifosfamide 5g/m^2+ doxorubicin 50mg/m^2 x6 (12/96) -> PR (flank) / SD(liver) 9/97 Surgery abdominal wall 11/97 Surgery neck & back 2/98 Carboplatin 610mg+Etoposide 120mg/m^2 ->PD	DOD - 8/98 43 months (25 months)
6. 10/92 R Buttock Surgery	12/94 - 2 large mets abdomen + LR 3/95 LR - R buttock + abdominal mets 8/97 R buttock recurrence 11/97 abdominal recurrences x 7	12/94 Surgery buttock 3/95 Surgery buttock & abdomen 4/95 Ifosf 5g/m^2+Doxo 50 mg/m^2 x4- adjuvant 8/97 Surgery on buttock recurrence 11/97 Debulking surgery	AWD 61 months (35 months)
7. 2/91 R Soft Palate	1/93 lung met (PM) 2/94 ascites, pelvic wall + ovarian mets 4/93 Probable bone met L4 vertebra	1/93 Pulmonary metastasectomy 5/93 RT Lumbar vertebra 9/94 Debulking Surgery 12/94 ifosfamide + doxorubicin x3 -> PD	DOD 6/96 64 months (41 months)

Surgery + RT	8/94 rec. retroperitoneal masses 4/95 R lumbar + increase retroperitoneal	5/95 surgery back	
8. 12/88 L Ischio-rectal fossa Surgery + RT	2/93 L thigh metastasis 5/95 L gluteus max. metastasis	2/90 Resection of Scar 2/93 Surgery + RT 5/95 Surgery	ADF 117 months (67 months)
9. 7/93 R Thigh Surgery + RT	12/94 parietal pleural mets (STM) 10/95 R supraclavicular fossa mass 11/95 abdominal wall metastasis 5/96 chest wall metastasis	12/94 Thoracotomy excision pleural mets 1/96 Surgery + RT 9/96 Surgery	ADF 62 months (45 months)
10. 11/93 L Buttock Surgery + RT	11/95 L ant abdominal wall	12/95 Surgery	ADF 57 months (33 months)
11. 12/82 R Thigh Surgery	12/85,8/86,12/86,11/87,1/91,2/92 LR 1/94 Amputation 10/94 cord comp + erector spinae mass	Till Referral 12/86 Surgery only; 2/87 RT 11/87-> 1/94 Surgery 10/94 Laminectomy + Excisional Surgery	DOD 4/95 148 months (6 months)
12. 6/90 L Thigh Surgery	9/92 axillary mass + pulmonary metastases 3/94 sternal subcutaneous metastasis + abdominal cavity metastases	9/92 Surgery axilla 9/92 Epirubicin 150 mg/m^2 X8 -> GPR 3/94 Surgery 4/94 ifosfamide 5g/m^2-> PD 6/94 Etoposide 75 mg/d - initial PR then PD 4/95 Debulking surgery abdomen	DOD 8/95 62 months (35 months)
13. 8/95 LThigh Surgery	1/96 Pulmonary Metastases	2/96 Ifosfamide + Doxo X8 -> GPR	DOD 7/98 35 Months (30 Months)

Key: LR = local recurrence, RT = radiotherapy, STM = soft tissue metastasis, PM = pulmonary metastasis, ADF = alive disease free, AWD = alive + residual disease, DOD = died of disease, PD = progressive disease, SD = stable disease, PR = partial response, GPR = good PR

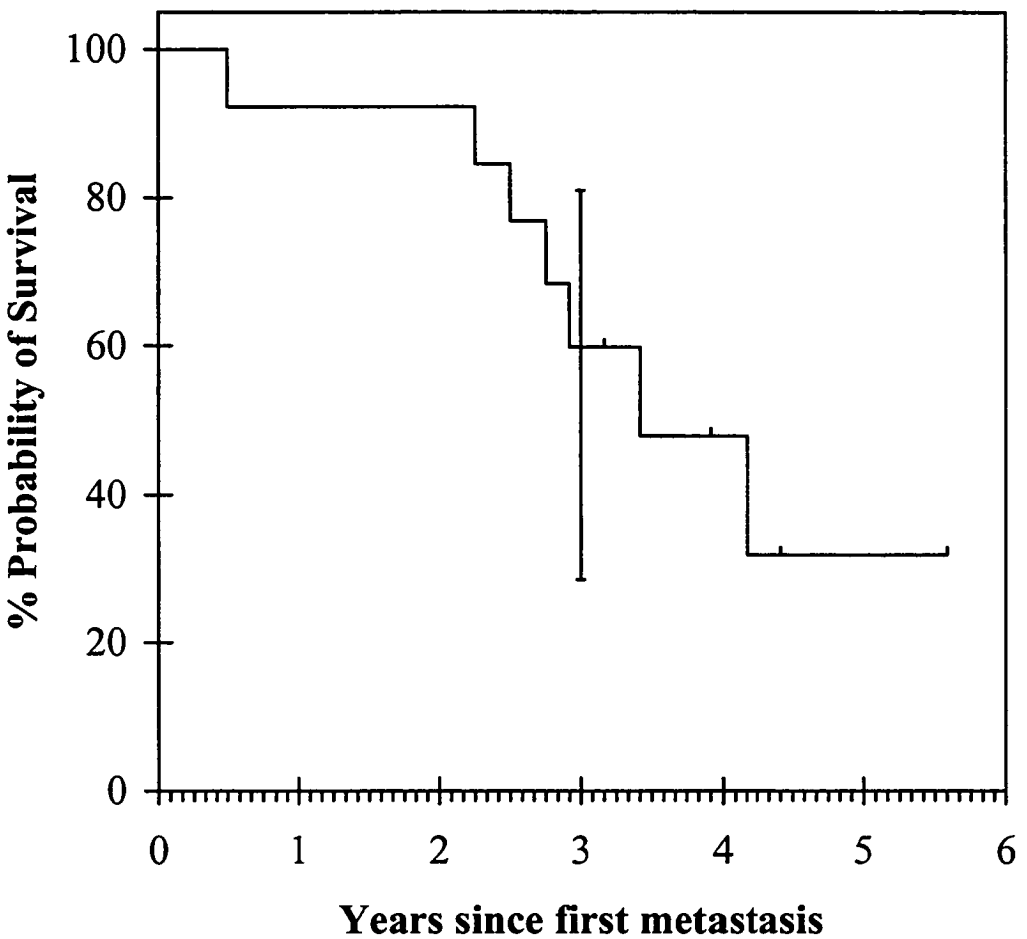
Chemotherapy for Metastatic Disease

Nine of the patients with STM had chemotherapy during their management and the patient with isolated lung metastasis also received chemotherapy. Further details of the chemotherapy regimes, timing and responses are detailed in Table 4.3. Six of the patients with STM had adjuvant radiotherapy at the time of treatment of their primary with 7 having radiotherapy to metastatic disease sites. All 12 patients with STM had further surgical procedures (up to 4) for treatment of their metastatic disease.

Survival After Metastasis

There were 6 patients still alive at between 30 - 67 months after their first metastasis, 4 of whom were disease free. There were 7 deaths, all disease related, ranging between 35 and 148 months (median 62 months) after first diagnosis and from 6 to 50 months after first metastasis. The survival plot of the 13 cases following first metastatic event is shown in Figure 4.1. Patients with STM were 4.5 times more likely to die compared to patients without STM. (Hazard Ratio 4.5, 95 % CI: 1.1 - 19; $p = 0.02$)

Figure 4.1 Survival following Metastasis



Non-metastatic Deaths

Assessing the other 37 patients who did not have any distant metastases, there have been 3 deaths all disease related. There were 2 deaths from patients with retroperitoneal sarcomas who died 12 and 43 months after diagnosis and 1 death following incompletely excised extensive abdominal wall and groin disease in an elderly woman who died at 19 months after diagnosis.

Survival and Prognostic Factors

For the whole series of 50 cases the overall 5 year and 7 year survival rates were 87 % and 69 %. An overall survival curve is shown in Figure 4.2. Table 4.4 examines the prognostic features of interest in this disease including gender, < 10 cm versus ≥ 10 cm size of primary, the presence of a round cell component in the primary tumour, the occurrence of a local recurrence event, occurrence of a soft tissue metastasis event, AJCC / UICC Stage and RMH Stage.

Figure 4.2 Overall Survival

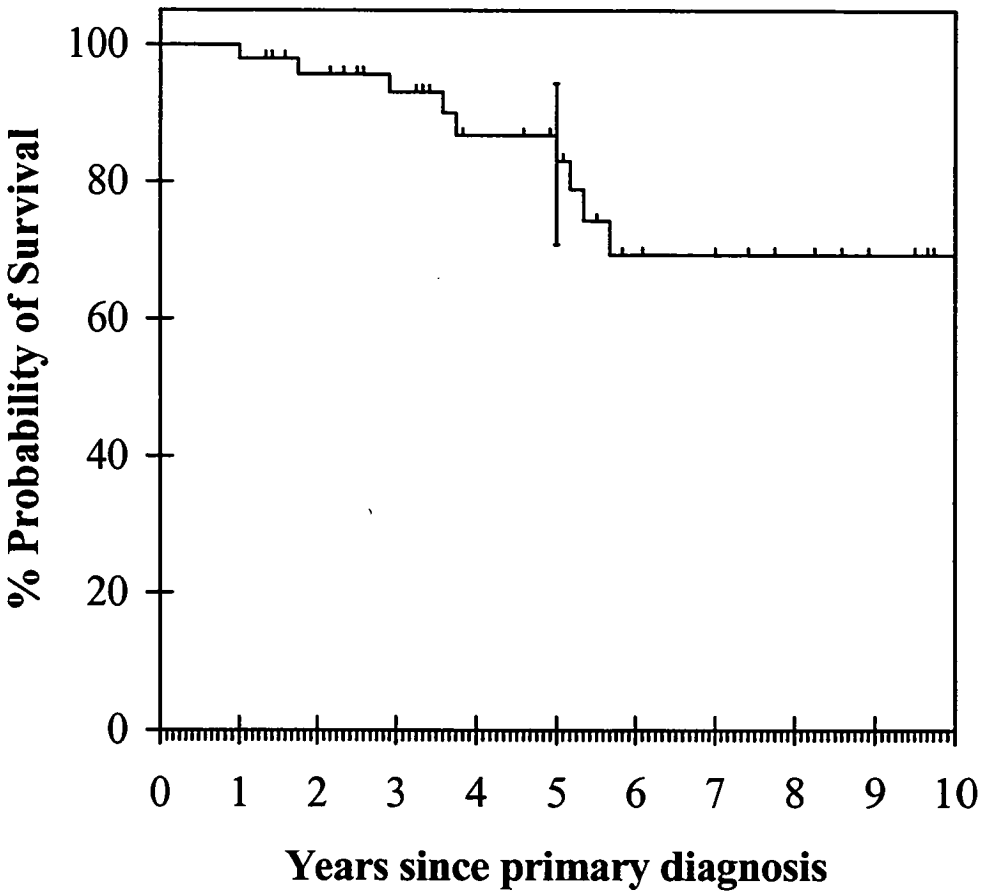


Table 4.4 Assessment of Prognostic Factors Associated with Survival in Myxoid Liposarcoma.

	No. Cases	Freedom from Local Recurrence %	Distant Metastasis Free Survival %	Overall Survival % [Predicted Survival] [11]
GENDER:				
MALE	24	74 (48-89) NS	62 (37-79) NS	83 (54-94) NS
FEMALE	26	89 (63-97)	77 (48-91)	83 (56-94)
SIZE:				
< 10 CM	16	91 (51-99) NS	69 (30-90) NS	87 (39-98) NS
≥ 10 CM	31	80 (57-91	71 (50-84)	80 (57-91)
unknown	3			
ROUND CELL COMPONENT:				
YES	16	80 (58-91) NS	42 (16-67) p = .01	75 (41-91) NS
NO	34	85 (52-96)	85 (65-94)	89 (69-96)
LOCAL RECURRENCE:				HAZARDS RATIO:
YES	7			2.37 (0.47-12) NS
NO	41			1.00
persistent local disease	2			
SOFT TISSUE METASTASIS:				HAZARDS RATIO
YES	12			4.54 (1.1-19) p .02
NO	38			1.00
AJCC / UICC STAGE:				
2A	25	77 (50-91) NS	75 (49-89) NS	81 (56-92) NS
3	16	85 (52-96)	59 (23-82)	78 (36-94)
[Predicted Survival]				[2A,B,C 81.8%, 3 51.65%]
RMH STAGE:				
1	10	86 (33-98)	88 (39-98)	100
2A	11	88 (43-98) NS	90 (47-90) NS	74 (29-93) NS
2B	18	73 (37-90)	30 (2-70)	54 (20-80)
3	7	86 (33-98)	71 (26-92)	75 (13-96)
[Predicted Survival]				[2A 74 %, 2B 61%, 3A 39%, 3B 18%]

( ) 95 % Confidence Interval

4.5 DISCUSSION

Soft tissue sarcomas typically metastasise to the lungs. If metastases are isolated (or several) there is potential for long term survival with pulmonary metastasectomy.[3] Therefore surveillance for local recurrence and lung metastasis forms the basis of follow up. Liposarcomas are the 2nd or 3rd most common STS in most series representing between 8 and 17.8 %.[1,2,4] Liposarcomas have a tendency to occur in a typical site distribution. Well-differentiated liposarcoma is the most frequent retroperitoneal sarcoma subtype. Liposarcoma is also one of the most common subtypes to occur in the proximal thigh. In a very large assessment of 1067 cases Enzinger and Weiss identified 19 % of all subtypes of liposarcomas combined arising in the retroperitoneum.[2] Kilpatrick et al. had 91 of 95 cases of myxoid and round cell liposarcoma arising in an extremity distribution.[6] This paper only assesses the myxoid subtype so the distribution of primary sites appears typical of this subtype of liposarcoma.

Liposarcomas have been reported to metastasise in 19 - 37 % of patients [5,7,8,14], which is comparable to this series. They have previously been noted to have a tendency to metastasise to soft tissues rather than the lungs when compared to other STS.[5,6,7,8,15] MLs form the major subset of liposarcomas and are usually described as being of low grade with low metastatic potential, similar to well-differentiated

liposarcoma.[8] A round cell component to ML is considered a higher grade version of ML and is thought to have increased potential for metastasis.[15] Pleomorphic and de-differentiated liposarcomas are also high grade and when they metastasise they mostly do so to lung. It has been our experience that compared to other types of STS only ML has a tendency to metastasise to non-pulmonary soft tissue sites, and does so more often than metastasising to lung parenchyma.The restriction of this phenomenon to ML has also been the observation of several authors [2,16] but not others.[8] Cheng et al. reported no association with histological subtype of liposarcoma but on review of their data 10 of 13 cases with first site metastases other than the lung were either myxoid or round cell subtypes. The other 3 cases of STM from other subtypes of liposarcoma were to liver in 2 and bone in 1.[8] In our series the most frequent sites of STM were the retroperitoneum, abdominal wall and abdominal cavity but there was a wide range of sites to both trunk and limbs. With time multiple sites of metastasis often occur.(see Table 3) There have been case reports of several unusual sites of metastasis including the heart.[5,17] Enzinger and Weiss suggest that for unknown reasons ML tend to produce secondary lesions on the serosal surfaces of the pleura, pericardium, and diaphragm, sometimes alone or in combination with metastases to the viscera.[2]

Not surprisingly soft tissue metastatic disease was associated with a significantly higher chance of dying ($p = 0.02$) but of interest is the median survival following first metastasis of 41 months with half the patients still alive. The characteristic of first metastasis occurring years after diagnosis has been previously reported [1,2,5,7] but from our data it is apparent that patients can enjoy medium-long term survival after developing metastatic disease. The median survival of 41 months after first metastasis in this series contrasts with figures reported by Vezeridis et al. for a cohort of 242 STS suggesting that if lung was the first site of metastasis the median survival is only 9.8 months.[1]

The difference in post-metastasis survival demonstrated for ML in this series when contrasted to "normal" STS post-metastasis survival is the basis for questioning the validity of applying the currently utilised STS staging systems to this subtype of STS. As can be seen from Table 4. neither the AJCC / UICC nor the RMH Staging Systems are particularly helpful in predicting 5 year survival rates. Certainly when comparing to the published predicted rates for all STS with the corresponding stage at presentation there are wide discrepancies with our data for ML in overall 5 year survival. The AJCC / UICC Staging Systems only gives 2 assessable subgroups with little separation of prognosis. The observed survival is quite unlike the predicted from the data available for survival for each stage studied. The RMH Staging System on the other hand gave

a more even separation of number of cases into more subgroups but the predicted and observed survivals were not particularly reliable. Admittedly with these small numbers the confidence limits are wide however within the limitations of the study I believe it is reasonable to conclude that the tested staging systems give poor prognostic information in this quite large subgroup of STS.

Assessment of prognostic factors in this series (Table 4.) is somewhat limited by the small numbers of cases. However, this study shows that local recurrence events are predictive of a worse outcome, presumably acting as a marker of biological aggressiveness. There is recent evidence in the literature that local recurrence events (at presentation to Memorial Sloan-Kettering Cancer Center) are predictive of worse survival.[18] Otherwise round cell component and the occurrence of a STM are also predictive of worse survival. Size and gender have no impact on outcome in this study.

The frequency of areas of round cell differentiation in this cohort (32 %) is similar to previously reports from series of myxoid liposarcoma. Kilpatrick et al. identified 43 % of cases with round cell areas.[6] They argued, similarly to Evans [5], that round cell liposarcoma should be regarded as the poorly differentiated form of ML. This argument is strengthened by the demonstration of the same chromosomal

translocation of t(12;16) (q13;p11) in both subtypes.[19] It has been demonstrated that ML containing more that 5 % round cell differentiation had a higher risk of death [15] while others state > 25 % is an adverse factor.[6] In our study the presence of any round cell component was associated with significantly greater chance of metastasis at 5 years and hence worse prognosis.

In this series 9 patients received chemotherapy, one of which was in a patient with no known residual disease after removal of a STM. There are too few patients from whom to calculate a response rate, however 5 of 8 patients who had chemotherapy for advanced disease had a significant response to chemotherapy and another enjoyed prolonged disease stabilisation. It seems reasonable to conclude that myxoid liposarcoma is relatively chemo sensitive compared with STS as a group given that published response rates in phase III trials are generally in the region of 25 %.[20] This series demonstrates that good palliation can be achieved with chemotherapy for STM and that there may not be cross-resistance between ifosfamide and doxorubicin, in either direction (Cases 2 & 3). This finding has not been widely reported in other types of sarcoma. We have experienced considerable improvement in resectability of STS after chemotherapy.

In conclusion, ML is a distinct subtype of liposarcoma which has a frequency of STM not seen in other types of STS. In this series 12 of 50 patients developed STM with only 1 other case having isolated pulmonary metastasis. The median time to first STM was 23 months and median survival after first STM was 41 months demonstrating that even after metastatic disease there is a good chance of medium-long term survival. Therefore aggressive treatment is warranted following STM and this most often involves further surgery. When a patient with ML originally presents and if metastatic disease occurs, it is prudent to include abdominal and pelvic computerised tomography scans in the staging work-up. When following up patients with ML it is sensible to carefully investigate what may initially seem quite odd symptomatology for a STS because of the unpredictable sites of recurrent disease. The currently available staging systems for STS provide inadequate information for patients presenting with ML and should not be used to give prognostic information at presentation in this subgroup of STS patients.

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CHAPTER 5.
EPITHELIOID SARCOMA - THE CLINICOPATHOLOGICAL COMPLEXITIES OF THIS RARE SOFT TISSUE SARCOMA.

(Spillane AJ, Thomas JM, Fisher C. Epithelioid Sarcoma - the clinicopathological complexities of this rare soft tissue sarcoma. Ann Surg Oncol 2000;7;3:218-225.)

5.1 SUMMARY

BACKGROUND: Epithelioid sarcoma (ES) is a rare high-grade soft tissue sarcoma (STS) with a known propensity for loco-regional recurrence. The literature is limited on other characteristics such as frequency of multifocal disease at presentation, the relationship of presenting size of the primary to prognosis and the ability of current staging systems to predict prognosis.

METHODS: Review of the Royal Marsden NHS Trust (RMH) experience of 37 cases over 21 years.

RESULTS: The mean age was 29 years with male predominance (2.7:1) and distal limb locations were most common (56 %). Five cases presented with multifocal local disease. Median follow up was 88 months in the 19 patients still alive. The 5 and 10 year actuarial overall survival was 70 % and 42 % respectively. Tumours deep to the investing fascia had a worse prognosis than superficial tumours. Regional metastasis events were also associated with significantly worse overall survival. Local recurrence, size ≥ 5 cm and regional metastasis events were predictive of worse distant metastasis free survival. Tumour size (< 5cm vs ≥ 5 cm), local recurrence events, gender and site were not

significant predictors of survival. The AJCC / UICC Staging Systems and recently proposed RMH Staging System provided poor differentiation of prognosis in ES. The 5-year actuarial local recurrence rate was 35 %. The 5-year actuarial regional nodal metastasis rate was 23 %. The actuarial 5 year distant metastasis rate was 40 % with pleuro-pulmonary metastases most the common site of metastatic disease. 35 % of pleuro-pulmonary metastases presented with pleural effusion. Median post-distant metastasis survival was 8 months.

CONCLUSION: ES has unusual clinical behaviour compared to other high grade STS. It has a propensity for multifocal disease at presentation, local recurrence, regional metastasis and particularly poor prognosis after regional or distant metastatic disease. Size and AJCC / UICC Stage are unreliable predictors of prognosis.

5.2 INTRODUCTION

Epithelioid sarcoma (ES) is a rare subtype of soft tissue sarcoma (STS) first described under its current designation in 1970.[1] ES is a tumour which shows both epithelial and mesenchymal differentiation.[2,3] ES has a propensity for young male adults and tends to favour limb locations, especially distal upper limb.[1,4-7] ES has an incidence of local recurrence up to 70 % in some series and an incidence of regional lymph node metastases up to 45 % but an overall 5 year survival of up to 70 %.[4-8] ES also features typical behaviour including a tendency to be multifocal at recurrence or by the time the patient is referred for specialist opinion. The multifocal disease can manifest as in-transit type metastases analogous to melanoma in some cases or appears more consistent with spread along musculotendinous planes in others.[5,6] ES may arise superficial to the body's investing fascia where it may ulcerate or it may originate from deeper structures. ES is regarded as a predominantly high grade STS [4,8] but the authors of most of the large series have not described the grade of their cases.[5-7]

The clinically important features of the disease, which are not emphasised in the literature, include the frequency of multifocal local disease at presentation and the difficulty ascribing a presentation size to the primary lesion because of this. This contributes to the difficulties deriving reliable prognostic information for patients with ES using the current AJCC /

UICC Staging Systems.[9,10] Also the unpredictable nature of metastatic events as judged by the size of the primary lesion has been mentioned but not emphasised in the past.[5] We have also noted a tendency for pleuro-pulmonary metastatic disease to cause pleural effusions with minimal thoracic disease volume which is unusual for other subtypes of STS. These issues are examined by reviewing the experience of the Royal Marsden NHS Trust Hospital (RMH).

5.3 METHODS

A review of the RMH records was performed from 1978 to the end of 1998. There were 37 patients identified from the hospital's prospective database with adequate information available. There were a further 10 cases identified but excluded from analysis because there was inadequate information or diagnostic uncertainty. Most of the information was obtained from the prospective RMH records after 1992 but was obtained from the hospital notes and communication with the referring hospitals prior to that time. All cases had their original histopathology reviewed at the RMH with all cases reviewed prospectively by one pathologist (CF) from 1985 and retrospectively by the same pathologist prior to that time. In 6 cases the size of the tumour was determined by clinical or radiological assessment while in one case the size of the original tumour was not documented as that patient presented with Stage 4 disease. The applicability of the current AJCC / UICC Staging Systems [9,10] and the recently proposed RMH Staging System [11] when applied to this case series was assessed by assuming all cases to be high grade unless otherwise stated in the RMH pathology review.

Definitions:

- The date of diagnosis is taken as the time of first histological confirmation of ES.

- In cases of multifocal local disease at presentation a summation of independent lesions was used to estimate original size.
- Cases referred with loco regional and / or distant recurrence where the original pathological analysis did not mention the microscopic margin were classified as marginal excisions based on the referral / operation report descriptions.
- Local recurrence is defined as recurrent disease in the area of the primary tumour following clearance of local disease by primary treatment. For continuity with other recurrence events time to local recurrence is taken from the date of diagnosis.
- For calculation of first disease free interval persistent local, regional and / or distant disease despite primary therapy was counted as local, regional and / or distant recurrence at 0 months.
- Survival data were calculated from the date of first diagnosis to the date of death or last review.

Survival, local recurrence free survival and distant metastasis free survival were compared between different groups using the log rank test. Life table curves were calculated using the Kaplan-Meier Method. Analysis of the effects of local and regional recurrence on distant metastasis free and overall survival was undertaken using the time of recurrence as a time dependent factor in Cox's regression.[12,13]

5.4 RESULTS

Demographics

The 37 cases identified had a mean age at diagnosis of 29 years (range 7 - 55 years). There was a male / female ratio of 2.7:1. The site distribution is shown in Table 5.1. At presentation to RMH there were 15 cases that had a localised primary lesion, 5 cases with multifocal localised primary disease, 4 cases with local recurrence (one of whom had widespread local recurrence in his forearm) and 13 cases with metastatic disease. At first diagnosis 5 cases had metastatic disease with 4 of these 5 cases having loco regional disease that was not completely resected during primary therapy (3 had chemotherapy alone).

Table 5.1 Site Distributions of Cases of Epithelioid Sarcoma.

LOCATION OF PRIMARY TUMOUR	**NUMBER**
DISTAL UPPER LIMB (EXCLUDING DISTAL TO WRIST)	9
DISTAL TO WRIST	8
PROXIMAL UPPER LIMB	4
DISTAL LOWER LIMB	4
PROXIMAL LOWER LIMB	3
BUTTOCK	2
TRUNK (PENIS OR VULVA OR PERINEUM)	6 (5)
HEAD & NECK	1

Diagnosis and Treatment

Eleven of the 37 cases had a diagnostic delay of between 4 months and 5 years due to misinterpretation of clinical signs or failure of prompt referral by their doctor. The method of diagnosis was excision biopsy in 22 cases (1 at RMH), incision biopsy in 13 cases (none at RMH) and core biopsy in 2 cases (1 at RMH). The primary treatment modality was surgery in 33 cases, chemotherapy in 3 cases and radiotherapy in 1 patient. There were 4 primary therapy amputations (3 of digits and 1 above elbow amputation) and 2 later amputations (1 penile and 1 above elbow amputation). In 12 cases the initial surgery was performed at RMH. There were 14 patients who received adjuvant radiotherapy and a further 10 who later received therapeutic radiotherapy for unresectable recurrence or metastatic disease. Nineteen cases had chemotherapy during their treatment with 14 receiving ifosfamide or doxorubicin (+/- in combination) most according to the specifications of the EORTC trial in which they were enrolled. Three (of the 5 cases who presented with regional or distant metastases) had neoadjuvant chemotherapy, 2 cases had adjuvant chemotherapy and the remainder had therapeutic chemotherapy. Only 1 case had pulmonary metastasectomy and she died 2 months later.

Pathological Features

The size distribution of the primary lesions is shown in Table 5.2. There were 5 cases who had multifocal disease at first presentation - 2 of whom had a combined total < 5 cm and 3 of whom the combined total was ≥ 5 - < 10 cm. All cases were high grade. There were 8 cases superficial to the investing fascia. The stage distribution comparing the AJCC / UICC Staging Systems [9,10] to the RMH Staging System [11] is shown in Table 5.3.

Table 5.2 Size Distributions of Cases.

SIZE RANGE OF PRIMARY TUMOUR	NUMBER OF CASES
< 2CM	5
≥ 2 - < 5 CM	17
≥ 5 - < 10 CM	11
≥ 10 - < 15 CM	2
≥ 15 CM	1
UNKNOWN	1

Table 5.3 Distribution of Epithelioid Sarcoma Cases by AJCC / UICC Stage [9,10] and RMH Stage.[11]

STAGE	AJCC / UICC STAGING SYSTEM - NUMBER OF CASES	RMH STAGING SYSTEM - NUMBER OF CASES
2A		21
2B	23	9
2C	2	
3	7	2
4	5	5

Disease Status and Follow up

There was a median follow-up of 88 months from diagnosis in the 19 patients still alive (range 6 - 249 months). At final analysis there were 17 patients who had died from ES at a median of 30 months from diagnosis (range 3 - 113 months) and 1 man who died from another malignancy 149 months after first diagnosis of ES. There were 3 patients who were alive with residual disease. The disease specific cause of death in this series was distant metastases in all but 1 case that had extensive retroperitoneal nodal metastatic disease.

Survival and Prognostic Factors

The overall 5 and 10-year survival rates from diagnosis were 70 % and 42 % respectively. An overall survival curve is shown in Figure 5.1. In Figure 5.2 the survival curve for the 32 patients without metastatic disease at presentation is demonstrated. Table 5.4 examines survival related to the previous prognostic factors discussed in the literature including gender, distal limb versus proximal limb and axial site of primary, superficial versus deep lesions, a local recurrence event, a regional lymph node metastasis event, < 5 cm versus ≥ 5 cm, AJCC / UICC Stage [9,10] and RMH Stage [11]. Further assessing those tumours that were < 5 cm compared to those ≥ 5 cm the crude figures demonstrate that 9 of the 21 cases (43 %) < 5 cm had died at assessment (1 case was censored as he died of another disease). This compared to 7 deaths from

the 14 cases whose tumours were ≥ 5 cm (50 %). There were 2 deaths from the 5 cases who had a primary tumour was < 2 cm at presentation.

Fig 5.1 The Overall Survival Curve for all cases of Epithelioid Sarcoma taken from time of first histological diagnosis. Censored events (short vertical bars) are limits of follow up for individual patients. Error bars indicate 95 % confidence limits for overall survival at 5 and 10 years.

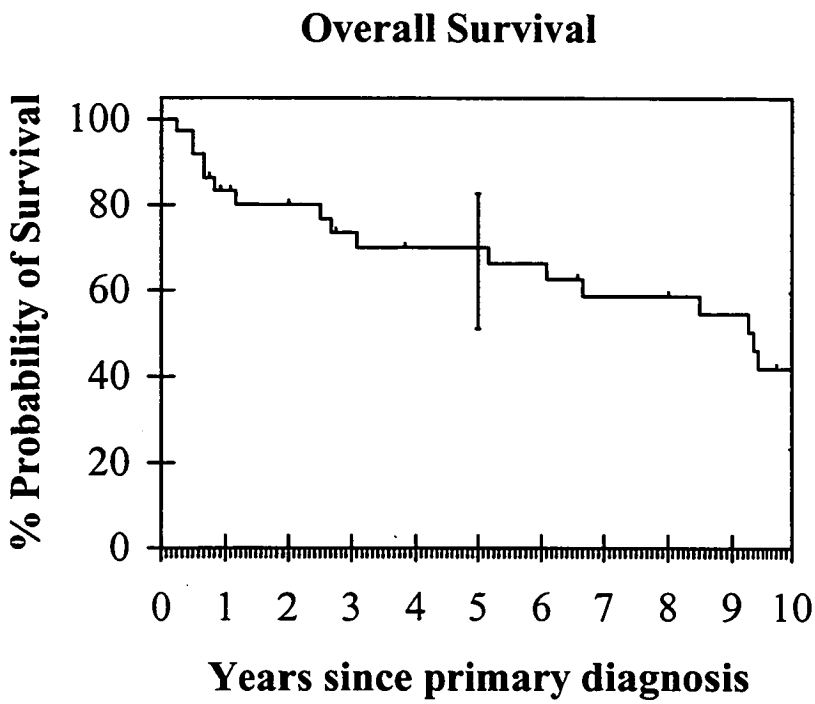

Fig 5.2 The Overall Survival Curve for Cases AJCC Stages I-III. Censored events (short vertical bars) are limits of follow up for individual patients. Error bars indicate 95 % confidence limits for overall survival at 5 years.

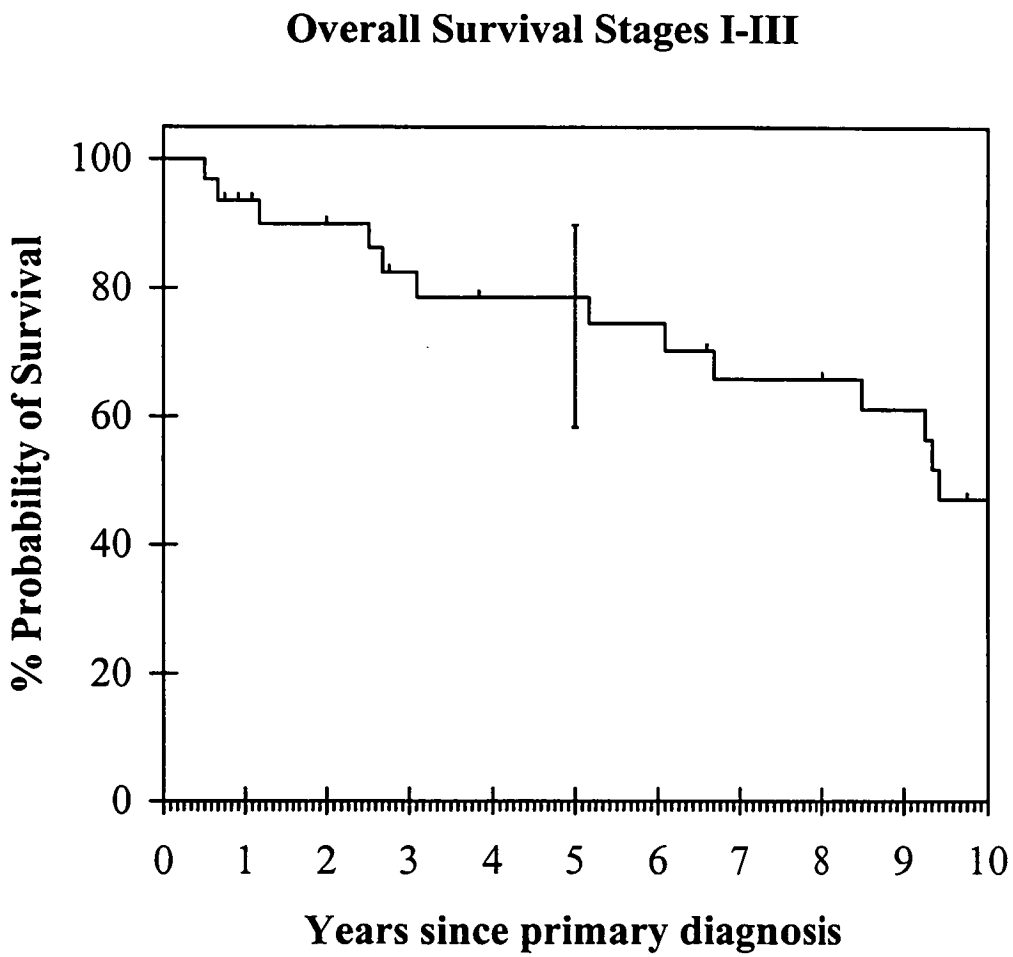

Table 5.4 Univariate Analysis of Prognostic Factors in Epithelioid Sarcoma.

	No. Cases	**Freedom from Local Recurrence % (CI)**		**Distant Metastasis Free Survival % (CI)**		**Overall Survival % (CI)**	
GENDER:							
MALE	27	55 (33 - 72)		65 (43 - 80)		75 (53 - 88)	
FEMALE	10	79 (38 - 94)	NS	47 (15 - 74)	NS	55 (19 - 81)	NS
SITE:							
PROXIMAL / AXIAL	16	59 (27 - 81)	NS	43 (16 - 67)	NS	56 (26 - 78)	NS
DISTAL	21	58 (33 - 77)		69 (43 - 85)		78 (52 - 91)	
LOCAL RECURRENC				(HAZARD RATIO)		(HAZARD RATIO)	
EYES	12*			3.7 (1.1 - 12.5)	p = 0.025	2.6 (0.91 - 7.9)	NS p = 0.06
NO	22			1.0		1.0	
REGIONAL NODE METASTASIS:				(HAZARD RATIO)		(HAZARD RATIO)	
YES	8#			5.9 (1.6 - 22)	p = 0.003	6.6 (2.4 - 18)	p = < 0.001
NO	27			1.0		1.0	
SIZE:							
< 5CM	22	69 (43 - 85)	NS	80 (54 - 92)	p = 0.04	81 (57 - 92)	NS p = 0.17
≥ 5CM	14$	50 (19 - 75)		33 (10 - 57)		49 (19 - 74)	
DEPTH:							
SUPERFICIAL	8	37 (9 - 67)	NS	87 (39 - 98)	NS	100	p = 0.013
DEEP	29	68 (46 - 83)		56 (36 - 73)	p = 0.06	61 (39 - 77)	
AJCC / UICC STAGE:							
2B	23	66 (41 - 82)	NS	76 (51 - 89)	NS	80 (56 - 92)	NS
2C / 3	9	62 (21 - 86)		52 (16 - 79)		73 (28 - 92)	
RMH STAGE:							
2A	21	67 (41 - 84)	NS	79 (52 - 91)	NS	84 (58 - 95) [74%]	NS
2B	9	52 (16 - 79)		51 (16 - 78)		71 (26 - 92) [61%]	

* 3 other cases had persistent local disease that was never cleared
# 2 other cases had regional nodal disease that was never cleared
$ 1 unknown size
CI = 95 % confidence interval
NS = not significant

First Disease Free Interval

There were 20 cases who developed recurrent disease and another 5 patients who had persistent disease after primary therapy. Median first disease free interval (DFI) for these 25 patients was 9 months with a range of 0 - 99 months. First site of disease relapse was isolated local recurrence in 9 cases, isolated regional recurrence in 3 cases and isolated distant metastatic disease in 6 cases. There were another 5 cases whose first site of disease relapse was a combination of locoregional and distant metastatic disease (one of whom had regional and distant recurrence with no local recurrence) while 2 cases had a combination of local and regional disease but no distant metastatic disease. If the 5 cases never cleared of disease following diagnosis are excluded the median first DFI was still only 13 months.

Local Recurrence

There were 12 cases (35 %) who developed local recurrence (LR) after initial treatment at a median of 13 months (range 6 - 82 months) and another 3 cases who had persistent local disease following primary therapy (as well as distant disease). One case of local recurrence involved multifocal widespread forearm recurrence. The actuarial 5-year LR rate was 35 %. Six of 12 cases (50 %) with one LR had further LR events. Comparing those who had adjuvant radiotherapy for extremity lesions to those who did not 3/10 versus 6/18 had LR.

Regional Recurrence

There were 8 cases (23 %) who developed regional nodal metastases (RM) after initial diagnosis at a median of 17 months (range 4 - 99 months) and another 2 who had regional nodal disease at presentation (as well as local and distant disease). The actuarial 5-year RM rate was 23 %. Median post-RM survival was 10 months with a range 3 - 140 months.

Metastatic Disease

There were 14 cases that developed distant recurrence after initial therapy at a median time of 29 months after diagnosis (range of 4 - 105 months) and another 5 cases that had metastatic disease at presentation. The actuarial 5-year metastasis rate was 40 %. The median post-metastatic survival was 8 months. The sites of distant metastatic disease included 17 patients with lung or pleural metastases, 3 cases with scalp soft tissue metastases (STM), 2 cases with other STM and 1 case of bone metastasis (some of the patients had multiple sites). Assessing the 17 cases with pleuro-pulmonary metastasis, 6 (35 %) presented with pleural effusion, often with minimal underlying parenchymal disease.

5.5 DISCUSSION

Epithelioid sarcoma (ES) is a rare soft tissue sarcoma (STS) with characteristic features both clinically and on pathological assessment. It is difficult to verify but ES probably comprises less than 1 % of STS as judged by Memorial Sloan-Kettering Cancer Center's recently published series of 18 cases from their prospective database of over 2600 STS at that time.[8] ES has a propensity for young male adults. ES occurs most often at distal upper limb locations but may occur at widespread sites including quite commonly the perineum, penis and vulva.[4,8] ES previously has been reported to infrequently involve the trunk and buttock [1,6] but did so in approximately 25 % of patients in our experience and 44 % in another recently published series.[8] ES rarely involves the head and neck.[1,4-8] Diagnosis is characterised by typical histology and immunohistochemical staining for epithelial markers. However there is often misinterpretation of histology and ES is misdiagnosed most commonly as benign granulomata, a wart, ulcerating squamous cell carcinoma, amelanotic melanoma, clear cell sarcoma and synovial sarcoma.[1,4,5] ES has a tendency to spread locally, presumably by way of lymphatics or along fascial planes, and may either present with multiple local nodules or the patient may develop these during the course of the illness.[1,4-6] In this series 5 cases (14 %) had multifocal disease at presentation and another developed multifocal local recurrence.

Precise information on survival and prognostic features is difficult to ascertain in this subtype of STS. The reason for this is the rarity of the disease has resulted in the authors of the larger series in the literature having to retrospectively diagnose ES from their pathology archives and databases, so as to include cases from well before 1970.[5,6] The overall survival has been reported to range between 58 % and 100 % in the literature reviewed by Bos et al. with their own series reporting around 70 % 5 year survival.[6] In a more recent series the overall 5 year survival was 66 % [8] and our figure of 70 % further supports this older data. The 10-year disease specific overall survival rate of 42 % demonstrates a sizeable ongoing disease related mortality after 5 years.

In previous series the prognosis for ES has been reported to depend on the size of the primary [5-7], depth of the tumour in relation to deep fascia [6], a history of a local recurrence event [14] and the presence of lymph node involvement.[6,7,14] Other tumour factors such as the mitotic count, presence or absence of necrosis, haemorrhage and lymphovascular invasion are probably not independent prognostic factors.[7] Distal limb tumours have been reported to do better than proximal limb and axial tumours.[1,5] Females are reported to have a better prognosis than males in some series [5,6,8] but not others [7]. Our data, which is a comparatively large series, suggests that deep lesions do worse in terms of overall survival and nearly reach significance in terms of their worse

metastases free survival. Regional nodal metastases imply a significantly worse distant metastasis free survival and overall survival. We also found local recurrence events to be predictors of significantly worse distant metastasis free survival and a trend towards significance for overall survival. Size < 5 cm compared to ≥ 5 cm was not a significant predictor for overall survival within the limitations of such a small study with little power to detect anything but a major difference. The smaller tumours did however, have a significantly better distant metastasis free survival.

When evaluating the impact of size of the primary tumour on prognosis, difficulty arises when the lesion is multifocal at presentation. This poses problems for the application of the commonly used AJCC / UICC Staging Systems [9,10] to cases of ES and makes useful prognostic information difficult to obtain. There were 3 cases where the individual lesions were very small but the total of the multifocal lesions exceeded 5 cm, thus by our methodology placing them into a higher risk stage. In an otherwise high-grade tumour the AJCC / UICC Staging Systems [9,10] can only differentiate based in size and depth so the impact of this summation of individual lesions is significant. The recently proposed RMH Staging System [11] does not give better discrimination in this subtype of STS as it relies equally on size and grade for differentiation. Therefore if all tumours are high grade and most < 5 cm diameter prognostic

differentiation is difficult. Table 4 demonstrates that neither the current AJCC / UICC or the RMH Staging Systems [9-11] usefully define prognosis for patients with ES with poor discrimination between stages for disease specific survival, which is the most important endpoint for a staging system.[15] Obviously a larger study may narrow the confidence intervals but the problem of assessment of multifocal lesions remains. The rarity of this subtype of STS is the major reason why the current staging systems are not valid and will never be suitably proven to be so. This subtype should therefore be excluded from the list of subtypes that the AJCC / UICC Staging Systems are said to be applicable to. (See Table 1.4)

ES has been reported to have a high incidence of local recurrence up to 77 % [5] but it only occurred in 35 % of our cases. The reason for the discrepancy is unclear and is not obviously related to improvements in treatment as a recent series reported a local recurrence rate of 69 %.[8] However, local recurrence rates published from the RMH and other larger series for all subtypes of STS typically range from 9 - 17 %, which is noticeably less than ES.[16,17] This clearly demonstrates the propensity for local recurrence with this disease. Recent evidence suggests that local recurrence events for STS may be associated with worse overall survival.[16]

Previous reports of a high incidence of lymph node metastases in ES (typically between 22 % and 45 % [6-8]) are consistent with the rate of 23 % in our series. There is no documented place for elective lymph node dissection as you would expect in such a rare disease, however, if lymph node involvement occurs then radical dissection of the lymph node basin for local tumour control is indicated for local disease control. The concept of sentinel node biopsy could be applied for focal ES [18], however there is no current data to validate the use of sentinel node biopsy specifically in this type of tumour. We only had one long-term survivor of the 10 cases with regional lymph node involvement. This man had an inguinal node block dissection 9 months after diagnosis and survived disease free for another 140 months to die of squamous cell carcinoma of the tongue. Otherwise regional metastases are associated with a poor prognosis in ES with a median survival of 10 months. As is the case in other subtypes of STS nodal metastases have the same severe prognostic implications as distant metastases.[15,19] Clearly ES has a propensity for regional lymph node involvement compared to a rate of 2.6 % for all subtypes of STS combined.[19]

Distant metastatic disease has been reported to occur in up to 45 % of cases of ES [1,8] with an actuarial 5-year rate of 40 % in this series. Most frequently ES metastasises to the lungs and pleural surfaces. In 35 % of our cases with metastatic intra-thoracic disease the patient presented

with a pleural effusion. This is frequent compared to other subtypes of STS, especially when considering most of these cases had only small volume of pleuro-pulmonary disease underlying the effusion. The frequent occurrence of pleural effusion with this disease largely explains the low incidence of pulmonary metastasectomy in this series. Other series report similar rates of pulmonary metastatic disease from 21 to 44 % but do not comment on the frequency of pleural effusion.[5,6,8,14] Interestingly ES is reported to metastasise to the scalp in up to 22 % of cases [1] but did so in only 3 cases (8 %) in our series.

At the RMH the treatment of primary disease is ideally wide local excision and, as with other high grade STS, usually adjuvant radiotherapy in an attempt to lower the risk of local recurrence. This is empirically based on previous demonstration that both external beam radiotherapy and brachytherapy have proven benefit for local control in high grade STS.[20-22] There is no good data on the role of radiotherapy for this subtype of STS with its particular biological behaviour and a tendency for multifocal disease. Shimm et al. did however report a low local recurrence rate in their series of ES following radiotherapy.[23] Amputation is unfortunately relatively frequent in ES because of the tendency for multiple and multifocal local recurrence events however the literature suggests there is no survival advantage from primary amputation.[6,24] The authors would only recommend amputation for

extensive recurrent disease unless there was an exceptional presentation with extensive local disease and no distant spread.

If metastatic disease occurs there is a poor prognosis with a median post-metastasis survival of only 8 months compared to typical post-metastasis survival of 11 months for large series of STS treated with chemotherapy.[25] Even though there is no good quality literature specifically on the chemo-sensitivity of this subtype of STS our patients have mostly received standard regimens of chemotherapy as prescribed by the EORTC protocol for the trial in which the patient was entered. This would typically include ifosfamide or doxorubicin regimens sometimes in combination.

In conclusion, this is a rare subtype of STS and a large series of this type adds to the overall pool of knowledge on this disease. ES has typical features, well described in the literature, such as frequent local recurrence and nodal metastases. However, the features of the disease not previously focused on include the high rate of multifocal local disease at presentation, the difficulty ascribing a presentation size to the primary lesion in these circumstances, and the difficulties of the current frequently used staging systems for predicting prognosis in this disease. We also identified a high frequency of pleural effusions at presentation of intra-thoracic metastatic disease. There is an overall poor prognosis for

regional or distant metastatic disease compared to other metastatic STS. We recommend a guarded prediction of prognosis be given to all cases of ES deep to the investing fascia even when they have small localised primary lesions.

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CHAPTER 6. THE EFFECTIVENESS OF EACH STAGING SYSTEM WHEN ASSESSING COMBINATION DATA FROM THE THREE SUBTYPES OF STS ASSESSED

6.1 COMBINED DATA

The data presented on individual subtypes of STS has identified problems and inadequacies with each of the currently available staging systems when related to that subtype. Table 6.1 summaries the deficiencies for each subtype when my relatively large series are applied to the currently available STS staging systems. Table 6.2 summarises any advantages of these staging system for each subtype of STS. Table 6.3 gives the raw data (without confidence limits) for 5 year predicted and observed survival for each stage for each subtype examined and also for the 3 subtypes combined. The data from each subtype of STS was combined from the period 1988 to present to allow for any major treatment changes of other bias in the epithelioid sarcoma group as this case series was from data gathered over 20 years. The resultant survival curves for each staging system are shown in Figure 6.1 and Figure 6.2.

Table 6.1 Deficiencies with each staging system for each subtype of STS

SUBTYPE STS	AJCC / UICC STAGING SYSTEMS	RMH STAGING SYSTEM
SYNOVIAL SARCOMA	• Essentially high grade, deep STS therefore effectively only stages 2B / 3 / 4 • 25 % of cases non-extremity so questionable whether valid for these sites	• Tumours < 5 cm did not separate from those 5 - 10cm • 25 % of cases non-extremity so questionable whether valid for these sites
MYXOID LIPOSARCOMA	• Separation into 2 stages with essentially the same 5 year survival • Most tumours > 5 cm • Distinct metastatic behaviour makes validity of staging system questionable	• Poor prognostic discrimination because large low/intermediate grade tumours had an indolent course • Most tumours > 5 cm • Distinct metastatic behaviour makes validity of staging system questionable
EPITHELIOID SARCOMA	• Small numbers make any assessment invalid • Multicentricity not accounted for • No separation of groups • All high grade • Distinct biology and small numbers makes unproven validity of staging system	• Small numbers make any assessment invalid • Multicentricity not accounted for • No separation of groups • All high grade • Distinct biology and small numbers makes unproven validity of staging system

Table 6.2 Advantages of each staging system for each subtype of STS

SUBTYPE STS	AJCC / UICC STAGING SYSTEMS	RMH STAGING SYSTEM
SYNOVIAL SARCOMA	• Reasonable approximation to predicted survival	• Multiple size brackets give more useful separation of prognosis for tumours.
MYXOID LIPOSARCOMA	• Close approximation to predicted survival for Stage 2A/B only	• With large numbers allowance for size gradient may be useful discriminator
EPITHELIOID SARCOMA	• None	• None

Table 6.3 compares the predicted 5 year survival with the observed for each subtype and overall.

	Predicted		Synovial		Myxoid		Epithelioid		Overall Observed	
STAGE	AJCC	RMH	AJCC	RMH	AJCC	RMH	AJCC	RMH	AJCC	RMH
1	98.8	100A 83B				100				
2A	81.8	74	75 A/B/C	71	81A/B	74	84		80	78
2B		61		68		54	71	80 2B	76	70
3A	51.6	39	53	43	78	75 A/B		73 (2C/3A)	55	55
3B		18		25						40
4		6		0					0	0

Figure 6.1 AJCC Staging System - Combined Data

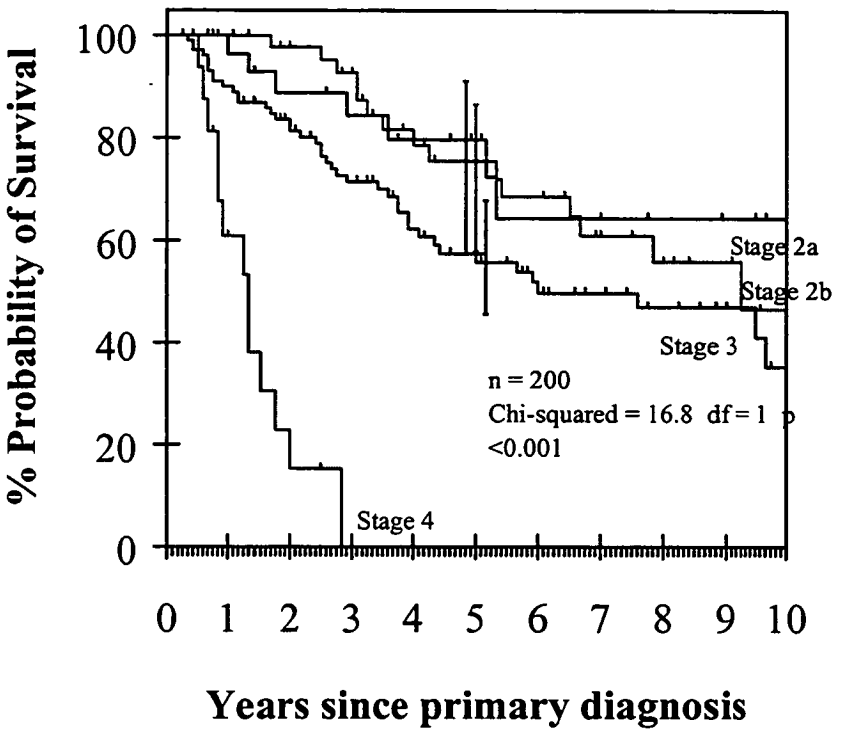
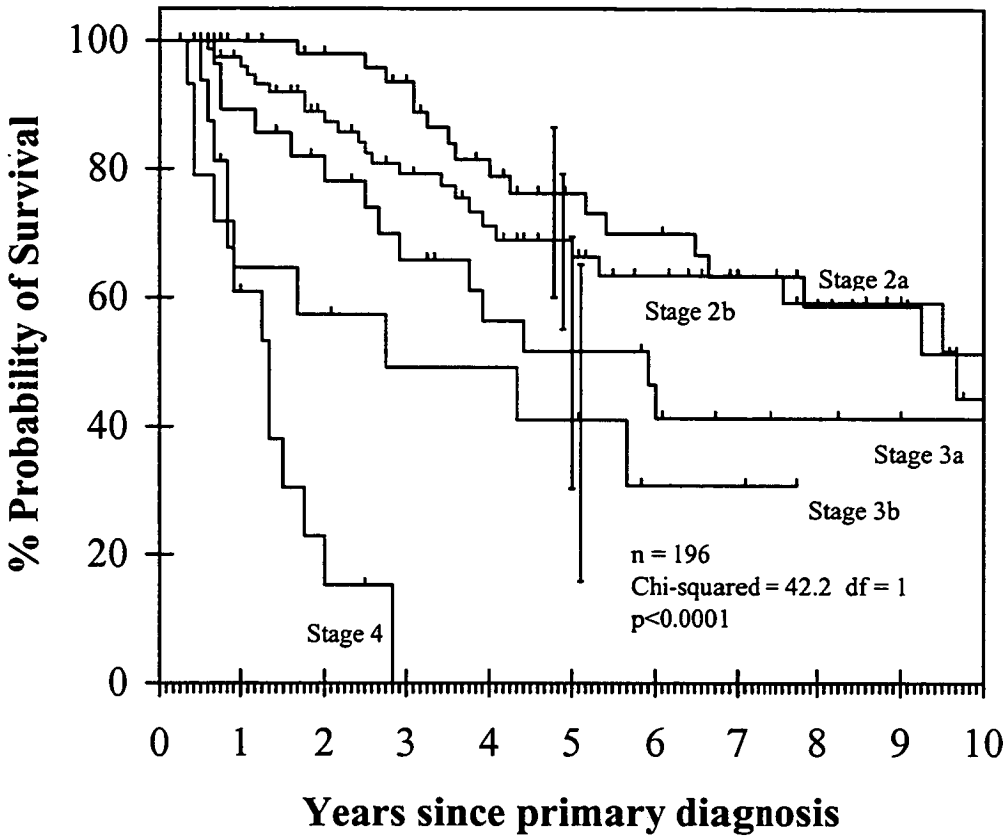


Fig 6.2 RMH Staging System - Combined Data



Note: The discrepancy in number of cases charted for AJCC / UICC vs RMH Staging Systems is because smaller stage groupings were not charted.

Assessment of Combined Data

As can be seen from the above figures, at 5 years there is a more even spread through the stages listed for the RMH Staging System than the AJCC / UICC Staging System. Effectively the AJCC / UICC Staging Systems have either a 75 – 80 % 5 year survival or a 60 % 5 years survival. These predictions are with the general range indicated by the AJCC Staging Manual [1] and support the validity of the current staging systems for an overall assessment of combined groups of STS. This compares to a more even distribution from 80 % down to 45 % 5 years survival for the RMH Staging System. The relatively large numbers contributed by the synovial sarcoma group undoubtedly heavily influences this data. This is indeed what happens in the large cohorts from the centres that have contributed towards the development of the current staging systems.

What can be ascertained from this information? Firstly that even though the AJCC / UICC Staging System gives less prognostic separation between stages it is overall the more accurate of the 2 staging systems at predicting the expected outcome when comparing to the published overall 5 year survival figures. The major problem with the RMH data is that the overall observed survival for stage 3A and 3B STS in this combination series is quite different from the predicted values. This is a reflection of the demonstrated inability of size to discriminate between outcome in

both myxoid and epithelioid sarcomas. The reason for failure to discriminate in myxoid liposarcoma is that large low and intermediate grade tumours behave generally very indolently. The reason why there is a failure of epithelioid sarcoma to be usefully separated into prognostic groups by the RMH Staging System is that most lesions are small (22 of 36 were < 5 cm) and sometimes multicentric and there were only small numbers available for study. Other evidence suggests that after combining all subtypes of STS, size is a continuous variable [2], which is more important than grade after 3 years of follow up.[2] This prognostic separation between stages is less striking overall than when the largest contributor, synovial sarcoma, is assessed individually.

The original RMH Staging System data [3] is much more robust than this retrospectively collected combination assessment, given that it was developed from a purely prospective database over a shorter duration of time and the study number was larger than the combined data here (271 vs 200 cases).

What can be concluded from this interesting but unscientific exercise of combining data is that different subtypes of STS have their own behaviour and have the power to influence the outcome of a staging system. The predicted overall survival outcomes published with a staging system represent an averaging of all the subtypes individual influences

which contributes relative to the percentage that subtype makes of the total. Therefore the ability to gain useful prognostic information for an individual with a specific subtype of STS is limited especially if the subtype is one of the less common ones. It also has implications when comparing results of treatment between centres where referral patterns dictate a different mix of subtypes (or primary locations) than is represented in population from which the staging system was developed.

The question as to what a staging system is trying to achieve is important. It is reasonable to say that the staging system is just trying to provide a core of uniform prediction of outcome for the whole group of STS independent of their individual behaviours. Added to this there should be individual modification of prognostic assessment and therapy depending on the subtype, site and other possible factors needs to be added into individual patient management. This reflects the need for high levels of expertise and a depth of understanding of STS individual subtype biology that would usually only be achieved at a larger tertiary referral centre.

6.2 REFERENCES

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6.3 THE PROBLEMS WITH SUBTYPE APPLICATION TO THE CURRENT AJCC STAGING SYSTEM FOR SOFT TISSUE SARCOMA.

(Formal text of presentation at the presentation at Society Surgical Oncology, Washington 2001; also submitted for publication Annals Surgical Oncology 3/2001)

ABSTRACT

Introduction: Staging systems are successful if widely applicable to the tumours intended provided they are simple, intuitive and reliable. Staging systems enable comparison between centres and give prognostic information for the patient and treating physician. The staging of soft tissue sarcoma (STS) is hampered by the heterogenicity of the tumour subtypes and widespread primary sites. The current AJCC Staging System is derived from prospective data on extremity STS but prescribed for application to most subtypes and most sites of STS.

Methods: Three relatively large case series of synovial sarcoma (SS, n = 150), myxoid liposarcoma (ML, n = 50) and epithelioid sarcoma (ES, n = 37) were examined for the applicability of the current AJCC Staging System to each individually and in combination. The data was compared to the Royal Marsden Hospital Staging System for each subtype.

Results: SS is principally a high grade, deep STS. A staging system based on grade, depth and only one size differential gives limited prognostic information with the majority of patients effectively having either a 82 %

or 52 % 5 year survival. The RMH Staging System is weighted towards size more evenly and has 4 groups with a more even decline in prognosis. ML is generally indolent with even the high-grade tumours having an unusually good prognosis. If metastatic disease does occur (26 %), there is a 41 months median survival, and the majority of metastases go to soft tissues and not lung parenchyma. The staging systems assessed provide poor prognostic information in ML with no significant difference in 5-year survival between stage groups. ES is an extremely rare, high grade STS and is < 5cm at presentation in 61 % of cases. Current staging systems provide limited prognostic information and the rarity of the disease makes it impossible to have significant separation between stages. Combination data for the 3 subtypes gives a bias towards the SS results. Conclusion: The current AJCC Staging System is not useful in providing prognostic information in 2 of the 3 subtypes examined and provides limited information for SS. Combination data eliminates individual subtype behaviour by the more common subtypes dominating the results. The problem with subtype and most probably site validation needs to be addressed. There should be further subtype restriction for the AJCC Staging System for STS.

INTRODUCTION

Staging systems for tumours are developed to give prognostic information about the disease for the benefit of the patient and the physicians involved. The more common tumours, such as breast and colorectal cancer, have dominant subtypes that are reasonably homogenous in their behaviour. Both these examples are obviously site specific, which generally limits the ability of local factors to impact on survival. In contrast, soft tissue sarcoma (STS) have a low incidence, occur in widespread locations, there are site specific factors that impact on successful treatment and prognosis (e.g. retroperitoneal sarcoma), and they are heterogeneous with many subtypes that often have particular biological characteristics and behaviour. There is also disagreement existing regarding the histogenesis and grading of many subtypes of STS as well as a lack of consensus regarding the value of various prognostic factors.[1]

THE CURRENT AJCC STAGING SYSTEM SPECIFICATIONS

The American Joint Committee for Cancer (AJCC) Staging System (5^{th} Edition) for STS was changed in 1997 [2] having been last modified in 1992.[3] The 5^{th} Edition AJCC Staging System [2] for STS has been challenged for their deficiencies in offering adequate prognostic differentiation for individual patients.[1,4-6] Recently a staging system from the Royal Marsden NHS Trust (RMH) was published which gave

equivalent weighting towards size and grade for determining prognosis of STS.[1] Table 6.31 compares the AJCC to the RMH Staging System. Both staging systems are discussed throughout this paper. Table 6.32 describes the specifications for the AJCC Staging System including subtypes allowed to be included / excluded and sites allowable for inclusion / exclusion.

Table 6.31 Comparison of Staging Systems discussed.

STAGE	RMH STAGING SYSTEM [1]	% 5 YEAR SURVIVAL	AJCC (5th EDN) STAGING SYSTEM [2]	% 5 YEAR SURVIVAL
1A	G1 T1	100	G1-2 T1a / b	
1B	G1 T2 G2 T1	83	G1-2 T2a	98.8
2A	G1 T3 G2T2 G3 T1	74	G1-2 T2b	
2B	G1 T4 G2 T3 G3T2	61	G3-4 T1a-b	81.8
2C	n/a		G3-4 T2a	
3A	G2 T4 G3T3	39	G3-4 T2b	51.6
3B	G3, T4	18		
4A	G 1-3, T 1-4, N1	6	G1-4 T1-2 N0-1 M1	
4B	G 1-3;T 1-4, N0-1, M1			

[Reproduced with permission - Eur J Surg Oncol 1999;25;6:559-561.]
n/a = not applicable

Table 6.32 AJCC 5th Edition Version Summary of Specifications

T1 ≤ 5 cm, T2 > 5 cm
a = superficial*, b = deep
G = grade
N0 = no nodal metastases,N1 = nodal metastases, M0 = no distant metastases, M1 = distant metastases

* Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumours.

The following histological types of malignant tumour are included:
Alveolar soft part sarcoma
Epithelioid sarcoma
Extraskeletal chondrosarcoma
Extraskeletal osteosarcoma
Fibrosarcoma
Leiomyosarcoma
Liposarcoma
Malignant fibrous histiocytoma
Malignant hemangiopericytoma
Malignant mesenchymoma
Malignant schwannoma
Rhabdomyosarcoma
Synovial sarcoma
Sarcoma NOS (not otherwise specified)

The following histological types of tumour are not included in the staging system assessment: Kaposi sarcoma
dermatofibrosarcoma (protuberans)
fibrosarcoma grade I (desmoid tumour)
sarcoma arising from the dura mater, brain, parenchymatous organs, or hollow viscera.

The T N M categories can be clinical / radiological or pathological.

THE PROBLEM WITH SUBTYPE APPLICATION

There are a wide variety of subtypes of STS. Each subtype makes up a different proportion of cases with the 5 most common subtypes covering 80 % of extremity cases.(Table 6.33) The reported frequency distribution of subtypes varies quite widely between institutions, even those that see large numbers of cases.(Table 6.33) The frequency distribution of subtypes also varies with different locations, a good example of this is extremity versus retroperitioneal .(Table 6.33.) As stated above the current staging systems of STS are derived principally from first presentation extremity STS cases. Therefore these data from which the staging systems discussed were developed have a different case mix of subtypes to STS from other series including truncal and retroperitoneal sites.

Table 6.33 The Distribution of the Subtypes of Soft Tissue Sarcoma. Demonstrating the differences between institutions and sites.

PATHOLOGY OF SOFT TISSUE SARCOMA	EXTREMITY % (RMH#)	EXTREMITY % MSKCC*	RETRO-PERITONEAL SARCOMA % MSKCC $
Malignant Fibrous Histiocytoma	21	25	7
Leiomyosarcoma	19	8	23
Liposarcoma	17	29	42
Synovial Sarcoma	12	12	
Not otherwise specified	11		
Malignant Peripheral Nerve Sheath Tumour	6	5	3
Dermatofibrosarcoma	3		
Rhabdomyosarcoma	2		
Soft Tissue Chondrosarcoma	2		
Clear Cell Sarcoma	1		
Alveolar Soft Part Sarcoma	1		
Haemangiosarcoma or Lymphangiosarcoma	2		
Soft Tissue Ewing's Sarcoma	1		
Primitive Neuroectodermal Tumour	1		
Haemangiopericytoma	1		
Embryonal Rhabdomyosarcoma	1		
Fibrosarcoma	0	10	8
Epithelioid Sarcoma	0		

RMH = Royal Marsden NHS Trust, * reference no. 7
MSKCC = Memorial Sloan-Kettering Cancer Center,
# reference no. 8. $ reference no. 9.

For the purposes of this review three previously published case series of different subtypes of STS (synovial sarcoma, myxoid liposarcoma and epithelioid sarcoma) [10-12] were assessed. Each subtype is specified as being appropriate for assessment in the AJCC manual and all cases were at sites allowed by the AJCC Staging System.[2] The individual subtype biological behaviour was related to the problems and reliability of the AJCC and RMH Staging Systems for each individually and then with all subtype data combined.

Synovial Sarcoma

Synovial sarcoma is an almost exclusively high grade, deep STS that favours extremity sites in at least 75 % of cases. By applying a cohort of cases to the current AJCC Staging System there are really only 2 assessable groups Stage 2B and 3 (high grade tumours smaller or equal to 5 cm and high grade tumours larger than 5 cm). However a staging system based more evenly on size and grade such as the proposed RMH System gives a more discriminating prognostic indication.[6,10] (Figure 6.31 & 6.32)

Fig. 6.31: Synovial Sarcoma: The overall survival plot by AJCC Stages. Short vertical bars indicate censored follow up events. The 5-year confidence limits are also included.[10]

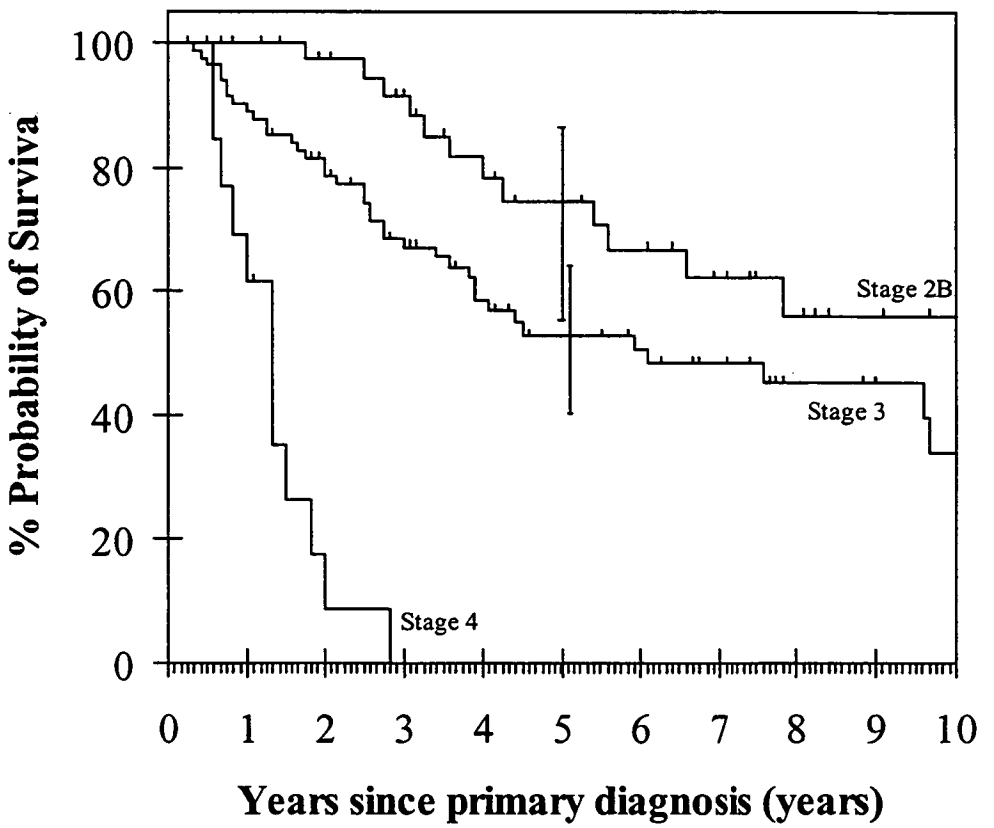
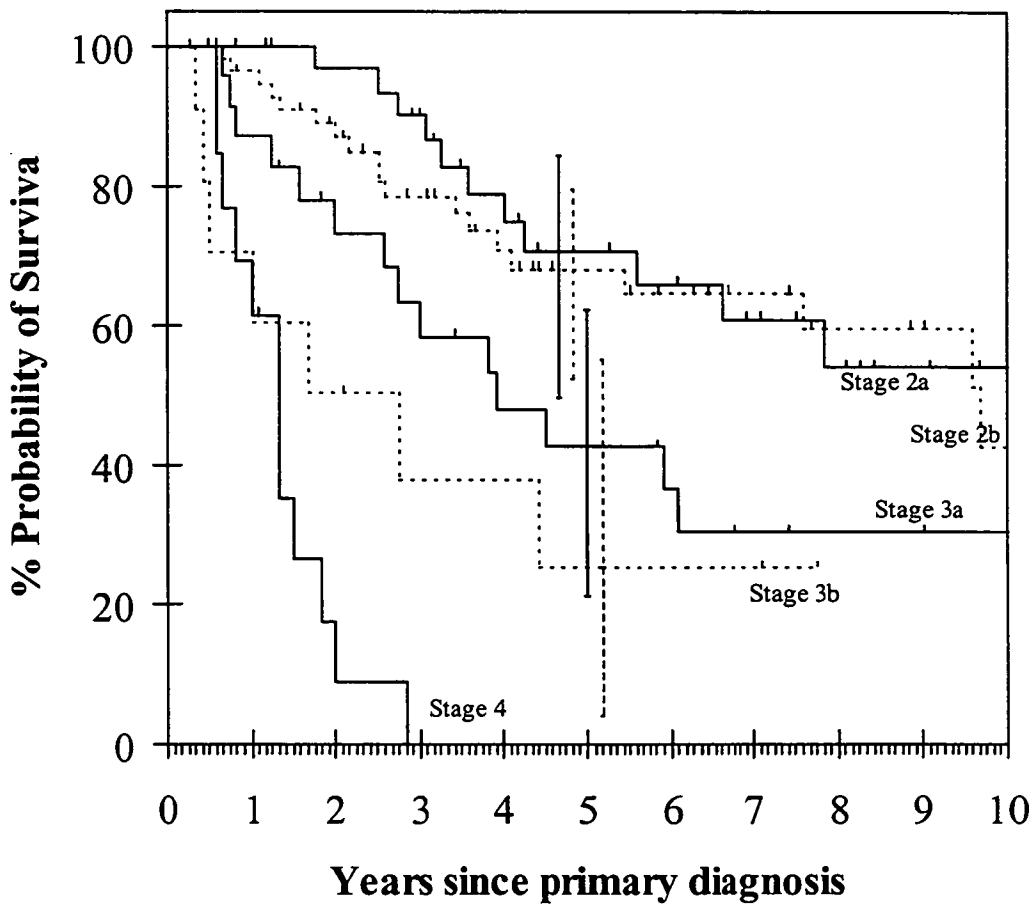


Fig. 6.32: Synovial Sarcoma: The overall survival plot by proposed RMH Stages. Short vertical bars indicate censored follow up events. The 5-year confidence limits are also included.[10]



Myxoid Liposarcoma

Myxoid liposarcoma (ML) represents half of the cases of liposarcoma, which is the second most common STS in most series.[13] ML generally behaves in an indolent manner but, as occurs in approximately 26 % of cases, when metastasis occurs they are unusually frequently soft tissue metastases (STM) compared to the typical pattern of metastatic STS where approximately 70 % of metastatic events occur in the pulmonary parenchyma. [11,14] When STM occur in ML there is an unexpectedly long median post-metastasis survival (41 months) compared to the median survival of a pooled group of metastatic STS which is of the under 12 months.(Figure 6.33)[11,15] Because of its particular biological behaviour ML represents another subtype of STS that has a prognosis not well described by the current staging systems.(see Table 6.34) The reason for this is that not only does the STS staging system have to be predictive of distant disease recurrence events, but also it has to be predictive of subsequent death in the majority of cases who recur in each stage group, and this should occur within 5 years from diagnosis. (The AJCC and RMH Staging systems have 5 year overall survival as their endpoint.)

Fig. 6.33: Survival following Myxoid Liposarcoma First Distant Metastasis

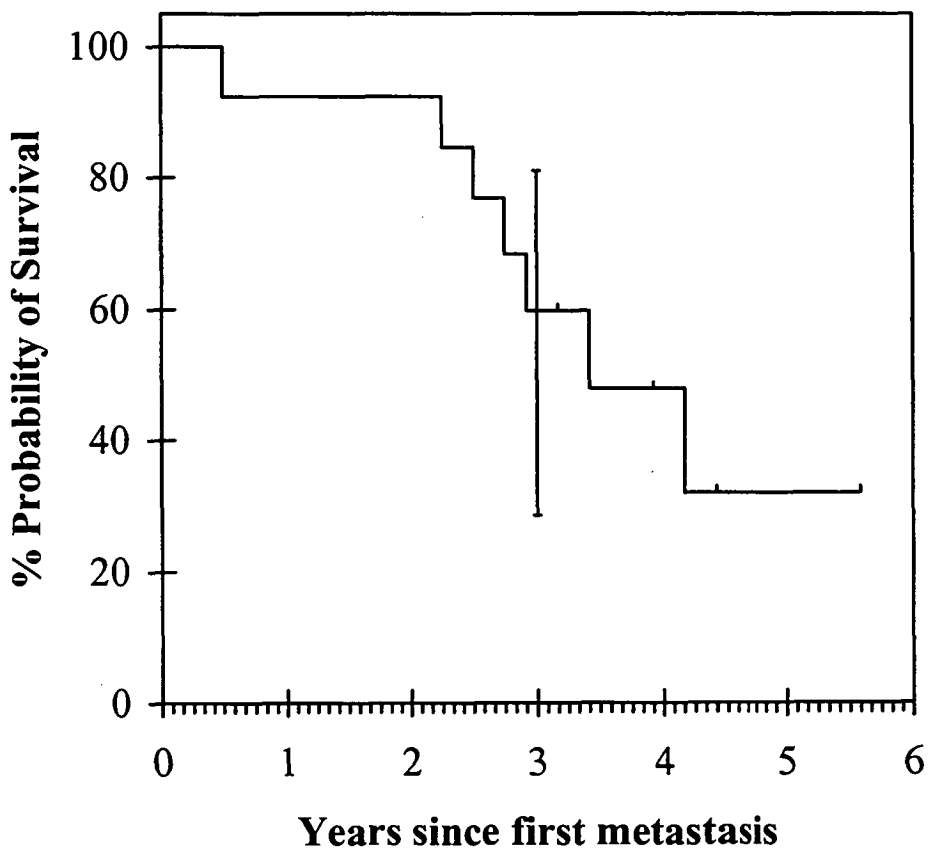


Table 6.34 Univariate Analysis of Prognostic Factors for Myxoid Liposarcoma.

	Number of Cases	**Overall Survival % [Predicted Survival]**
AJCC / UICC STAGE:		
2A	25	81 (56-92) NS
3	16	78 (36-94)
RMH STAGE:		
1	10	100
2A	11	74 (29-93) NS
2B	18	54 (20-80)
3	7	75 (13-96)
LOCAL RECURRENCE:		HAZARDS RATIO:
YES	7	2.37 (0.47-12) NS
NO	41	1.00
persistent local disease	2	
SOFT TISSUE METASTASIS:		HAZARDS RATIO
YES	12	4.54 (1.1-19) p =.02
NO	38	1.00

( ) 95 % Confidence Interval

Epithelioid Sarcoma

Other problems with the wider application of a staging system to all STS include the rarity of certain subtypes of STS with specific biological behaviour. For instance, epithelioid sarcoma typically involves the extremity of young adults and metastases to lymph nodes frequently.[12,16] It is often both less than 5 cm maximum size dimension and multifocal at presentation.[12] However at this size the tumour metastases unusually frequently with subsequent poor outcome.[12] This specific biological behaviour is hidden within the large numbers of more common STS that make up the cohorts from which staging systems for STS are developed. For example in 1997 MSKCC published their experience with 16 cases of ES from their current database of 2678 patients at that time.[17] Despite this ES is listed as one of the subtypes of STS where the AJCC Staging System is applicable. Table 6.35 is used to demonstrate the lack of discrimination between stage groups for ES for both the staging systems assessed. The wide confidence intervals are indicative of the small number of cases. In effect no prognostic information can be derived from the staging systems for patients with this subtype of STS.

Table 6.35: Univariate Analysis of Prognostic Factors in Epithelioid Sarcoma.

	Number of Cases	**Overall Survival % (CI)**	
AJCC / UICC STAGE:			
2B	23	80 (56 - 92)	NS
2C / 3	9	73 (28 - 92)	
RMH STAGE:			
2A	21	84 (58 - 95)	NS
2B	9	71 (26 - 92)	
LOCAL RECURRENCE		(HAZARD RATIO)	
YES	12*	2.6 (0.91 - 7.9)	NS
NO	22	1.0	p = 0.06
REGIONAL NODE METASTASIS:		(HAZARD RATIO)	
YES	8#	6.6 (2.4 - 18)	p = < 0.001
NO	27	1.0	
SIZE:			
< 5CM	22	81 (57 - 92)	NS
≥ 5CM	14$	49 (19 - 74)	p = 0.17
DEPTH:			
SUPERFICIAL	8	100	p = 0.013
DEEP	29	61 (39 - 77)	

* 3 other cases had persistent local disease that was never cleared
# 2 other cases had regional nodal disease that was never cleared
$ 1 unknown size
CI = 95 % confidence interval
NS = not significant

Combined Data

A simple confirmation of the way the current staging systems are developed and how the more common STS bias the staging systems towards an average of their own biological behaviours is demonstrated by combining the data for the 3 subtypes assessed.(Figure 6.34 & 6.35) Clearly the survival plot is quite similar to that of SS and the specific characteristics elicited for ML and ES are all but lost in this exercise. These data are reinforced more succinctly in Table 6.36.

Figure 6.34 AJCC Staging System - Combined Data

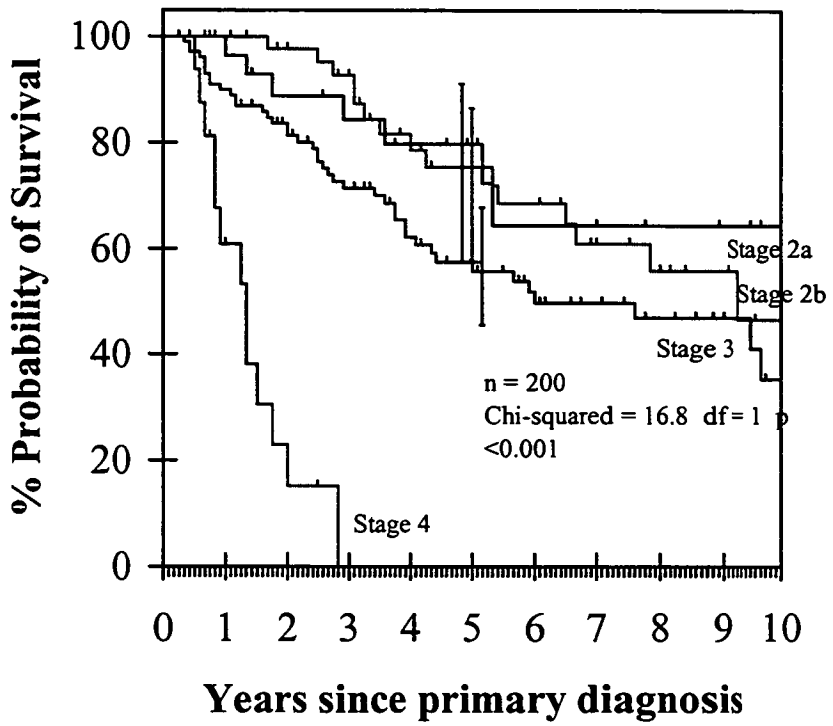


Fig. 6.35: RMH Staging System - Combined Data

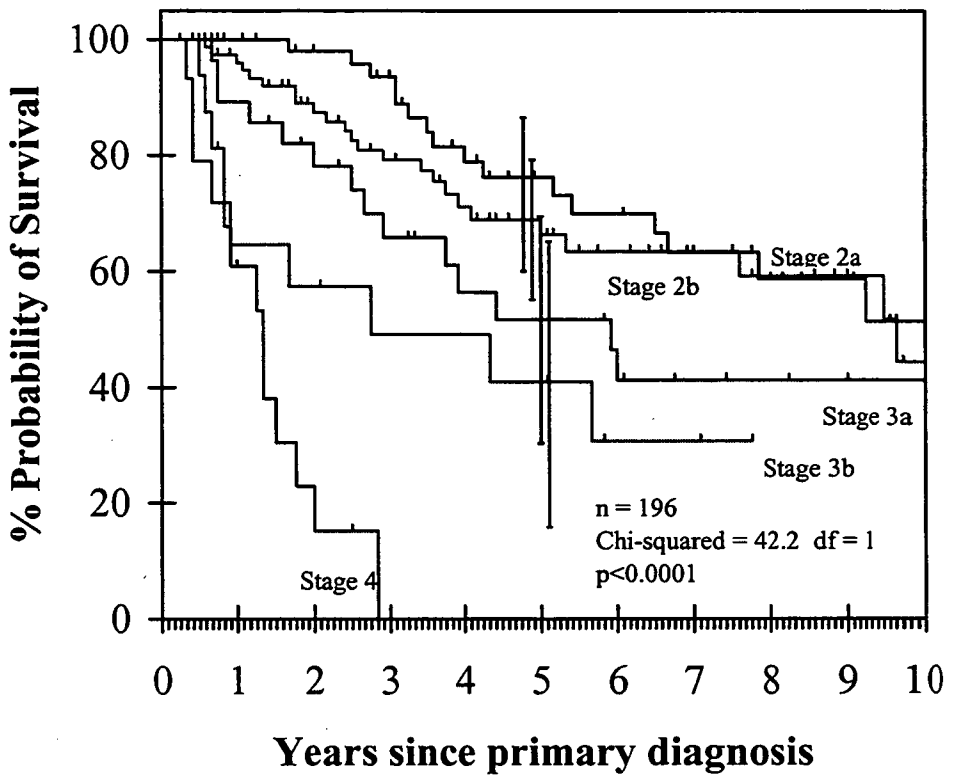


Table 6.36 Comparison between the predicted 5 year survival with the observed for each subtype and overall.

	Predicted		Synovial		Myxoid		Epithelioid		Overall Observed	
STAGE	AJCC	RMH	AJCC	RMH	AJCC	RMH	AJCC	RMH	AJCC	RMH
1	98.8	100A 83B				100				
2A	81.8	74	75 A/B/C	71	81A/B	74	84		80	78
2B		61		68		54	71	80 2B	76	70
3A	51.6	39	53	43	78	75 A/B		73 (2C/3A)	55	55
3B		18		25						40
4		6		0					0	0

SITE SPECIFIC BEHAVIOUR

The most recent version of the AJCC Staging Systems and the RMH Staging System are based primarily on prospectively collected databases of extremity STS.[1,2] Despite this, these staging systems have been prescribed for wider site application with various qualifications such as defining retroperitoneal and visceral lesions as deep and excluding application to brain, parenchymatous organs and hollow viscera.(see Table 6.32)[2,3] This wider application is largely untested and the associated problems are exemplified when the staging systems are applied to the special sites such as the retroperitoneum and head and neck. Both of these sites have particular biological influences with patients dying of transperitoneal spread / local recurrence and local recurrence respectively, which is otherwise unusual for STS.[18,19]

Prognostic assessments of large numbers of cases of retroperitoneal sarcoma indicate that resectability is the most important prognostic factor. Secondly, grade is of importance but size is not.[9,20,21] By definition all retroperitoneal sarcomas are deep.[2] Therefore as far as the current staging systems are concerned the most important prognostic factor is not assessed for tumours at this site and grade is the only relevant discriminator.

SUMMARY

In conclusion, the staging of STS is still evolving. This is necessary because of the above problems and the ongoing development of the understanding of the complexities of STS biology. The assessments presented provide significant evidence that the validity of the current staging systems for STS is undermined by too broad an application to subtypes and sites without adequate validation. If a truly effective staging system is to be developed for all STS, it has to be developed from prospectively collected databases, compared to equal quality data from other sources, and assessed for specific sites and subtypes of STS before being widely introduced. In the meantime the AJCC Staging System needs to have further subtype and probably further site restrictions introduced. There is no point in having a staging system inclusive of such a heterogeneous group of tumours unless it is adequately validated.

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CHAPTER 7.
RETROPERITONEAL SARCOMA – TIME FOR A CHANGE IN ATTITUDE ?

(Spillane AJ. Retroperitoneal Sarcoma – Time for a change in attitude? Aust NZ J Surg.2001;71;5:303-308.)

7.1 ABSTRACT

BACKGROUND: Retroperitoneal sarcoma (RPS) is considered a disease with poor prognosis partly because of the difficulty with diagnosis at an early stage. This review assesses the current best practice principles for RPS and finds evidence suggesting a better outlook for appropriately managed cases. Recommendations are made for improving diagnostic certainty before laparotomy and inappropriate transperitoneal biopsy occurs.

METHODS: A critical review of the English language literature using Medline software and searching the terms - retroperitoneal sarcoma alone or in combination with prognosis, surgery and adjuvant therapy.

CONCLUSIONS: RPS is a rare disease but when appropriately managed the disease free survival can be improved and may even approach that of extremity soft tissue sarcoma. One of the greatest barriers to improving outcome is the misinterpretation of clinical signs and an over-reliance on ultrasound diagnosis in pelvic presentations, or misinterpretation of clinical signs and / or CT Scans in abdominal masses. Physicians referred patients with a retroperitoneal mass should more frequently consider the less common differential diagnoses of an abdominopelvic mass including

retroperitoneal sarcoma. This is especially so in circumstances where there is a circumscribed, predominantly solid tumour, with clinical or radiological signs of vascular or rectal displacement, ureteric obstruction, and / or classic renal rotational displacement. The more frequent utilisation of CT Scan with intravenous and oral contrast with referral prior to inappropriate transperitoneal biopsy is recommended. In atypical cases where preoperative biopsy is necessary extra peritoneal routes are preferable. Complete en bloc surgical excision at the first laparotomy is the treatment of choice in RPS. Macroscopic clearance may necessitate resection of adjacent viscera, neurovascular structures or abdominopelvic walls but if achieved may lead to long-term survival depending on individual tumour biology.

Key Words:
retroperitoneal, soft tissue sarcoma, survival, transperitoneal spread

7.2 BACKGROUND

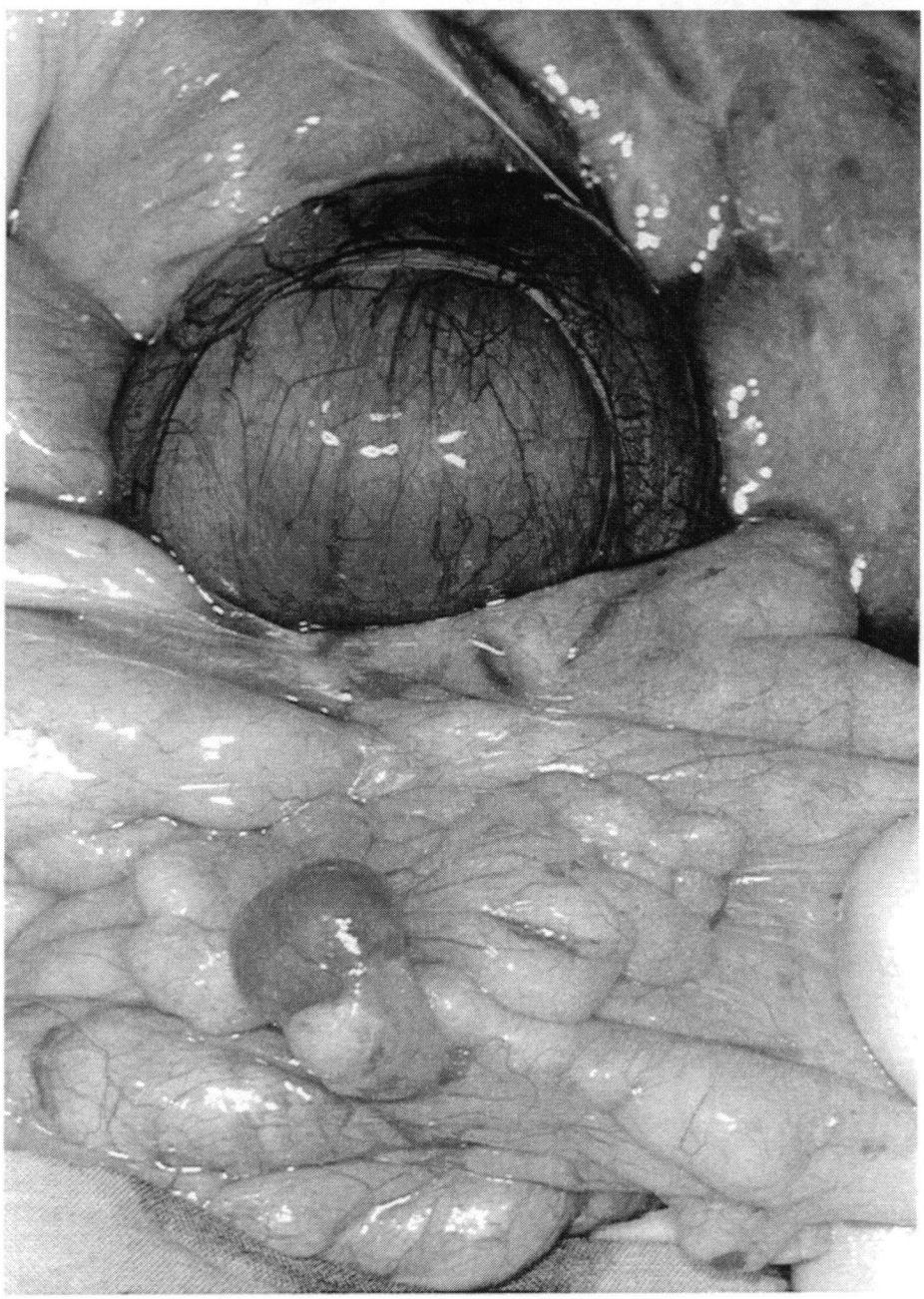
Retroperitoneal sarcoma (RPS) is rare and often presents insidiously. They often do not come to clinical attention until having reached considerable size. Diagnosis is ideally by CT Scan with intravascular and oral contrast and when taken with clinical information a confident diagnosis can be made in most cases. When assessing a RPS, if definitive resection is thought to be possible and there is no metastatic disease, pre-operative transperitoneal biopsy is contraindicated because of the risk of transperitoneal spread.[1,2] The problem with obtaining an adequate surgical resection of many RPS is the insidious presentation, which often results in apparent tumour involvement of adjacent visceral and neurovascular structures by the time of presentation. This direct extension results in a high percentage of surgical resections with margins that would not be accepted as adequate in extremity STS. Even if macroscopic clearance is achieved, as it is in the majority of cases, the microscopic margins are often positive.

The literature reports a poor overall prognosis for RPS with 5 year survival rates between 12-54 % [1,3-11] with rare exception.[12] Patients with RPS die from local recurrence alone or more often in association with bulky transperitoneal disease. Only occasionally are there liver and / or distant metastases. The best prognosis group is the low grade tumours where macroscopic clearance of the tumours is obtained at the first

laparotomy.[1,3,11,13-15] However, even in favourable circumstances there is a 41 - 85 % chance of local recurrence at 5 years.[1,11]

The rarity of RPS and their location makes it common for these tumours to be mis-diagnosed pre-operatively. Most often, in the author's experience, RPS are mis-diagnosed as ovarian malignancy but other diagnoses are possible including genitourinary and gastrointestinal tumours; adrenal tumours; metastatic tumours and lymphoma.[16] Mis-diagnoses occurs too frequently and in many instances results in unnecessary laparotomy by surgeons inexperienced in dealing with retroperitoneal tumours. The result is inappropriate transperitoneal biopsy and potential seeding of the sarcoma.(Figure 7.1) This sequence of events may prejudice the patient's chances of a long disease free interval if not adversely affecting the chances of cure.[16]

Figure 7.1 Several sites of seeding following previous open biopsy for a retroperitoneal sarcoma.



By understanding the radiological features of RPS and by appropriate investigation of atypical presentations of pelvic and abdominal masses inappropriate laparotomy should be avoided. Patients should be managed by a surgeon involved in a multidisciplinary team that is experienced in the management of malignancy at this site

7.3 METHODS

A critical review of the English language literature using Medline software and searching the terms - retroperitoneal sarcoma alone or in combination with prognosis, surgery and adjuvant therapy. Significant contributions were assessed and used to give an overview of RPS as well as develop concepts based on a personal perspective of the disease process.

7.4 DEMOGRAPHICS

Soft tissue sarcomas (STS) comprise approximately 1 % of solid tumours, with an incidence of approximately 2/100 000. Approximately 15 % of all STS will be retroperitoneal in location. The peak incidence is in the 5th decade of life but there is a wide age range.[1,11,15] There is a male predominance with a ratio of approximately 3:2.[3,11]

7.5 PRESENTATION

The most frequent presentation for RPS is a new abdominal mass. This occurs in 80 – 90 % of cases. The mass may be painful or uncomfortable. In low-grade tumours the mass effect may be misinterpreted as mid-life abdominal girth expansion due to obesity. However the distribution is abdominal and may occur in the face of nutritional depletion in other areas of the body.

Other presentations include neurological sequelae either from traction on the lumbosacral plexus, femoral nerve or obturator nerve. A patient with neurofibromatosis who develops rapidly progressive symptoms related to the retroperitoneum should be considered to have a malignant peripheral nerve sheath tumour until proven otherwise. Less frequently obstruction of an abdominal viscus or renal failure from bilateral ureteric obstruction (usually from pelvic disease) may occur. Direct invasion of a viscus is found in 10 – 15 % of cases. This may lead to presentation with gastrointestinal bleeding. Less commonly tumour necrosis may lead to fever and unexplained leucocytosis.[17] Infected necrosis in retroperitoneal sarcoma has been reported and is most probably due to direct communication of the bowel with the tumour but possibly from haematogenous seeding. Infected necrosis in a RPS seems to be associated with a particularly poor prognosis.[18] The finding of a retroperitoneal tumour as an incidental finding on imaging for other

reasons is increasingly common and would most often be a low grade, slowly growing RPS or benign retroperitoneal tumours such as a schwannoma.

One frequent method of diagnosis of a RPS is the incorrect preoperative assessment of ovarian or other pathology with resultant inappropriate laparotomy.[16] A relatively unrecognised phenomenon is the unusually high frequency of soft tissue metastases (STM) from myxoid liposarcoma. These STM most often involve the retroperitoneum as well as other intra abdominal and abdominal wall sites.[19] Despite the metastatic nature of this disease these cases can have excellent medium to long term survival if appropriately managed.[19]

RPS should be differentiated from Gastrointestinal Stromal Tumours (GIST) as these tumours have a different spectrum of clinical and metastatic behaviour. Two good reviews of these tumours has recently been published.[20,21]

7.6 PATHOLOGY

Lewis et al. reports the size distribution at initial presentation is 71 % > 10 cm, 23 % between 5 and 10 cm and only 6 % are < 5 cm. They found 60 % of their cases were high grade and 40 % were low grade.[11] There is a wide range of subtypes of STS reported to occur in the

retroperitoneum but compared to extremity locations liposarcoma and leiomyosarcoma are relatively more frequent.(Table 7.1)

Table 7.1 Distributions of Subtypes of STS by Site.

SUBTYPE OF STS	RETROPERITONEAL SARCOMA - % OF CASES BY SUBTYPE[11]	EXTREMITY LOCATIONS - % OF CASES BY SUBTYPE[29]
LIPOSARCOMA	42	29
LEIOMYOSARCOMA	23	8
OTHERS	17	24
FIBROSARCOMA	8	10
MFH	7	25
MPNST	3	5

MFH - malignant fibrous histiocytoma, MPNST – malignant peripheral nerve sheath tumour

7.7 RADIOLOGY

High quality abdominal CT Scan with oral and intravascular contrast is the key to accurate diagnosis of RPS. As in other sites for STS there is no convincing evidence that MRI is superior for defining any diagnostically / therapeutically helpful criteria that a good quality contrast CT Scan can not identify.[22] There are typical features of RPS which make an almost certain radiological diagnosis. A heterogenous mass that is predominantly solid with areas of liquefaction is characteristic. The mass often arises adjacent to abdominal structures and displaces them. This is characterised by the pathognomic anterior rotational displacement which frequently occurs with the kidney.(Figure 7.2) Sarcoma tends to push the adjacent solid viscera however bowel can become intricately enmeshed in the tumour mass particularly when it pushes forwards within the mesenteric folds. Vascular displacement is also the norm, however, encasement occasionally occurs. A good example is with tumours arising from the pelvis where the iliac vessels are characteristically displaced and tent over the anterior margin of the RPS.(Figure 7.3) The so called "floating aorta", where the aorta is immersed in tumour, is almost certainly lymphoma and not a RPS for the same reasoning.(Figure 7.4)

Figure 7.2 The classical rotational displacement seen in retroperitoneal sarcomas arising form the perinephric fat.

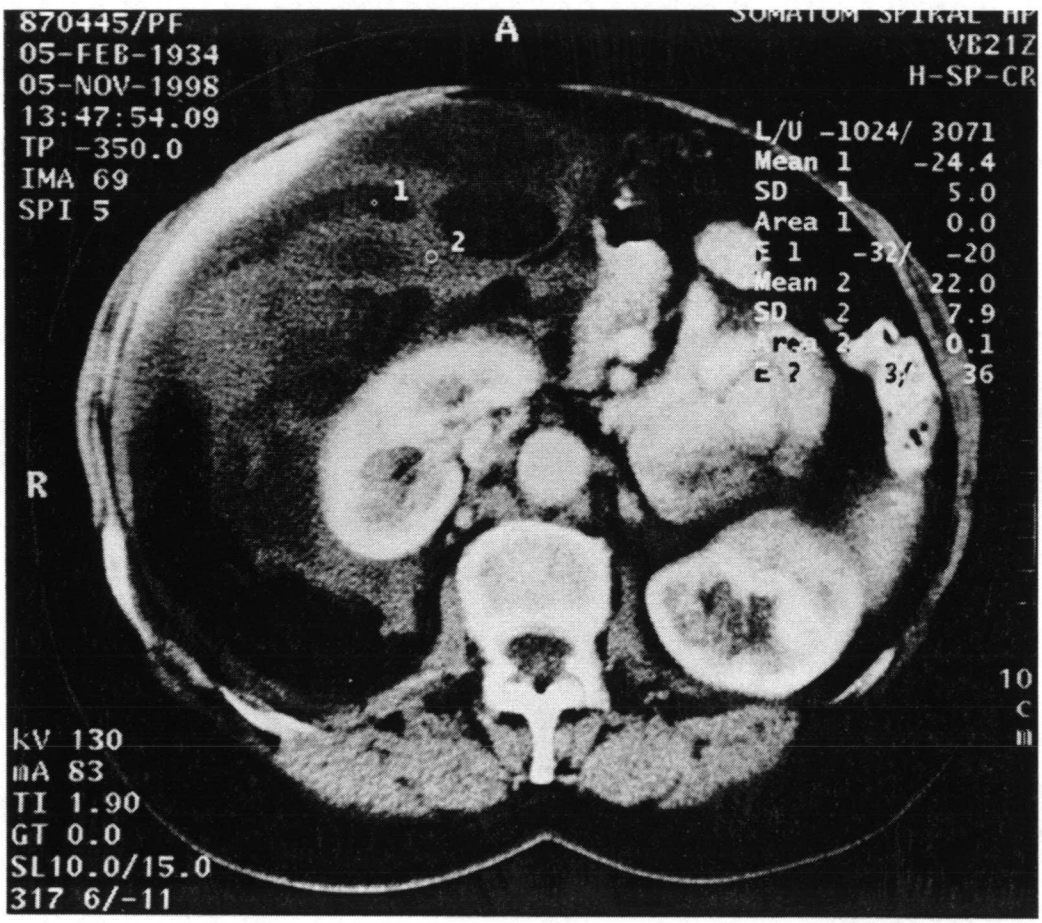


Figure 7.3 Left pelvic side wall metastatic myxoid liposarcoma (before chemotherapy). Iliac vessel anterior displacement without encasement, rectal displacement and effacement of the pelvic side wall is noted.

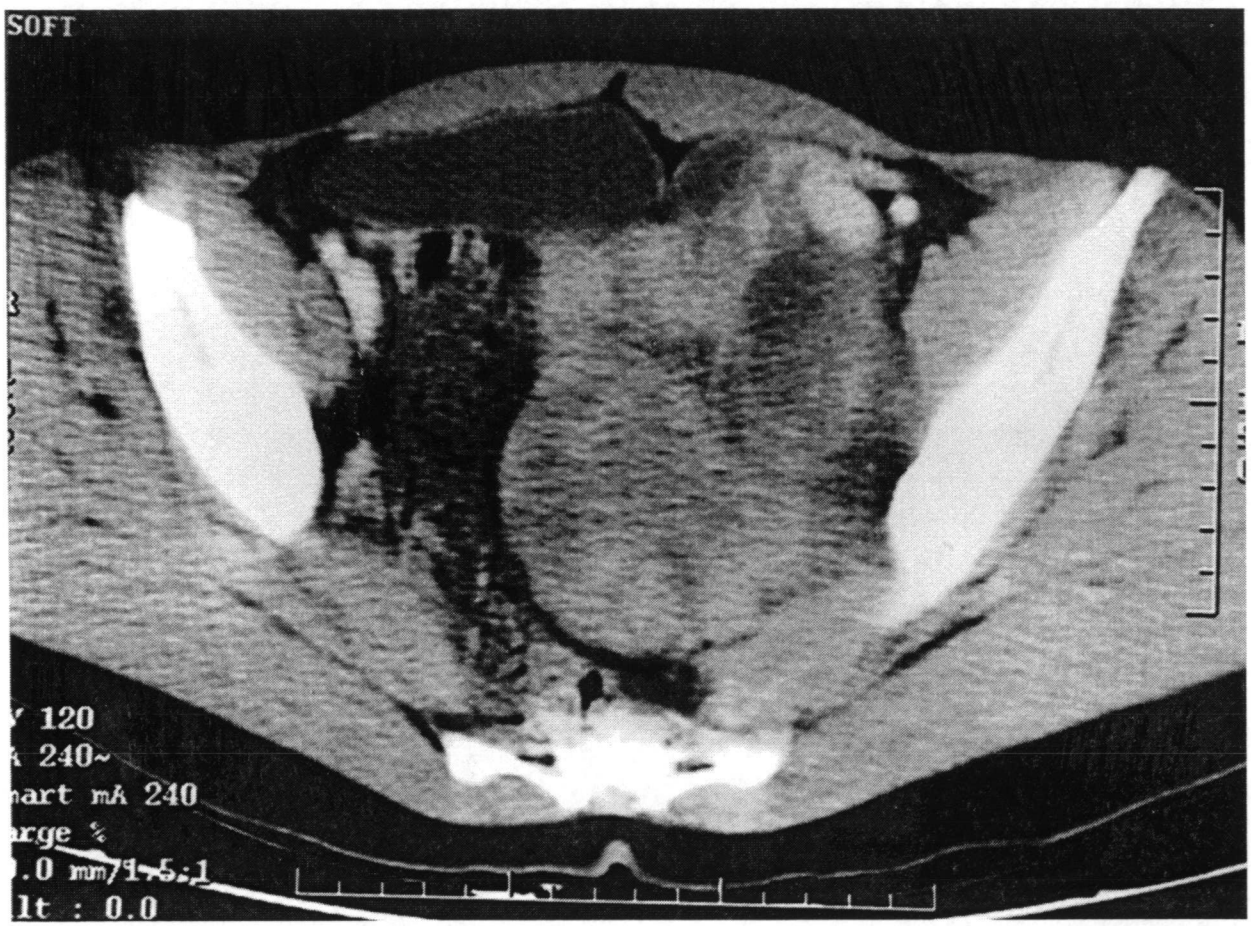
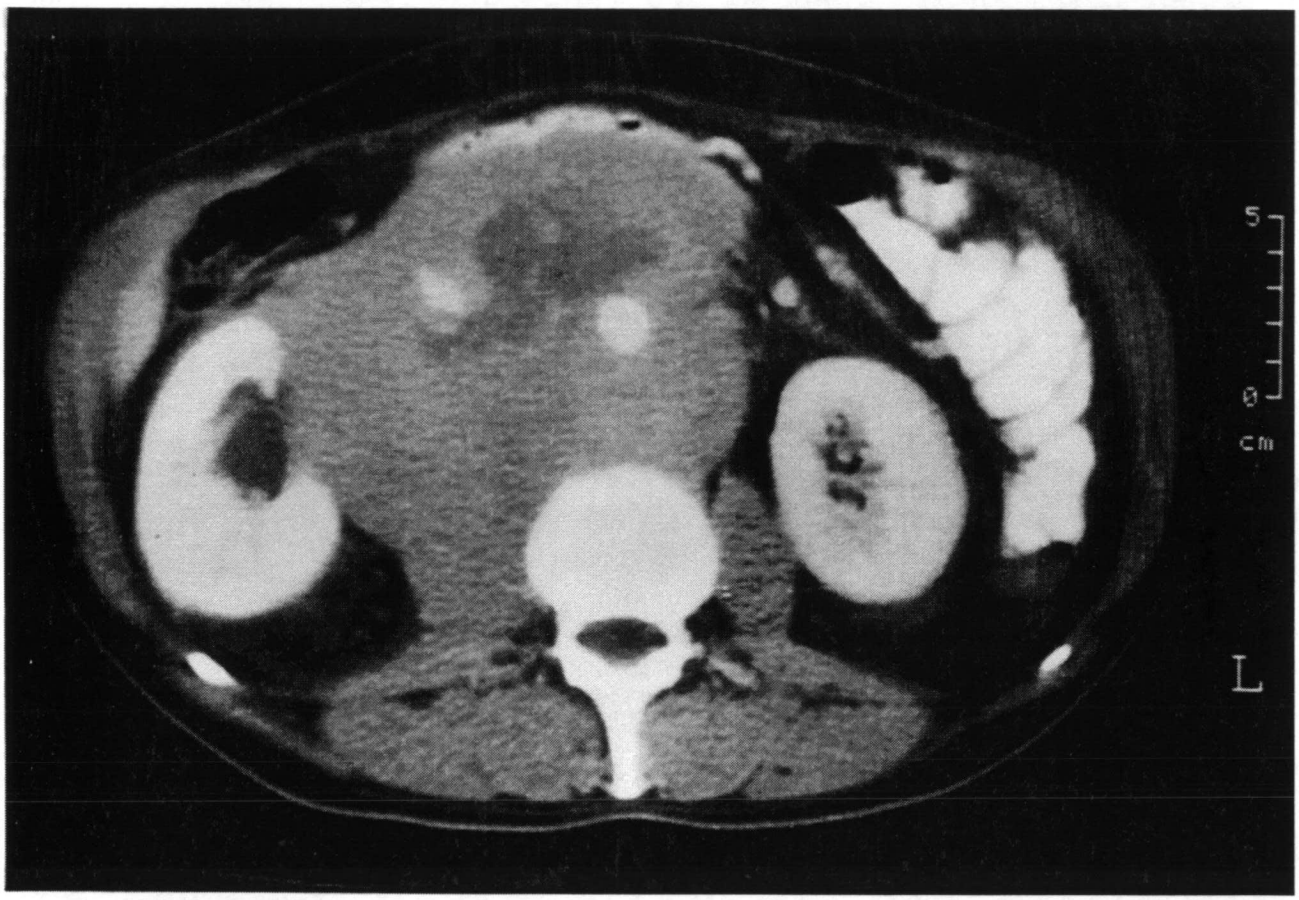


Figure 7.4 Floating aorta (and inferior vena cava) from extensive intra-abdominal lymphoma.



The location of a retroperitoneal sarcoma may suggest alternative diagnoses that need to be excluded. For example, adrenal tumours or pancreatic endocrine tumours. Generally speaking gastrointestinal stromal tumours have a characteristic appearance with relationship to a hollow viscus, most frequently the stomach.

Further imaging with barium contrast studies, MRI or angiography would only be indicated if site-specific questions need to be answered. CT Scan of the chest would exclude the occasional lung parenchymal metastasis. More importantly in upper abdominal RPS the CT Scan may help to delineate any diaphragmatic involvement with possible trans- or retro-diaphragmatic extension.

Foshager et al. recognised that it can be difficult to differentiate masses that can mimic gynaecologic disease on CT scan and MRI. They identified several imaging signs that can help to differentiate intra- from extra-peritoneal masses. These signs include displacement of the pelvic ureter, effacement or encasement of the external iliac vessels, effacement of pelvic side wall musculature and displacement of the rectum.[23] (Figure 7.3)

7.8 DIFFERENTIAL DIAGNOSIS

The differential diagnosis of RPS includes the more frequent processes such as locally advanced gynaecological, genitourinary and gastrointestinal tumours; adrenal tumours; metastatic tumours and lymphoma. Occasionally non-neoplastic processes such as complex appendiceal or diverticular collections can be misdiagnosed instead of a RPS.[23] In a series of 675 patients with a retroperitoneal neoplasm, 82 % were malignant and 18% benign. Assessing the group with malignancy - 40 % were lymphoma or some variety of urogenital cancer and 55 % were RPS.[17,24]

The key point to remember is that if there is diagnostic uncertainty or if the surgeon thinks that pre-operative biopsy has the potential to alter the next appropriate step in management, then percutaneous extra-peritoneal biopsy with core biopsy is acceptable. This is particularly the case where lymphoma is a possibility. Lymphoma can present in odd situations and is an important differential diagnosis. Certainly if the CT Scan is atypical for RPS and there are any Type B symptoms (weight loss, night sweats or fever) then pre-operative biopsy is indicated. Metastatic germ cell tumours can present with a para-aortic mass or a mass below the left renal vein. Therefore examination of the scrotum and serum (AFP and B HCG) markers is wise particularly in a younger man.

Masses in the vicinity of the adrenals glands should be assessed to exclude a primary adrenal tumour. Occasionally perivesicular or other extra-adrenal phaeochromocytomas present with a pelvic mass. An associated history of hypertension warrants serum VMA, HMAA and other metabolites.

A past history of malignancy and a new pelvic mass obviously raises the possibility of metastatic disease. Despite having a recent past history of thigh myxoid liposarcoma the gynaecologist referred the tumour in Figure 7.3 thought the most likely diagnosis to be ovarian cancer![16]

Most other malignant retroperitoneal tumours should be approached with the same surgical principles as a RPS. In the occasional case that CT Scan does not diagnose RPS accurately the patient would still have the same definitive operation without the risks of intraperitoneal seeding.[16]

7.9 SURGICAL TECHNIQUES

If laparoscopy or laparotomy is performed and findings are of a retroperitoneal tumour rather than the expected general surgical or gynaecological disease then CT Scan with intravenous contrast is indicated, not proceeding with an open biopsy. If RPS is suspected at laparotomy, unless the surgeon is experienced enough to be confident that

he / she will be able to remove the tumour en bloc with at least macroscopic clearance, it may be more appropriate to close the abdomen and organise referral to a more experienced centre. Intra-operative open biopsy and frozen section is unlikely to change the management at the time (the tumour will still be resectable or not) and again it exposes the patient to the risk of seeding the tumour.

Karakousis et al. report the highest resectability rate for RPS. They claim aggressive visceral and vascular resections as well as en-bloc resection of adjacent retroperitoneal muscles including in the lesser pelvis enable them to achieve these figures.[12]

The question of adjacent kidney removal in RPS that arise in the perinephric fat has been addressed by Russo et al. from Memorial Sloan-Kettering Cancer Center (MSKCC).[25] They concluded that even though direct invasion of the kidney, capsule or renal vein occurred in only 28 %, gross resectability was markedly improved in the majority of cases. Generally speaking the kidney should be taken if it enables complete resection.[25] Similar concepts should be expected for other adjacent viscera and vascular structures however the rarity of the disease has precluded definitive data to date. In the same context, if there is no way of obtaining a plane of clearance at one point, within the upper psoas muscle

for instance [26], then there is no logical reason to aggressively resect the kidney or inferior vena cava which may have a similar abutting margin.

Various manoeuvres have been described for determination of resectability of RPS.[17] The great variability of subtypes, extent and anatomical origins makes standardisation of the operative procedure inappropriate. Individualisation of the operation based on imaging and operative findings to achieve the best margin with minimal morbidity is more important.

Lewis et al. report 83 % (231/278) of their first presentation of cases with RPS were thought to be resectable. Following surgery 185 (80 %) of these "resectable" RPS were assessed to have had a complete (macroscopic +/- microscopic) clearance.[11] Interestingly 57 % of first time locally recurrent RPS were resectable and 33 % of second time locally recurrent RPS were still able to have a complete macroscopic resection.[11]

As will be discussed below, in most cases, if the tumour is definitely unable to be cleared macroscopically then surgery is not indicated, as there is no survival advantage to debulking. Patients with low-grade liposarcoma provide an exception to this rule. These patients often develop relentless local and transperitoneal recurrence over a period of years. There is no doubt that these people benefit from debulking surgery

for symptom control; even when macroscopic clearance of disease is unlikely. The typical pattern of recurrent disease in these cases is multiple local / transperitoneal recurrences that become symptomatic at a shorter interval each time. Each recurrence also seems to have more foci of disease. This pattern can be interrupted by de-differentiation, which can cause a more rapid acceleration of the disease but up to this time the patient can live for many years with interval debulking of disease.

It should be emphasised that even if a RPS appears on imaging to be of doubtful resectability the findings at laparotomy are often less worrying and macroscopic clearance can be achieved. This is particularly the case at the first presentation. The reason for this is the pushing nature of most RPS.

7.10 STAGING AND PROGNOSTIC FACTORS

The current AJCC / UICC Staging Systems for STS state that they are able to be applied to RPS.[27,28] This application is largely untested as the most recent editions of the staging systems were derived from prospective data assessing extremity STS.[27] It is unlikely that the staging systems' application to RPS is appropriate because of the different biology of RPS as compared to extremity STS. That is, most patients with RPS develop local or transperitoneal recurrence, which is usually responsible for their death. In extremity STS most people that die

do so from distant metastases.[29] There is certainly evidence that the prognostic factors for local recurrence are different to distant disease in patients with extremity STS.[29] Unfortunately Lewis et al. [11] did not apply their large cohort of 500 cases to the AJCC Staging System [27] to test whether it provided relevant prognostic information in STS at this site, however recently Linehan et al. have demonstrated that, with regards to liposarcoma, retroperitoneal / visceral primary sites have a worse prognosis that extremity / truncal sites.[30] Size, depth and grade are the prognosis determining factors of these staging systems. Size is T2 (> 5 cm) in the majority of RPS.[11] Singer et al. have previously demonstrated that size is not a significant prognostic indicator in RPS.[15] By definition all RPS are deep.[27,28] Therefore grade is the only discriminator. In the 5th Edition of the AJCC / UICC Staging System grade is effectively either high or low as grade 1 & 2 and grade 3 & 4 are always grouped together.[27,28] One would therefore assume effectively only 2 stage groups in RPS. The author has previously argued [31] that the current AJCC / UICC Staging Systems [27,28] are inadequate in a number of areas. These inadequacies include the application to certain subtypes of STS with distinctive biological behaviour when these subtypes have not been specifically assessed in relationship to the staging systems. As discussed in relation to RPS, most likely the 5th Edition AJCC / UICC Staging Systems also have too broad a site application.[30] These problems seriously undermine their validity.[31-34]

From the very large review of the MSKCC experience with RPS two key prognostic factors were identified.[11,14] Firstly resectability – if the tumour was not macroscopically resectable the prognosis was the same as undertaking no operation. Secondly, if the tumour was resectable grade was the most important prognostic factor. If the RPS was locally recurrent the same prognostic factors applied.[11] Singer et al. also identified (low versus intermediate or high) grade, as well as resection margin (clear versus microscopic or macroscopic) as significant predictors of overall survival. Size in the ranges < 5 cm, 5 to 10 cm, > 10 cm did not predict overall survival.[15]

7.11 ADJUVANT THERAPY

To date, there has been little success with either adjuvant chemotherapy or radiotherapy in the local control of disease or the improvement of overall survival in RPS. Randomised trials of radiotherapy and chemotherapy have not shown a survival benefit.[35,36]

Chemotherapy in STS has only a 25 % response rate even with the best known single agent or multi-agent regimen.[37] In RPS where gastrointestinal symptoms may already occur due to the mechanical pressures, tolerating the addition of chemotherapy can be difficult.

The greatest limitation to radiotherapy has been collateral visceral toxicity. Attempts to lessen radiation toxicity to adjacent viscera by placing intraabdominal spacers has been reported but to date no definite improvements in outcome measures reported.[38] The experience at MSKCC has suggested limited benefit to intraabdominal spacers but with some "spectacular complications".(D. Coit personal communication) Several centres have advocated intraoperative brachytherapy to the tumour bed.[30,36] There is no long term data but indications are not suggestive of a future significant impact on disease management. In isolated cases with a particularly favourable location theoretical benefit could be derived, providing collateral toxicity can be avoided.

7.12 OVERALL AND RECURRENCE FREE SURVIVAL

RPS are a difficult group of tumours to manage. In a collective review, the complete resectability rate was 53 %, the overall 5 year survival rate was 34 %, while the local recurrence rate was 72 % at 5 years and 91 % at 10 years.[17] The MSKCC series of 500 cases confirmed that the best prognosis is seen in low grade tumours with macroscopically clear margins (74 % of those macroscopically cleared were microscopically clear as well). Overall in that series there was a median survival of 103 months for patients with resectable tumour. Conversely, the median survival of patients undergoing incomplete resection was 18 months, which was no different from no attempt at resection.[11] Karakousis et al.

claim a 95 % resection rate for primary RPS, 39 % local recurrence at 5 years and a 66 % 5 year survival - which is similar to extremity STS.[12] It must be stated that these figures stand apart from other soft tissue centres and may be a reflection of being based on referrals for surgery rather than all referrals to the institution.[11]

Heslin et al. demonstrated that even in those cases that are disease free at 5 years, approximately 40 % would recur in the next 5 years. Gross complete resection was the only factor identified to be associated with continued long-term freedom from tumour related mortality.[14] The 5 year survival rate for those with complete resection of RPS is 54 % in one review.[17] However in subgroup analysis for grade - grade 1 tumours had a 5 year survival of 74 % and for grade 2 and 3 tumours it was only 24 %.

7.13 INDICATIONS FOR REOPERATION

Even when macroscopic disease is cleared at the initial operation the recurrence rate is still high compared to extremity STS. The disease free interval is commonly related to the grade and intrinsic biological aggressiveness of the tumour. A short disease free interval of several months after macroscopic clearance makes long-term survival very unlikely. If there is only one focus of disease it may be better to wait several months and re-assess the situation rather than immediately

reoperating only to find peritoneal seeding at laparotomy. The next disease free interval is usually shorter than the first. At the other extreme a long disease free interval of several years with only one focus of recurrent disease makes it highly likely that further resection will provide significant benefit.

The frequency of imaging (and for that matter whether or not it should be done in the absence of symptoms) is a matter for individual unit policy. The demonstration of recurrent disease is not always an indication for re-operation whereas it is always a source of great patient anxiety. If imaging suggests the disease is easily resectable and it is asymptomatic then taken in the context of the above principles, it is often better to wait until symptoms develop or the tumour is approaching an unresectable stage before re-operation. This will help to prolong the re-operation interval, which is a particularly pertinent principle in low-grade liposarcoma. The MSKCC experience emphasises that complete macroscopic resection is achievable in most cases of isolated recurrence.[11]

7.14 CONCLUSION

Despite sophisticated imaging studies being available, it is often basic errors in clinical and radiological interpretation that lead to inappropriate management of patients with retroperitoneal tumours who often present to a general surgeon or gynaecologist as the first specialist referral.

Increased awareness of the differential diagnosis of pelvic and other retroperitoneal masses, more liberal use of staging CT Scan with intravenous contrast and recognition of the radiological features that alert the clinician to the probability of a RPS will help to lower morbidity for patients in this situation. Percutaneous transperitoneal biopsy should be avoided because of the risk of seeding malignancy. Referral to a specialist centre will give these patients the best chance of a long disease free interval and possibly an improved chance of cure.

Aggressive attempts at en bloc resection are indicated even for locally recurrent disease. Unless en bloc resection can be achieved survival is not improved by debulking surgery with the probable exception of low-grade liposarcoma.

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CHAPTER 8.
THE CLINICAL AND ACADEMIC IMPACT OF THIS THESIS

The data presented provide significant evidence that the currently available staging systems for soft tissue sarcoma are flawed in a number of ways that limit their applicability to at least the individual subtypes of STS investigated. I have demonstrated that for all 3 subtypes of STS the currently available staging systems for STS provide inadequate prognostic information for often apparently opposing reasons. The hypothesis I make to explain these findings is that in reality the staging systems that have been developed for STS are an averaging of the different behaviours of the broad group of tumours. Although these subtypes have common characteristics they are essentially a heterogeneous group of malignancies. Furthermore because of the heterogeneous nature of the subtypes of STS I would argue that the most obvious interpretation of the evidence presented is that without further subtype restriction or subtype validation, at present, all published staging systems for STS are of academic interest only. The current staging systems provide guidelines which identify the parameters of grade, size and depth as generally important when considering an individual's prognosis. Otherwise they provide unreliable information for individual patients, especially those with tumour subtypes and locations that have not been well represented in the

datasets from which the staging systems have been developed. This is especially so for subtypes of STS with their own characteristic behaviour and (even though not fully investigated in this thesis) for those from particular locations e.g. retroperitoneal sarcoma or head and neck lesions. This point has recently been independently identified in a study on liposarcoma which identified retroperitoneal / visceral primary sites as an independent prognostic factor that implied a worse prognosis.[1] This was put down to the different biology at the 2 sites. In RPS local recurrence was responsible for death in the majority of cases, which contrasts with the behaviour of extremity STS.[1] These points have been argued by me from the start of this thesis and in earlier publications.[2-6]

The analysis of the synovial sarcoma experience of the Royal Marsden Hospital demonstrates other clinically relevant information previously not emphasised in the medical literature. The concept of SS being related to large joints because of its derivation from synovial tissues has been proven incorrect on a clinical level (Fig 3.1). The demonstration of SS's particular sensitivity to chemotherapy is important. This should add to other evidence that despite current studies being unable to demonstrate a

survival advantage for adjuvant chemotherapy in STS there are certain subtypes or subgroups of STS patients that may benefit. This should be the focus of future multi-institutional adjuvant trials. The demonstration that local recurrence (which often corresponds to poor local treatment in this series and many others) is associated with a worse overall survival is a warning to those who continue to fail to recognise, diagnose and refer STS appropriately. The demonstration that small SS cases (< 5cm) have an unexpectedly poor overall 5 year survival is contrary to other centres who have published in this area in the past, however, other recent data also supports the concept that small high grade STS need to be managed aggressively. In light of this evidence and the demonstrated chemo-sensitivity of SS adjuvant treatment should not be denied to this subgroup of patients (and other high risk patients). This should be tested in the context of multicentric randomised controlled trials.

The data presented for myxoid liposarcoma serves to highlight that this subtype of STS has a characteristic clinical behaviour of metastasising to the soft tissues other than the lung parenchyma. Therefore to apply the same initial assessment as well as post-treatment follow up (clinical and imaging) to this subtype of STS, as is usual for other STS, may result in failure to treat these

patients appropriately. This may result in missing recurrent disease whilst it is at a stage that could be amenable to long-term control. The post-event data for patients with soft tissue metastases demonstrates that aggressive management of metastatic disease in this subtype of STS often leads to medium-long term survivors. This is a characteristic of this subtype of STS not previously emphasised in the literature, and is quite unlike other subtypes of STS that tend to have a post-metastasis survival of around 12 - 15 months. The myxoid liposarcoma assessment also demonstrated surprising and previously unrecognised data on the chemo-sensitivity of this subtype of STS as well as identifying that non-cross resistance to ifosfamide and doxorubicin can occur for this subtype of STS. This is a rarely recognised event in any subtype of STS.

The review of the relatively large experience of epithelioid sarcoma has added substantially to the literature on this topic. Formerly there has been limited recognition of what our evidence suggests are characteristic features of this STS. The propensity for regional metastasis and local recurrence has been recognised previously but the tendency for multifocality and difficulties of staging and management associated with this are important new material. Also the particularly poor outcome following any regional or distant metastatic disease has not been

emphasised in the past. The propensity for pleura effusion formation, with metastatic disease to the lung, has not been previously reported.

In conclusion, staging systems for soft tissue sarcoma are flawed in that they do not adequately predict the prognosis for subtypes of STS assessed in this thesis and possibly others subtypes particularly those with "non-standard" behaviour. The identified problems may result in inappropriate information being given to individuals without taking into account the variability in clinical behaviour seen between the different subtypes of STS or the different sites of primary STS. More research needs to be done to develop reliable disease patterns for all the subtypes of STS. Most reliably the multi-institution pooling of prospectively collected case series with centrally reviewed pathology material, could be used to then develop a staging system (or individual staging systems / prognostic profiles) that take into account this variability between subtypes of STS. The currently published staging systems for STS are not clinically relevant in many individual cases and should only be used as a guide to prognosis assessment that has to be enhanced by disease subtype and site specific knowledge.

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CHAPTER 9.
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