

https://dspace.org/

A multimodality approach to the management of soft tissue sarcomas of the extremities, with emphasis on limb preservation.

Krawitz, Hedley Eltan

1990
https://hdl.handle.net/10539/26229

Downloaded from a DSpace repository. https://dspace.org/

A MULTIMODALITY APPROACH TO THE MANAGEMENT OF SOFT TISSUE SARCOMAS OF THE EXTREMITIES, WITH EMPHASIS ON LIMB PRESERVATION

Hedley Eltan Krawitz

1990

A MULTIMODALITY APPROACH TO THE MANAGEMENT OF SOFT TISSUE SARCOMAS OF THE EXTREMITIES, WITH EMPHASIS ON LIMB PRESERVATION

Hedley Eltan Krawitz

A thesis submitted to the Faculty of Medicine, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Medicine in Therapeutic Radiology.

1990

GRADUATED WITH DISTINCTION 27 JUNE 1991

PREFACE

Soft tissue sarcomas of the extremities were previously treated either with wide excision alone, leading to a 30 to 50% local recurrence rate, or amputation, which although lead to a recurreuce rate of less than 5%, caused significant physical and psychological morbidity. In addition to the risk of local recurrence, distant metastases occur in 30 to 50% of high grade lesions.

In 1984 a multimodality soft tissue sarcoma clinic was established at the Department of Radiotherapy, Hillbrow Hospital. Where possible, limb preservation was advocated and radiotherapy and chemotherapy were used as adjuvants to decrease the incidence of local recurrence and distant metastases.

This study will retrospectively analyse the results of patients treated at the sarcoma clinic Hillbrow Hospital from 1984 tc 1988. Survival, prognostic factors and complications of treatment will be assessed.

I would like to acknowledge the assistance given by Professor M.M. Nissenbaum, Dr R. Uijs, and Dr B. Donde. I would also like to thank the staff of The Department of Radiation Therapy, Hillbrow Hospital.

Declaration

I declare that this dissertation is my own unaided work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

Hedley Eitan Krawitz

30 November 1990.

CONTENTS

Introduction and Epidemiology	1
Aetiology	2
Pathology	4
Clinical Presentation	18
Diagnostic Evaluation and Staging Workup	18
Staging	20
Prognostic Factors	22
Treatment	
Surgery	25
Radiotherapy	28
Chemotherapy	43
Sarcoma Clinic - Management and Results	48
Results	52
Complications	64
Recurrence and Salvage	66
Discussion	72
Conclusion	77
List of References	78

LIST OF TABLES AND FIGURES

Table 1	53
Table 2	53
Table 3	54
Table 4	58
Table 5	68
Table 6	70
Table 7	71
Figure 1	56
Figure 2	57
Figure 3	60
Figure 4	69

INTRODUCTION AND EPIDEMIOLOGY

Soft tissue sarcomas are malignant tumours arising in mesenchymal soft tissues - the extraskeletal connective tissues of the body that connect, support and surround other discrete anatomic structures. They arise in all anatomic sites - 40-45% in the lower extremities, 25-30% in the trunk, 15-25% in the upper extremities, and 5-15% in the head and neck area(1).

Despite the fact that soft connective and supporting tissues comprise a large proportion of the body mass, soft tissue sarcomas are uncommon. In the United States, the estimated number of newly diagnosed soft tissue sarcomas for 1987 was 5300, which constitutes about 0.6% of all invasive neoplasms diagnosed that year(2). In individuals below the age of 25, they comprise 6,5% of all cancers(3). The male to female ratio is 1,2:1.

AETIOLOGY

The aetiology of soft tissue sarcomas cannot be identified in the vast majority of cases. The following factors have been implicated:

1. Radiation: It is well established that soft tissue sarcomas may arise following irradiation, although this is uncommon(4). Beck noted this association in 1922 when he reported a higher incidence of pleomorphic spindle cell sarcomas in patients who had been irradiated for tuberculous arthritis(5). Davidson et al reported on 20 patients who developed soft tissue sarcomas following irradiation. The patients received doses of 8,8 Gy to 70 Gy using either orthovoltage or megavoltage equipment. He found that there is no decrease in risk with the use of megavoltage equipment and higher doses do not seem to decrease the risk of carcinogenesis(6). Halperin reported a 0.9% risk of sarcoma in 5 year survivors of Hodgkin's disease treated with radiotherapy with or without chemotherapy(7).
2. Chemical agents: Sarcomas can be induced in the soft tissues of rodents by injection of methylcholanthrene and benzpyrine. In human studies, there have been conflicting reports suggesting a link between phenoxyherbicides and soft tissue sarcomas. Several chemical agents, including thorotrast and vinylchoride, are definitely associated with hepatic angiosarcomas(5).

3. Sarcomas may develop in the chronic lymphoedema of the arm which may develop post mastectomy. This is known as the Stewart-Treves syndrome.
4. Inherited conditions: Certain inherited conditions are associated with an increased incidence of soft tissue sarcomas. Malignant schwannomas are more common among patients with Von Recklinghausen's disease and various soft tissue tumours occur with a higher incidence in patients with Gardner's syndrome and the familial form of retinoblastoma.
5. Genetic factors: Chromosomal abnormalities have been recorded in patients with various soft tissue sarcomas. For example a translocation of t(x;18) has been found in synovial sarcomas(5). These abnormalities may have diagnostic and therapeutic implications.
6. Trauma: Although many patients with soft tissue sarcomas present with a recent history of trauma, there is no known aetiological relationship. It is likely that minor trauma merely brings a preexisting lesion to the patient's attention.

PATHOLOGY

Soft tissue sarcomas have a tendency to extensively invade surrounding tissues. As the tumour expands, it presses on the surrounding normal tissue, thereby creating a pseudocapsule composed of reactive normal tissue and tumour tissue. This pseudocapsule does not form an effective barrier to tumour spread and satellite lesions away from the main tumour mass are common(8). Spread usually occurs within the tissue compartments in which the tumour originates.

Soft tissue sarcomas may resemble fibrous, adipose, vascular, muscular or synovial tissue. They are classified according to the normal soft tissue they most resemble. Whether the tumour originates from one of the soft tissues or from a multipotential primitive mesenchymal cell remains unresolved. Recently the use of immunohistochemistry and electron microscopy has enhanced the accuracy of classification. There is some evidence that the natural clinical course and response to treatment varies amongst the different histological types of sarcomas but the tumour grade is of most value to the clinician.

Grade: This is the most important factor in staging and is based on the number of mitoses per high power field, absence or presence of necrosis, degree of cellularity, nuclear pleomorphism and neovascularity. A grading system based on the degree of nuclear atypia and number of mitoses per high power field was developed in the 1940's by Broder et al(9). This system was occasionally applied to soft tissue sarcomas. In 1969 the American Joint Committee on staging and end results applied a grading system which classified sarcomas into low (grade1), medium (grade2) and high grade (grade3). This grading system was based primarily on the number of mitoses per high power field. Various authors agree that not all sarcomas can be accurately graded. The following histological types are almost uniformly high grade: synovial sarcoma, embryonal rhabdomyosarcoma, and angiosarcoma.

High grade lesions are more likely to recur locally and spread distally. In lesions less than five centimetres, Lindberg found local recurrence in 6,3% of grade 1, 10,4% of grade 2 and 31,6% of grade 3 tumours(10). In a study of grading related to prognosis at the National Cancer Institute (NCI), patients with low grade tumours did significantly better than those with intermediate or high grade tumours. However, there was no difference in survival between intermediate and high grade tumours(11).

Spread to Nodes

Spread to regional lymph nodes is an infrequent event in the natural history of patients with soft tissue sarcomas. In a study of 323 patients treated at the Massachusetts General Hospital (MGH), 19 (5,9%) had regional lymph node metastases at presentation(12). The frequency of lymph node metastases correlated with grade - none with grade 1, 2% with grade 2, and 12% with grade 3 lesions developed lymph node metastases. Lymphatic spread is more common in rhabdomyosarcoma, alveolar soft part sarcoma, clear cell sarcoma, epithelioid sarcoma and synovial sarcoma. 10 - 20% of these have regional lymph node involvement at presentation(12).

Distant Metastases

Haematogenous metastases develop in 30 to 50% of patients with high grade tumours(13). The lungs are the most common site of metastases, accounting for up to 80% of all metastases. Other sites of metastatic spread include regional lymph nodes, bone, and subcutaneous tissue.

Histological Subtypes

The Enziger and Weiss classification is base on the histogenesis concept. Each lesion is related to a cell type.

Fibrous Tissue

Fibrosarcoma: 70% of cases occur between the ages of 20 and 50. 25% are on the trunk, 25% on the lower extremity, 15% in the head and neck region and 15% on the upper extremity. Grossly the lesions are firm, soft, greyish-white and homogeneous. Histologically, they consist of a relatively uniform population of spindle cells which exhibit moderate to strong anaplasia and an increased number of mitotic figures(14). Giant cells are not a feature(15). There are no other differentiating features, other than the production of a fibrous stroma.

Dermatofibrosarcoma Protuberans: This is a low grade fibrosarcoma occurring primarily in the 3rd or 4th decade on the trunk or scalp. 30% of these lesions recur after simple excision. The lesion is predominantly an intracutaneous growth arising as single or multiple nodules or plaques. It tends to invade surrounding tissues but rarely metastasizes. Microscopically, the appearance is that of a uniform cellular growth with spindle cells arranged in an interwoven pattern.

Aggressive Fibromatosis: These are extremely indolent tumours. They derive primarily from fascial sheaths and musculo-aponeurotic structures throughout the body. They are unencapsulated, infiltrating and locally destructive. They may recur repeatedly without metastasizing. Microscopically, the fibroblasts are well differentiated and tend to form interlacing bundles.

Infantile Fibrosarcoma: These have histological feature of a high grade malignancy. They occur in infants less than 5 years of age and have a good prognosis.

Fibrohistiocytic tumours: In many recent series, malignant fibrous histiocytoma was the most common type of soft tissue sarcoma reported. These tumours commonly occur in the proximal extremities especially the thigh, more often in deep seated tissues. Grossly, most are poorly defined multinodular masses of soft or firm yellowish grey tissues with cystic and necrotic areas.

The following subtypes have been defined:

a. Storiform pleomorphic

b. Myxoid - better prognosis

c. Giant cell

d. Inflammatory - worse prognosis

e. Angiomatoid

Microscopically, a spindle-cell stroma and large numbers of pleomorphic histiocytes or xanthoma cells and bizarre giant cells are found. There is almost always a storiform pattern in parts of the tumour. Without this feature it may be difficult to distinguish the tumour from pleomorphic rhabdomyosarcoma or liposarcoma. It is hypothesized that proliferating histiocytes transform into fibroblast-like cells with collagen synthesizing ability and so are responsible for the fibroblastic component of these tumours. Xanthomatous cells and giant cells are also believed to be derived from histiocytes.

Adipose Tissue

Liposarcoma: These occur almost anywhere that fat is present. They are usually malignant from inception, only rarely arising from lipomas. They are most common between 40 and 60 years of age and are commoner in men. 44% occur on the lower extremity, 14% in the retroperitoneum, 14% on the trunk, and 8% on the upper extremity(16).

Grossly, the tumours have multiple convolutions and are often yellowish. They may give the false impression of encapsulation, but they regularly infiltrate surrounding structures. They may be divided into several distinct varieties:

1. Well differentiated which includes lipoma-like, sclerosing and inflammatory subtypes. These retain a lobular architecture and are composed mostly of mature fat cells with variable amounts of mucoid and myxomatous tissue. They are usually well circumscribed and rarely metastasize. They have a better prognosis.
2. Myxoid liposarcoma. This is the most common subtype. They may be well or poorly differentiated. The well differentiated type is composed of a vascular meshwork of fusiform and stellate cells in a myxomatous background. The poorly differentiated type contains in addition to embryonal and adult fat cells, large numbers of anaplastic and bizarre giant cells. There may be cartilagenous or osseous metaplasia.
3. Pleomorphic. These show the least resemblance to fat tissue and have the highest degree of anaplasia and number of mitotic figures. Bizarre lipoblastic cells can usually be demonstrated. These tumours have a high rate of local recurrence and distant metastases.

Tenosynovial Tissue

Synovial Sarcoma: These occur primarily in children and young adults. The male to female ratio is 3:2(15). Only 10% develop within joint cavities. Grossly these tumours are firm and grey with areas of calcification and haemorrhage. They are partially or completely surrounded by a pseudocapsule formed by compressed adjacent non-tumorous tissue. 10 - 20% have nodal involvement(16).

Microscopically, they have the appearance of synovial tissues but the tumours rarely involve joint synovium. Two elements should be present:

1. An adenomatous structure, with cells resembling epithelium arranged in pseudoglandular structures. The cells vary in shape from cuboidal to columnar and may secrete a mucopolysaccharide, probably hyaluronic acid.
2. A sarcomatous stroma composed of fairly uniform spindle shaped cells with hyperchromatic nuclei. The cells are densely packed in bands or sheets.

This biphasic pattern has been confirmed with electron microscopy. The histogenesis of the tumour is unclear. The similarity of the cells to the two types of cells found in normal synovium is suggestive of synovial origin, but the extra-articular origin of most of the tumours and their behaviour in tissue culture is not consistent with this hypothesis.

Subtypes:

1. Monophasic - (fibrous or epithelial). The fibrous or spindle cell variety is the most common. It is an aggressive high grade lesion. The epithelial or pseudoglandular type is rare.
2. Biphasic - both spindle cell and pseudoglandular patterns are present together.

Muscle

Striated

Rhabdomyosarcoma: These account for about 15% of all sarcomas(15). They are divided into three types;

1. Adult pleomorphic type (13%) These arise most frequently in the extremities, especially in the quadriceps, adductors, semimembranosus, biceps and brachialis muscles. They occur most commonly in the 5th decade. Grossly, they appear firm and well circumscribed, but are locally destructive. Microscopically, they have a high degree of cellular pleomorphism. Large and small spindle shaped cells predominate. The long strap-like cells often show longitudinal fibrils but cross striations are rarely demonstrated. The diagnosis is restricted to tumours occurring in skeletal muscle.

2. Alveolar type (41%): These tumours occur primarily in children and young adults, mainly on the extremities. Grossly, the tumour is greyish white, with cystic areas. Histologically, it is characterised by a pulmonary alveolar like appearance. Tumour cells are large and oval or rounded with scanty cytoplasm. Many have strongly acidophilic cytoplasm in which myofibrils are discernible. Alveolar rhabdomyosarcoma has a grave prognosis.

3. Embryonal type (46%): These occur most commonly in the head and neck regions, the genitourinary tract and the orbit. A relatively small percentage occur in the extremities and retroperitoneum. Microscopically, small round and stellate cells with scanty cytoplasm are scattered in a loose myxomatous matrix. In addition, rhabdomyoblastic elements are recognisable.

Smooth Muscle

Leiomyosarcoma: They occur most commonly in the gastrointestinal tract, genitourinary tract, vascular systems and the retroperitoneum. Only 76/462 occurred on the extremities(17). Leiomyosarcomas appear as large rounded nodular masses of firm greyish brown tissue with areas of haemorrhage and necrosis. Microscopically, they consist of long spindle shaped cells of more or less uniform size, arranged in interlacing bundles. The nuclei are elongated, and myofibrils can usually be demonstrated in the pink staining cytoplasm. There are often less well differentiated areas with giant cells, strap cells or round cells. Cytologic criteria for the distinction of benign from malignant leiomyomatous growths are not always reliable. Smooth muscle tumours over 5 cm in size in the deep soft tissues of adults are almost invariably malignant.

Blood Vessels

Haemangiosarcoma: These most frequently occur in the scalp, breast and liver. They comprise only 2% of soft tissue sarcomas(3).

Malignant Haemangiopericytoma: These may occur at any age or site. They are thought to arise from the pericyte cells of smooth muscle origin that lie around small vessels.

Lymphangiosarcoma: These arise in chronically oedematous extremities. They occur following 1% of mastectomies and the average post mastectomy interval is 10 years(18). They are typically multifocal and spread rapidly. The mean survival after diagnosis is 19 months.

Tumours of Peripheral Nerves

Neurofibrosarcoma (malignant schwannoma): These tumours arise from schwann cells anywhere in the body. They commonly occur along the major nerves and spinal nerve roots. Although schwann cells arise from the neural tube of the primitive ectoderm, schwannomas are included in the category of soft tissue sarcomas because of similarities in anatomical sites of origin, clinical presentation and behaviour to other soft tissue sarcomas. There is an association between neurofibrosarcoma and Von Recklinghausen's disease. About 10% of patients with Von Recklinghausen's disease develop neurofibrosarcoma.

Bone and Cartilage

Extraskeletal Osteosarcoma: These are extremely rare. They arise primarily in skeletal muscle of the extremities, especially the lower limbs. They occur predominantly in middle and old age. On section these tumours are firm greyish-white and gritty, with areas of necrosis and haemorrhage. Microscopically, they are similar to osteosarcomatous lesions of bone.

Extraskeletal Chondrosarcoma: These rare tumours are predominantly found in the extremities. The majority are situated in muscle. Grossly, they consist of a mass of soft mucoid to moderately firm grey tissue, in which there may be nodular areas of cartilagenous consistency. Microscopically, they resemble chondrosarcomas of bone but with larger areas of mucoid or myxomatous matrix and fewer foci of mature hyaline cartilage.

Uncertain Histogenesis

Alveolar Soft Part Sarcoma: The cell of origin is not known although a myogenous origin has been suggested. It occurs predominantly in adolescents and young adults, more often in females. It has a slow clinical course and is associated with a prolonged survival, even in the presence of metastatic disease. It usually occurs in the extremities,

more commonly in the lower limbs. The tumour is frequently well circumscribed or partly encapsulated. On section, the tumour is firm and grey-yellow. Fibrous trabeculae may divide it into lobules. Microscopically, there are rounded or cord-like aggregates of cells separated by delicate fibrous septa and thin walled vascular spaces.

Epithelioid Sarcoma: These are usually found around the wrist, hand and foot. They have been cited as the most common type of soft tissue sarcoma occurring on the hand(19). They often spread to the regional lymph nodes. They have a greater propensity than other soft tissue sarcomas to spread to noncontiguous areas of skin, subcutaneous tissue, fat and bone.

Malignant Mesenchymoma: These may occur at any age. They have a predilection for the deeper structures of the extremities and the retroperitoneum. They consist of mature and immature tissues, including two or more sarcomatous elements of different histogenesis (such as leiomyosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma). The degree of malignancy is determined by the most malignant element.

Clear Cell Sarcoma: These are now classified as malignant melanoma of the soft parts(20). They are rare, and tend to occur along the tendons in the extremities, especially the feet or hands. Microscopically, they consist of nests of

more commonly in the lower limbs. The tumour is frequently well circumscribed or partly encapsulated. On section, the tumour is firm and grey-yellow. Fibrous trabeculae may divide it into lobules. Microscopically, there are rounded or cord-like aggregates of cells separated by delicate fibrous septa and thin walled vascular spaces.

Epithelioid Sarcoma: These are usually found around the wrist, hand and foot. They have been cited as the most common type of soft tissue sarcoma occurring on the hand(19). They often spread to the regional lymph nodes. They have a greater propensity than other soft tissue sarcomas to spread to noncontiguous areas of skin, subcutaneous tissue, fat and bone.

Malignant Mesenchymoma: These may occur at any age. They have a predilection for the deeper structures of the extremities and the retroperitoneum. They consist of mature and immature tissues, including two or more sarcomatous elements of different histogenesis (such as leiomyosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma). The degree of malignancy is determined by the most malignant element.

Clear Cell Sarcoma: These are now classified as malignant melanoma of the soft parts(20). They are rare, and tend to occur along the tendons in the extremities, especially the feet or hands. Microscopically, they consist of nests of

pale fusiform cells surrounded by fibrous septa. They behave more like soft tissue sarcomas than cutaneous melanomas despite their melanocytic nature.

Unclassified

These comprise 10 - 20% of all sarcomas.

CLINICAL PRESENTATION

Soft tissue sarcomas usually present as asymptomatic soft tissue masses. Because they arise in compressible tissues and are often far from vital organs, symptoms are few until the lesions are quite large in relation to the anatomic part. Symptoms generally result from pressure or traction on adjacent nerves or muscles.

Only 4-11% present with clinical metastases(3).

DIAGNOSTIC EVALUATION AND STAGING WORKUP

1. Complete history and physical examination. Examination includes evaluation of the site, size, and assessment of the presence and degree of involvement of skin, major vessels, nerves or bone. The regional lymph nodes are also evaluated.
2. Biopsy and histopathologic study to establish diagnosis. Fine needle aspiration cytology is not adequate as large tissue specimens are usually necessary to determine histologic type and degree of differentiation.
3. Radiologic procedures:

    a. X-ray of the involved area to assess the soft tissue mass and whether there is bony involvement.

    b. C.T Scan or Magnetic resonance imaging (MRI) of the mass assists in assessing tumour extent, involvement of vital structures and resectability.

Most of the soft tissue density is different from that of normal muscle and therefore these tumours appear as relatively clearly delineated soft tissue masses.

c. Chest x-ray and in high grade lesions C.T. scan of the chest to exclude lung metastases.

d. Bone Scan. Although sarcomas rarely invade bone, soft tissue reaction in the periosteum may be estimated by bone scan. A positive scan may serve as a guide to wide resection near the bone or to removing periosteum or a portion of bone in the area that is positive on the scan.

e. Arteriography. This demonstrates the relationship to large vessels and the major venous drainage that needs early control to limit embolization. This is not a routine investigation.

4. Routine full blood count, urea and electrolytes and liver functions tests serve as baseline investigations prior to therapy.

STAGING

Systems for staging have been developed by the American Joint Committee (AJC) and the Union Internationale Contre Cancer (UICC). The revised AJC staging protocol is based on a T, N, M and G system(21). "T" represents the primary tumour, with an associated number to describe the size or extensions. "N" indicates regional lymph node involvement and "M" represents distant metastases. "G" refers to the histological grade of the lesion.

T - Primary tumour
T1 - Tumour 5 cm or less in greatest dimension
T2 - Tumour greater than 5 cm in greatest dimension
T3 - Tumour of any size that invades bone, major vessels or nerves.

G - Histological grade of malignancy
G1 - Well differentiated, low grade
G2 - Moderately differentiated, intermediate grade
G3 - Poorly differentiated, high grade

N - Regional lymph nodes
N0 - No histologically verified metastases to regional lymph nodes
N1 - Histologically verified lymph node metastases

M - Distant metastases

M0 - No distant metastases

M1 - Distant metastases

Stage Grouping

Stage 1A - G1 T1 N0 M0

Stage 1B - G1 T2 N0 M0

Stage 2A - G2 T1 N0 M0

Stage 2B - G2 T2 N0 M0

Stage 3A - G3 T1 N0 M0

Stage 3B - G3 T2 N0 M0

Stage 3C - G1-3 T1-2 N1 M0

Stage 4A - G1-3 T3 N0 M0

Stage 4B - G1-3 T1-3 N0-1 M1

PROGNOSTIC FACTORS

A simple comparison of local control and disease free survival between different institutions may be misleading if prognostic factors are not taken into account. These include host, tumour and treatment related factors.

Host Factors:

age Appears to be of little prognostic importance. However, fibrosarcomas and liposarcomas tend to have a better prognosis in children.

sex Has not been found to be a significant prognostic factor

symptoms In a study of 423 patients with localised soft tissue sarcomas of the extremities treated at the Memorial Sloan Kettering Cancer Centre (MSKCC), patients presenting with a painful mass had a significantly reduced median survival (63 months) when compared to those without local symptoms (167 months)(22). Painful tumours were predominantly high grade and were more likely to be deeply invasive.

Tumour related Factors

upper vs lower extremity

This has not been found to significantly affect prognosis.

site — Location proximal to the knee or elbow has been correlated with reduce curability in some studies but not in others(22). This has been attributed to greater difficulties in gaining local control of proximal tumours. Proximal tumours are more likely to be large and located deep to the fascia(23).

size — Tumour size has been clearly related to survival in several studies using a 5 cm diameter as the cutoff(1,22). Larger tumours have a significantly greater tendency to be high grade, proximal in location and deep to the fascia(22).

histological type

There was no evidence of a correlation between histological type and recurrence frequency in reports by Suit and the NCI(11,19,25).

grade — The correlation of tumour grade with survival has been well documented.

compartmental status

Intracompartmental lesions include those contained within the major muscle compartments, those within joints and those superficial to the deep fascia. Tumours in other tissues are considered extracompartmental. There is a higher risk of recurrence in extracompartmental lesions(22).

nodal status

The presence of regional node metastases is frequently a sign of disseminated disease and these patients have a poor survival(22,24).

skin involvement

In a study by Suit et al, this was found to be an indicator of a poorer prognosis(25).

Treatment related factors

surgical margins

The risk of local failure increases as the margin of excision decreases(19,26).

recurrent lesions

Most studies show an association between local recurrence and poorer survival(23,27,28). However, one cannot conclude that local recurrence causes dissemination and death. The relationship may be explained by the hypothesis that tumours prone to metastasize also have a greater tendency for local recurrence(29).

TREATMENT

Patients with soft tissue sarcomas are managed using a multimodality approach. Ideally, this should be by a sarcoma team at a major centre where patients with soft tissue sarcomas are seen in substantial numbers. The team should comprise sarcoma pathologists, surgeons (orthopaedic and general surgeons), medical and paediatric oncologists, diagnostic radiologists and radiation therapists.

Modalities of Treatment

Surgery has been the primary modality in the treatment of soft tissue sarcomas. More recently, radiation therapy and chemotherapy have become important components of tumour management.

Surgery

In the first half of this century, simple excisions of soft tissue sarcomas were frequently carried out. Local recurrence rates ranged from 33% to 66%(5). Following these early studies which suggested the need for adequate surgery, sarcomas were treated more aggressively, often with amputation. Although the recurrence rate decreased to 2% to 34%, these surgical procedures were disfiguring and debilitating(5,30).

Several groups showed that treatment of nonresectable sarcomas with high dose radiation lead to frequent tumour shrinkage and occasionally sterilization. Suit et al demonstrated that some soft tissue sarcomas could be treated with limited resections and postoperative radiotherapy with acceptable recurrence and survival rates(25). This approach has been associated with some improvements in both local and disease free survival rates(31).

Surgical Approach:

1. Biopsy: In order that future surgical options are not compromised by the biopsy, there should be a high degree of suspicion for soft tissue sarcomas. Incisional biopsies or, if the lesion is small, excisional biopsies are desirable for making the diagnosis and establishing the histological grade. The incision should be placed longitudinally, where it can easily be re-excised during the definitive procedure. Haemostasis is important as haematoma formation can lead to dissemination of malignant cells. Wound drainage is undesirable.
2. Simple excision: The removal of gross tumour with its pseudocapsule is followed by recurrence in 70-90% of patients.
3. Wide excision - conservative resection: The resection includes a wide margin of grossly normal tissue around the tumour. The local recurrence rate following this procedure varies from 25% to 40%(27).

4. Radical resection: The whole anatomic compartment is removed. The line of excision is separated from the tumour and its tissue of origin by at least one anatomical structure or tissue plane. The recurrence rate varies from 10% to 20%(8). Radical resection often entails amputation. In certain sites such as the shoulder or pelvic girdles, amputation may not remove the whole anatomic compartment, and therefore would not be radical by definition.

Prior to the definitive surgical procedure, meticulous preoperative evaluation and planning is required. This includes diagnostic imaging procedures, including C.T. Scans and MRI scans, to determine the feasibility of limb sparing surgery. Many believe that if there is definite bony, critical vascular or major nerve involvement, amputation is required. However, prosthetic bone, vascular and nerve grafts can be successful in allowing limb preservation. If irradiation of an extensive tumour would require irradiation of the entire limb circumference to a high dose, radical surgery should be considered.

The objective of limb sparing surgery is to excise the biopsy site en bloc with the tumour, maintaining a wide margin of normal tissue around the tumour. The tumour should not be visualised during the procedure. At the completion of the resection, metallic clips should be placed at the limits of dissection, in order to facilitate

radiotherapy planning. There is no good evidence to recommend compartmental resections if widely negative margins can be obtained.

Prophylactic lymph node dissections are not indicated as the incidence of lymph node involvement is low.

Resection of Sarcoma metastases: Sarcomas metastasize most frequently to the lungs. Many series have shown that pulmonary metastectomy can result in long term eradication of metastatic disease. In a NCI study, resection of pulmonary metastases led to ≥ 30% 5 year survival following pulmonary resection(32,26).

Radiotherapy

The combination of radiotherapy and conservative surgery can produce local control while maintaining a good functional result. The surgery is used to remove the primary tumour mass. The radiation is used to treat microscopic tumour extensions. These can be controlled by moderately high doses of radiation. The patient is thus spared the removal of large amounts of apparently normal tissue.

Radiation therapy may be given postoperatively or preoperatively.

Postoperative Irradiation:

The advantages include:

1. The entire specimen is available for histological study to determine type and grade.
2. The exact size and extent of the tumour are defined.
3. Delays in wound healing that may follow preoperative irradiation are avoided.
4. There is no delay in surgery (a psychological advantage in some patients).

Extent of Surgery Prior to Postoperative Irradiation

There is some controversy over the amount of surgery to be performed when postoperative radiotherapy is planned. While all gross tumour should be removed, some advocate minimal excision of surrounding normal tissues and others advocate the maximum wide excision possible compatible with reasonable morbidity and function of the limb. However, larger surgical excisions require the use of wider radiotherapy fields and reduce the functional result.

Dose: The doses used range from 64 to 66 Gy, at 2 Gy per fraction. This dose produces local control in 85% of cases, which is comparable to that achieved with radical surgery(10).

Radiation given postoperatively should start 10 to 12 days following surgery to allow wound healing. Following resection of large tumours, there may be a need to wait 3 to 4 weeks to allow the seroma to resorb.

Preoperative Irradiation

The advantages include:

1. Preoperative irradiation to a dose of 45 to 50 Gy will inactivate 90% of tumour cells. This will decrease the chance of tumour implantation during surgery. Cells shed into the circulation would not be viable and therefore not able to cause metastases.
2 The radiation therapist need only treat tissues thought to be at risk for tumour involvement, and radiation fields need not include all areas that will be manipulated during surgery.
3 Some patients who would have needed an amputation initially may become suitable for conservative surgery following preoperative irradiation.

The drawbacks of preoperative irradiation include problems with postsurgical healing. This can be minimized by using a preoperative dose of not more than 45 to 50 Gy and then waiting 3 to 4 weeks prior to surgery. At surgery the incision wound should not be brought together under tension.

Postoperatively a boost or supplemental dose consisting of 10 to 15 Gy is given to the tumour bed.

Preoperative Regional Chemotherapy and Irradiation

Eilber et al have used infusion chemotherapy - adriamycin 30 mg per day over 3 days through an intraarterial catheter together with radiation therapy at a dose of 35 Gy in 10 fractions given 1 to 2 weeks prior to surgery(33). Later, the irradiation dose was reduced. However, it became clear that a dose of 35 Gy was much more effective in terms of local control and in effecting histological necrosis than a reduced dose of radiation therapy. Results show a 95% limb salvage rate with a local recurrence rate of less than 8%(26). This scheme uses a high dose per fraction, which would be expected to show increased late morbidity. In fact 13 out of 100 patients developed wound sloughing, 4 developed chronic lymphoedema, and 5 patients developed fractures of the long bones.

Brachytherapy:

Brachytherapy is used as an adjuvant to conservative surgery, either alone or combined with external beam therapy. The advantages are that a high dose can be delivered locally with a rapid fall-off with distance, thereby protecting nearby normal tissues. In addition, the administration of radiotherapy by this technique has a theoretical radiobiologic advantage of treating the tumour cells in a well oxygenated state, before scarring takes

place. The joint attendance of the surgeon and radiotherapist at the time of surgery assures the most accurate mapping of the tumour-bearing tissues to be treated(34). At the Memorial Hospital, the tumour bed was implanted following conservative resection with ^{192}Ir. Catheters were placed on the tumour bed at surgery and 72 hours later Iridium sources were inserted. 40 Gy was given over 4 to 5 days. Local control was good but serious wound complications occurred in 9/33 patients. 80% of patients achieved good to excellent preservation of limb function(35). Mills et al at Groote Schuur treated 17 patients with large soft tissue sarcomas close to vital structures with brachytherapy with or without external beam therapy(36). 9 had gross disease left post excision while the rest had microscopic residual disease. Brachytherapy comprised 40 to 100% of the total dose. Local control was obtained in 16/17 cases. 3/17 developed complications but there were no neuropathies or vascular complications.

Brachytherapy appears to be applicable to a selected group of patients who have smaller lesions. It requires a high degree of expertise.

Hypofractionation

Ashby et al used 6,6 Gy weekly with no advantage over normal fractionation(37).

Irradiation Alone

This approach should only be used when combined irradiation and surgical resection cannot be employed. Tepper and Suit reported a 33% local control rate with photon irradiation alone. Patients received 1,8 to 2 Gy per fraction to 64 to 65 Gy. 41/51 patients had tumours greater than 5 cm(38). Other studies have shown a local control rate with photon irradiation alone of 20 to 36%(39). This low response rate to photon irradiation may be related to the slow cell turnover time of soft tissue sarcomas, the ability to repair sublethal damage and the protective effect of certain sections of the mitotic cycle(40).

High LET irradiation: Neutrons alone have led to apparently improved local control in inoperable lesions. The theoretical advantages of neutrons over photons include minimal recovery from potentially lethal damage and a response independent of the cell's position in the cell cycle. Pickering et al treated 50 patients with soft tissue sarcomas with fast neutrons alone and achieved a local control rate of 50%. 62% of the lesions were greater than 10 cm(39). In a review of 286 patients with large inoperable soft tissue sarcomas a local control rate of 50% was obtained(3). There was a severe complication rate of 30%, consisting mainly of severe fibrosis and skin necrosis. However, treatments were given with fast neutron beams that do not give depth dose characteristics

comparable with modern photon beams. The use of more penetrating fast neutron beams may reduce the frequency and severity of complications.

Radiotherapy Techniques

Careful planning, including assessment of clinical, histopathologic, radiographic and operative findings, is essential. A knowledge of the anatomy of the muscle compartments is important in the placing of treatment fields.

Anatomy

Thigh: The thigh is divided into anterior, medial and posterior compartments.

Anterior thigh compartment consists of the quadriceps (rectus femoris, vastus medialis, intermedius and lateralis) and sartorius muscles and the femoral artery, vein and nerve. Tumours of the lateral portion of the anterior compartment can be adequately treated with opposed oblique fields, directed from anteromedial to posterolateral. In general, the field need not extend proximal to the femoral neck or distal to the patella.

Medial thigh compartment. This contains the adductor brevis, longus, magnus and pectineus muscles. The obturator nerve supplies the compartment. Irradiation of this area may be difficult especially with proximally located tumours, as it is usually necessary to irradiate the medial thigh, groin and perineum. These are usually treated with opposing anterior posterior fields. The field generally extends from the pubic symphysis at the superomedial margin with the middle of the femur as the lateral margin(41).

Posterior thigh compartment This consists of the hamstring muscles (semimembranosus, semitendinosus and biceps femoris), the posterior portion of the adductor magnus and the sciatic nerve. When treating tumours in this compartment, it may be useful to place the patient on his side with his thighs separated.

Leg

The leg is divided into three compartments: the anterior, posterior and a small lateral compartment. The interosseous membrane between tibia and fibula, which separates the anterior from the posterior compartment, acts as a fairly effective barrier to tumour spread.

Anterior compartment contains four muscles which all act as dorsiflexors of the foot - tibialis anterior, extensor digitorum longus, extensor hallucis longus, and peroneous

tertius. Tumours in this compartment can be irradiated with obliquely opposed fields directed from anteromedially to posterolaterally. The posterior margin of the field is set posteriorly to the interosseous membrane. The knee and ankle joints can usually be avoided.

Posterior compartment contains the gastrocnemius, soleus, popliteus, flexor hallicus longus, flexor digitorum longus and tibialis posterior muscles. Tumours in this compartment can be irradiated with lateral fields. A small strip of skin and soft tissue over the achilles tendon and the soft tissue overlying the anterior tibia should be spared. Both of these structures are susceptible to frequent traumatisation.

Lateral compartment This consists of the peroneus longus and brevis muscles. This compartment can be treated with simple anterior posterior fields.

Arm

The arm is divided into anterior and posterior compartments.

The anterior compartment contains the biceps brachii, coracobrachialis and brachialis muscles.

The posterior compartment contains the triceps brachii muscle.

In irradiation of arm tumours, the arm is held in an immobilization device constructed to limit forearm rotation and to angle the arm away from the trunk.

Forearm

This is divided into anterior and posterior compartments. The interosseous membrane connecting the radius and ulna usually acts as an effective barrier to local tumour spread. The forearm should be mobilized moderately far from the trunk with the hand positioned so that the edge of the field is roughly parallel to the interosseous membrane. For most tumours it is possible to avoid irradiation of the hand joints and elbow.

Radiation Fields

The target volume must be defined in three dimensions, and must include a wide margin of normal tissues around the tumour. As extremity sarcomas tend to grow longitudinally, wide margins proximal and distal to the primary tumour mass must be used - from 5 to 10 cm beyond gross disease. As they do not spread so much circumferentially, one can usually avoid treating the whole circumference of the limb,

which limits late morbidity. Ideally, one third of the circumference of the extremity should be spared. If not feasible, the minimal width of spare tissue should be 2 cm for the forearm, 3 cm for the lower leg and 4 cm for the thigh. It is not necessary for the entire anatomical compartment to be included in the target volume.

Shrinking field techniques: Morbidity can be reduced if the size of the field is reduced progressively during the course of therapy. The initial field should include all areas where there is a probability of microscopic tumour involvement, to a dose of 45 - 50 Gy. Preoperatively, the initial target volume will include detectable tumour with wide margins. Postoperatively, the initial volume must include the entire surgical field and the skin incision. The reduced target volume covers the macroscopic tumour with a 5 cm margin or, following resection, the tumour bed with a 4 cm margin. This volume should be treated to 56 - 60 Gy. The final boost target volume will be treated in patients with gross or microscopic residual disease following surgery or in those treated with irradiation alone. The boost includes the detectable tumour with a 2 cm margin. The boost should include the incision in patients with tumours located close to the skin. When this is so, the scar area may need to be bolused throughout the treatment course. If the lesion is deeply situated, the scar need not be boosted. The final boost target volume should receive a total of 70 Gy when treated with

irradiation alone and 64 - 68 Gy post surgery. The daily dose fractionation should be 1,8 to 2 Gy in 4 to 5 fractions per week.

Gapping techniques: Occasionally, abutting fields are required to cover a large target volume. This may lead to cold and hot spots at the junction. In such cases a moving gap technique is recommended whereby the abutting edges of the fields are moved by 1 cm each week in order to blur the hot and cold regions.

Immobilization

The extremity must be adequately immobilized during therapy in order to ensure setup reproducibility. Immobilization is achieved using plaster or some other casting device which can be reproducibly and reliably applied at each treatment. Sometimes customized devices are needed to remove the opposite extremity from the radiation field.

Custom Shaped Fields

Individualized blocks are used to spare uninvolved normal tissue. They are also necessary in order to avoid irradiating the full circumference of the extremity. If possible, a portion of the uninvolved circumference of the bone should be spared, as this may increase the long term strength of the bone. Specific areas that are relatively

predisposed to radiation damage because of their susceptibility to trauma should not be included within the tumour volume if they are not at risk for tumour. These include the elbow, groin, skin of the medial thigh, skin overlying the patella and the anterior tibia, the achilles tendon, and the heel and sole of the foot.

Gonadal Shielding

As soft tissue sarcomas often occur in young adults, the gonadal dose should be minimized. Testicular shields are used to reduce the gonadal dose and thereby avoid sterility(41). Thermoluminescent dosimetry must be performed to ensure that the dose to the testis does not exceed tolerance.

Field Arrangement

Opposing anterior posterior fields may not always be the best field arrangement for treating extremity sarcomas. Oblique fields frequently give the best dose distribution, and are often combined with wedges or tissue compensators to minimise the dose variation within the tumour.

Beam Energy

For most soft tissue sarcomas, it is important to deliver an adequate dose to the skin in the immediate vicinity of

the scar. Therefore, low energy (6 Mev or less) megavoltage x-ray beams are ideal for the treatment of extremity tumours. If the scar is not being treated tangentially, bolus on the scar is necessary to ensure an adequate surface dose.

Complications of Radiotherapy

Functional results are good in most patients i.e. little pain, no or minimal oedema, near normal range of motion and good limb function. However, significant functional defects can occur(3). A series of 300 extremity sarcoma patients treated with postoperative external beam irradiation had a major wound complication rate of 7%(10). Preoperative irradiation in another series of extremity sarcoma patients resulted in a 27% incidence of wound complications(42).

Complications in irradiation of the hand and foot

Some believe that it is not possible to irradiate the hand or foot to a high dose without producing significant morbidity such as stiffness, loss of function, fibrosis and obliteration of lymphatics predisposing to severe lymphoedema(43). However, in a study from the NCI, 10 patients with sarcomas arising in the hand or foot were treated with combined modality therapy including limited surgery, radiotherapy and combination chemotherapy(44). The majority of patients had no or mild functional limitations

after therapy. Only one patient had major functional limitations requiring an orthopaedic appliance.

Results

Local failure rates with conservative surgery with irradiation vary from 5 to 26% in various studies(2). At the M.D. Anderson, Lindberg reported a 20% local recurrence rate. There was a five year disease free survival of 61%. 80% of those who developed local recurrence obtained local control with additional surgery(10).

At the NCI, Rosenberg et al performed the only randomised study comparing limb sparing surgery and irradiation to amputation. Local recurrence was more common in the irradiated patients (4/27 vs 0/16) but this was not reflected in the survival rates. 5 year disease free survival was 78% after irradiation compared to 81% after amputation(45).

At the Massachussetts General Hospital (MGH), the overall 5 year actuarial control with pre or postoperative irradiation was 80% and the five year disease free survival was 70%. 11% failed locally(46).

Comparison of these results with other studies of patients treated with amputations shows that there is no increase in metastases or decrease in survival rates with the use of conservative therapy.

Chemotherapy

Advanced Disease

Despite the advances in local control, 40 to 60% of patients with high grade tumours die of metastatic disease within 5 years(1). Initially chemotherapy was used in patients with advanced metastatic disease. Prior to the use of adriamycin patients were treated with cyclophosphamide, actinomycin and vincristine. The response rate was less than 20%. Adriamycin alone yields an objective response rate of 25%(47). The dose intensity of adriamycin is important: a dose of at least 25 mg/m^2 must be given in order to obtain response rates exceeding 20%(3). DTIC alone gives a response rate of 17%(47,56).

Combinations of adriamycin and DTIC: In four nonrandomized studies by the South Western Oncology Group (SWOG), adriamycin plus DTIC (ADIC) resulted in significant improvement in overall survival compared with adriamycin alone(56). ADIC led to a 42% response rate(49). However in a randomized Eastern Cooperative Oncology Group (ECOG) study, ADIC enhanced the frequency of objective responses but did not influence survival(57). The addition of vincristine to ADIC did not improve the response rate or survival(48). In a nonrandomized trial CYVADIC (cyclophosphamide, vincristine, adriamycin, and DTIC) resulted in a major response rate of 47%(49). Ifosphamide is now being investigated with and without ADIC. Alone it

has shown a response rate of 20%. The combination of adriamycin, ifosphamide and DTIC has produced objective responses in 42% of patients(50).

Currently, an adriamycin based regime is considered to be the standard therapy for advanced unresectable soft tissue sarcomas. The addition of DTIC is controversial at present.

Adjuvant Chemotherapy

This is theoretically intended to eradicate micrometastases present at diagnosis. Compared with historical controls, early nonrandomized studies evaluating adjuvant chemotherapy were encouraging(3,5,51). However, in recent randomized trials, the survival of the observation arms has been better than historical controls. Therefore, randomized trials are necessary in order to evaluate whether adjuvant chemotherapy improves survival. A number of randomized trials comparing either adriamycin or combination chemotherapy with observation alone have been done.

Adriamycin vs Observation:

In a study of 77 patients, Gherlinzoni found that the addition of adriamycin resulted in significantly better disease free survival and overall survival (3 year disease free survival - 68% vs 42%, 3 year actuarial survival - 86% vs 68%)(5). However, randomized trials at MGH, ECOG, Intergroup Sarcoma Study Group (ISSG) and UCLA failed to

show a significant difference in disease free or overall survival(26,52).

Combination motherapy vs Observation

In a randomized trial from the MD Anderson, Lindberg et al compared adriamycin, vincristine and cyclophosphamide for 7 cycles followed by substitution of actinomycin for adriamycin for 18 months, with observation. Poorer disease free survival (76 vs 83%) and poorer overall survival were observed in the chemotherapy arm. This was possibly because there were more large high grade lesions in the chemotherapy arm(5).

At the NCI, in a study by Rosenberg et al, 67 patients with stage 2A to 4A extremity sarcomas were randomized to chemotherapy with adriamycin 50 to 70 mg/m^2, cyclophosphamide and high dose methotrexate or observation. At a median 7 year followup, disease free survival was better in the combination chemotherapy arm but overall survival was not significantly different(53).

A study at the Mayo Clinic randomized 61 patients with stage 1 to 4B disease to 8 alternating cycles of cyclophosphamide, vincristine, dactinomycin, and vincristine, adriamycin and DTIC or observation. At a median followup of 64 months, 88% of the chemotherapy treated patients remained disease free vs 67% of untreated patients (p=0.01). The five year overall survival was the same in both groups as a result of aggressive salvage

surgery(49,54). With longer followup, the metastasis free survival curves converged suggesting that chemotherapy delayed but did not prevent metastases. Local control was not significantly improved by chemotherapy. There was a 28% local recurrence rate possibly because radiotherapy was not used.

Toxicity

Adriamycin: In the ECOG study, no lethal or life-threatening toxicities were reported in the patients on the adriamycin arm. The most frequent reactions were alopecia, nausea and vomiting, and leukopenia. 24% of the patients experienced at least 1 severe reaction. There were no moderate or severe cardiac toxicities(55). In a trial at the NCI, 14% of the chemotherapy treated patients developed congestive cardiac failure(48). At a cumulative dose of 550 mg/m^2 about 11% of patients will develop congestive heart failure. 35% of patients will show a decrease in left ventricular ejection fraction(45).

DTIC: Toxicity includes nausea and vomiting, especially on the first day of chemotherapy(53). Other side effects include increased myelosuppresion when added to adriamycin and a rare flu-like syndrome.

CYVADIC: In a study using CYVADIC, toxicities included nausea and vomiting (85%), fever and neutropenia (22%), vincristine neuropathy (13%), pneumonia and septicaemia (9%), stomatitis (4%), and adriamycin cardiomyopathy (2%)(54).

In conclusion, adjuvant combination chemotherapy appears to increase disease free survival but not overall survival.

MANAGEMENT AND RESULTS OF PATIENTS TREATED AT THE SARCOMA CLINIC, HILLBROW HOSPITAL

In 1984 a multimodality soft tissue sarcoma clinic was established at the department of radiotherapy, Hillbrow Hospital. All new patients referred with the diagnosis of soft tissue sarcoma were assessed by surgeons, radiotherapists, pathologists and chemotherapists. The histology of each case was reviewed by an experienced pathologist who assessed the tumour type and grade, and the status of the resection margins. A full diagnostic workup was performed. This included:

1. History and physical examination.
2. X-ray of the involved area.
3. C.T. Scan or MRI scan of the involved area where indicated.
4. Chest x-ray and, in high grade lesions, C.T. scan of the chest
5. Full blood count, urea and electrolytes and liver function tests.

The patients were staged according to the G, T and N classification. G2 and G3 lesions were grouped together as high grade and included in stage 3. This report reviews the management of the 90 patients with soft tissue sarcomas of

the extremities who were seen at the combined clinic between 1984 and 1988. Patients with demonstrable distant metastases at the time of presentation were excluded.

The policies for the management of soft tissue sarcomas of the extremities were as follows:

Operable Lesions: Wide excision was recommended. If the lines of excision were involved by tumour, re-excision was advised if primary closure was possible. Thereafter, once the wounds had healed, low grade lesions greater than 5 cm in diameter and all high grade lesions received postoperative irradiation. A total dose of 60 to 66 Gy was given, depending on the status of the resection margins. 50 Gy was given to an initial wide volume, followed by a booster of 10 to 16 Gy. This was given at 2 Gy per fraction, 5 daily fractions per week. Radiation was administered by means of either megavoltage photon beams or a combination of photon and electron beams. Simulation and verification films were checked to ensure accurate placement of the fields prior to commencement of therapy. Immobilization casts were used to ensure daily setup reproducibility. All cases were reviewed regularly during treatment to check for untoward reactions. Patients with high grade lesions received adjuvant chemotherapy. 3 weekly cycles of adriamycin 60 mg/m^2 and DTIC 400 mg/m^2 were administered intravenously prior to commencement of radiotherapy. A further 3 courses were given after

completion of radiotherapy. The ejection fraction was determined prior to the commencement of chemotherapy. An ejection fraction of less than 50% was considered a contraindication to chemotherapy.

Inoperable Lesions

This group included those patients with lesions too large for excision with limb preservation. These patients received preoperative radiotherapy. Preoperative chemotherapy was added for high grade lesions.

Preoperative irradiation: Patients received 50 Gy at 2 Gy per fraction, 5 daily fractions per week, to the tumour with a 5 cm margin.

Preoperative chemotherapy: Patients received 3 courses of adriamycin 60 mg/m^2 and DTIC 400 mg/m^2 prior to radiotherapy.

The response was assessed after 6 weeks. Resectable lesions were excised and this was followed with postoperative radiotherapy. If the lesion was high grade, chemotherapy was added.

Postoperative irradiation: 16 Gy at 2 Gy per fraction, 5 daily fractions per week, was given to the tumour bed.

Postoperative chemotherapy: 3 courses of adriamycin and DTIC were given following the postoperative radiotherapy.

Followup

Patients were followed up 3 monthly during the first year post treatment, 4 monthly during the second year and then 6 monthly. Suspected recurrences were biopsied, and regular chest x-rays were performed. Survival curves were constructed using the Kaplan Meier method. The logrank test was used to identify independent variables predicting survival. Prognostic factors with statistical significance were those with p values of less than 0.05. p values were derived from the results of the chi-square statistic for each parameter.

RESULTS

90 patients treated between 1984 and 1988 were evaluated. Childhood rhabdomyosarcoma was excluded from the study. Table 1 summarizes the characteristics of these patients. 52 % of the patients were male and 48% female. The mean age was 44 years with a range of 5 to 79 years.

Tumour characteristics of the patients studied are shown in table 2. 60 (56%) of the tumours arose in the lower extremities, and 40 (44%) occurred in the upper extremities. 33 (37%) were low grade. Of these, 15 (45%) were less than 5cm in diameter, 9 (27%) were 5 - 10 cm and 6 (18%) were greater than 10 cm. The size was not recorded in 3 patients. 57 (63%) of patients had high grade lesions, of which 14 (25%) were less than 5 cm, 19 (33%) were 5 - 10 cm and 19 (33%) were greater than 10 cm in diameter. In 5 patients the size was not recorded.

The histological subtypes encountered in this review are listed in table 3. Malignant fibrous histiocytoma (MFH) was the commonest type (18,9% of cases), followed by malignant schwannoma, liposarcoma and leiomyosarcoma.

PATIENT CHARACTERISTICS

TOTAL NUMBER		90
SEX	MALES	47
	FEMALES	43
RACE	BLACK	49
	WHITE	39
	COLOURED	1
	ASIATIC	1
AGE	5 - 20	10
	20 - 30	17
	30 - 40	14
	40 - 50	10
	50 - 60	13
	60 - 70	15
	70 - 80	2
	MEAN AGE	44

TABLE 1

TUMOUR CHARACTERISTICS

		HIGH GRADE	LOW GRADE
TOTAL		57	33
SITE	UPPER ARM	7	3
	LOWER ARM	17	7
	UPPER LEG	25	11
	LOWER LEG	8	6
SIZE	< 5CM	14	15
	5 - 10 CM	19	9
	> 10 CM	19	6
	UNKNOWN	5	3
LYMPH NODES		3	0

TABLE 2

HISTOLOGICAL SUBTYPES AND GRADE

HISTOLOGY	NUMBER	PERCENTAGE	LOW GRADE	HIGH GRADE
MALIGNANT FIBROUS HISTIOCYTOMA	17	18,9	2	15
MALIGNANT SCHWANNOMA	15	16,7	1	14
LIPOSARCOMA	12	13,3	9	3
LEIOMYOSARCOMA	11	12,2	5	6
DERMATOFIBROSARCOMA PROTUBERANS	8	8,9	8	0
FIBROSARCOMA	7	7,8	4	3
SYNOVIAL SARCOMA	4	4,4	1	3
RHABDOMYOSARCOMA	2	2,2	0	2
EPITHELIOID SARCOMA	2	2,2	1	1
EXTRASKELETAL CHONDROSARCOMA	2	2,2	0	2
AGGRESSIVE FIBROMATOSIS	2	2,2	2	0
EXTRASKELETAL EWING'S	1	1,1	0	1
ALVEOLAR SOFT PART SARCOMA	1	1,1	0	1
MALIGNANT MESENCHYMOMA	1	1,1	0	1
UNCLASSIFIED	5	5,7	0	5
TOTAL	90	100	33	57

TABLE 3

Followup Data

The median followup of patients was 30 months with a mean of 33 months. 27 patients were lost to followup, 6 patients with disease and 21 patients with no evidence of disease. The patients lost to followup had a mean followup of 10 months. 4 patients died of intercurrent disease, 6 died with evidence of disease and 49 were alive with no evidence of disease at the end of the followup period. 4 were alive with disease, 2 with local recurrence, 1 with persistent local disease and 1 with persistent disease and metastases.

Overall Survival

The overall survival was 79% at 5 years, using the Kaplan Meier Curve . The overall survival for patients with low grade tumours was 93%, whereas the overall survival for patients with high grade lesions was 71% (see fig. 1).

Disease Free Survival

The disease free survival for the whole group was 61% at 5 years, 60% for low grade lesions and 54% for high grade lesions (see fig 2).

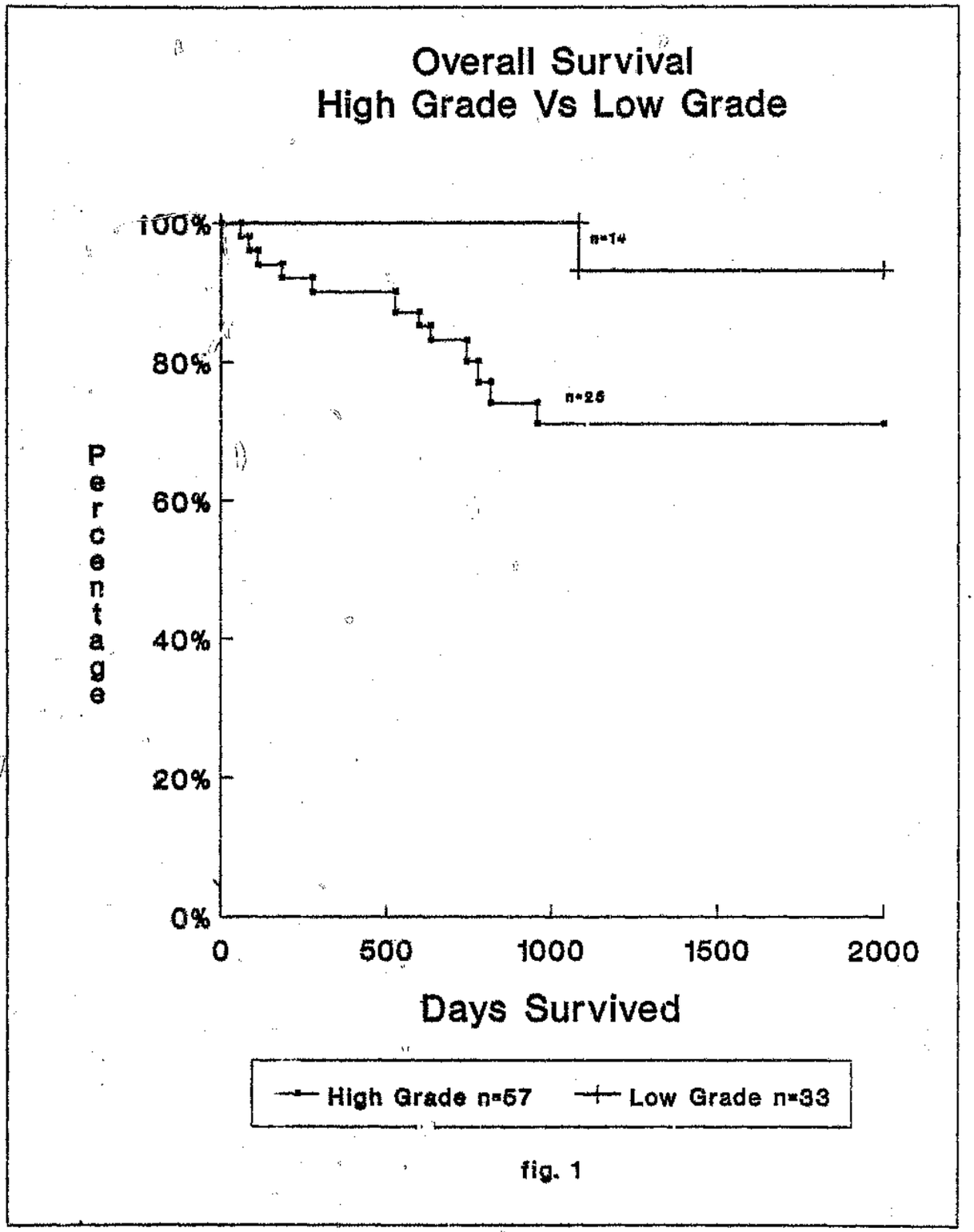

Overall Survival
High Grade Vs Low Grade
100%
80%
60%
40%
20%
0%
Percentage
n=14
n=26
0
500
1000
1500
2000
Days Survived
High Grade n=57
Low Grade n=33

fig. 1

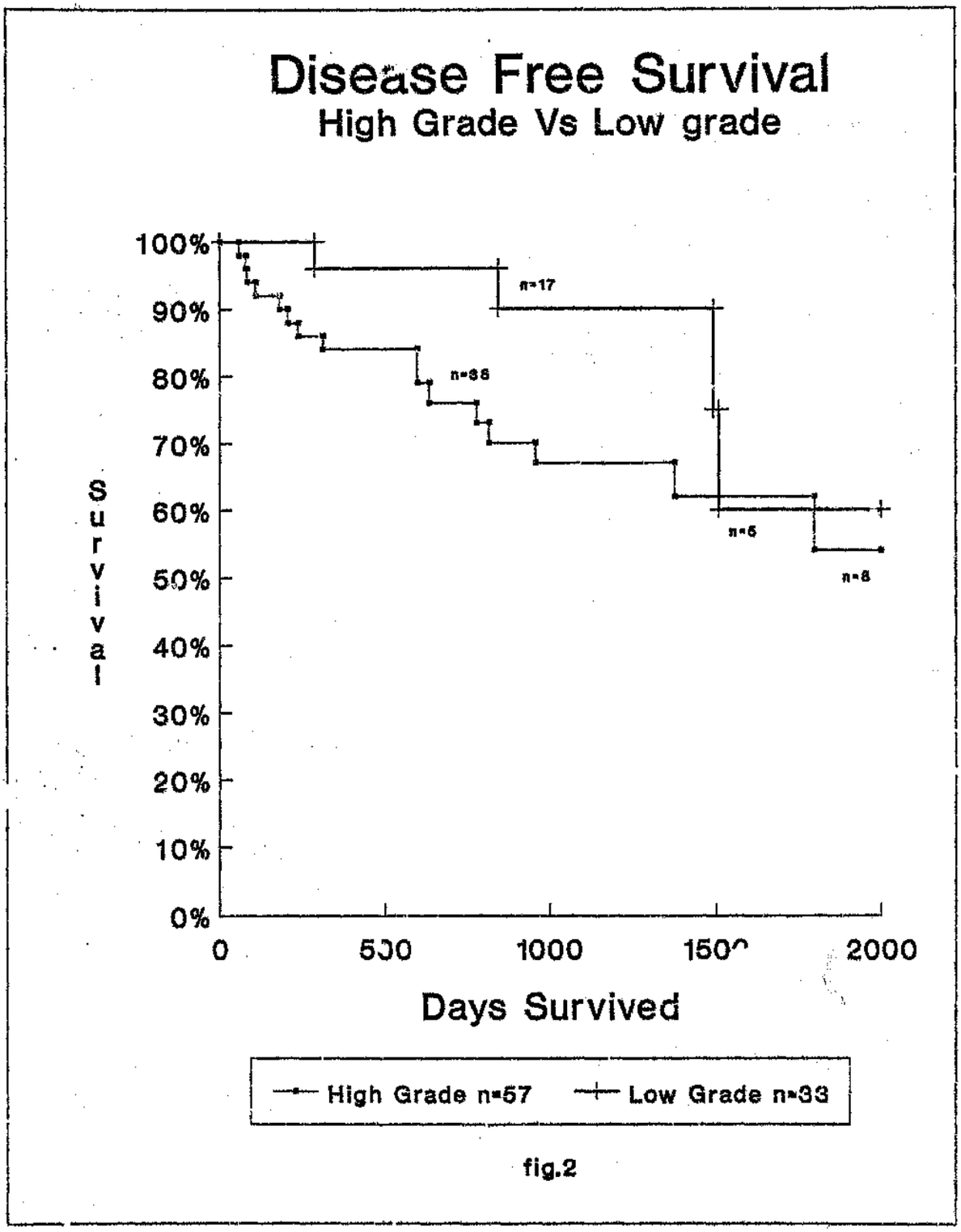

Disease Free Survival
High Grade Vs Low grade
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Survival
n=17
n=36
n=6
n=8
0
500
1000
1500
2000
Days Survived
High Grade n=57
Low Grade n=33

fig.2

Prognostic Factors

The disease free survival rates according to various variables are shown in table 4.

DISEASE FREE SURVIVAL RATES ACCORDING TO VARIABLES

VARIABLE	N	5 YEAR DISEASE FREE SURVIVAL(%)	p VALUE	SIGNIFICANCE
UPPER EXTREMITY	40	59	p< 0,5	NOT SIGNIFICANT
LOWER EXTREMITY	50	70		
AGE				
>50	37	61	p< 0,5	NOT SIGNIFICANT
<50	53	61		
SEX				
MALE	47	60	p< 0,5	NOT SIGNIFICANT
FEMALE	43	68		
SITE				
PROXIMAL	52	62	p< 0,9	NOT SIGNIFICANT
DISTAL	38	55		
SIZE				
< 5CM	30	75	p< 0,01	SIGNIFICANT
5-10CM	28	49	p< 0,05	NOT SIGNIFICANT
> 10CM	25	62		
GRADE				
HIGH	57	54	p< 0,5	NOT SIGNIFICANT
LOW	33	69		
NODES				
POSITIVE	3		p< 0,025	SIGNIFICANT
NEGATIVE	87			
INVASION	13	34	p< 0,5	NOT SIGNIFICANT
NO INVASION	77	64		
SKIN INV.	6		P< 0,5	NOT SIGNIFICANT
NO SKIN INV.	84			
MARGINS				
ADEQUATE	24	86	p< 0,5	NOT SIGNIFICANT
MARGINAL	58	60	p< 0,005	SIGNIFICANT
INADEQUATE	8	56		

TABLE 4

Upper vs Lower Extremity Since there was no survival difference ($p < 0,5$) between patients with upper and lower extremity tumours, the remainder of the analysis reflects the combined data from both groups.

Age There was no significant difference in disease free survival ($p < 0,5$), when comparing those older than 50 years to those younger than 50 years of age, either for high grade or low grade lesions.

Sex There was no significant difference in disease free survival between males and females ($p < 0,5$).

Site There was no survival difference between proximal and distal lesions ($p < 0,9$).

Size Patients with tumours less than 5 cm had a significantly better disease free survival compared to those with lesions greater than 5 cm ($p < 0,005$). However, there was no significant difference between those with tumours between 5 and 10 cm, and those greater than 10 cm ($p < 0,95$). Size did not appear to influence survival in low grade lesions whereas it did in those with high grade lesions (see fig 3).

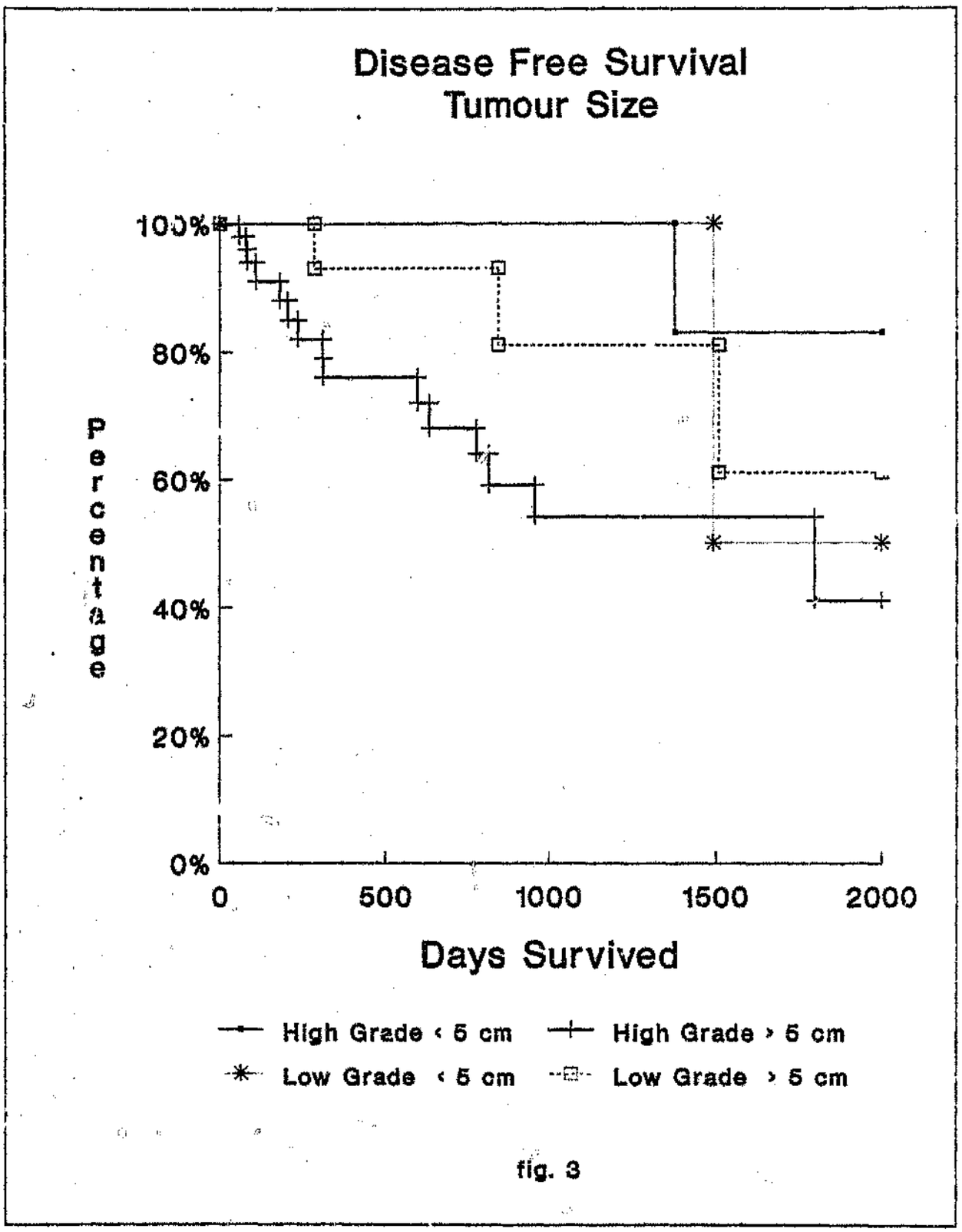

Disease Free Survival
Tumour Size
100%
80%
60%
40%
20%
0%
Percentage
0
500
1000
1500
2000
Days Survived
High Grade < 5 cm
High Grade > 5 cm
Low Grade < 5 cm
Low Grade > 5 cm

fig. 3

Grade There was no significant difference in disease free survival between low and high grade tumours ($p < 0,5$). However, overall survival was significantly better in low grade lesions compared to high grade lesions ($p < 0,025$). 8/57 patients with high grade lesions developed metastases as opposed to 1/33 with low grade lesions (see fig 2).

Nodal Involvement Only 3 patients (3,3%) had regional lymph node involvement. The histologies of these patients were spindle cell sarcoma, alveolar rhabdomyosarcoma and alveolar soft part sarcoma. One patient is still alive at 5 years, while the other 2 died with disease at 27 and 196 months.

Skin Involvement 6 patients had skin involvement at presentation. Of these, 4 had high grade tumours. Only one patient in this group developed local recurrence.

Local Invasion 10 patients had tumours associated with invasion of blood vessels, nerves or bone. 8 were high grade. 3 developed local recurrence and one developed metastatic disease. These patients had a 34% disease free survival at 5 years.

Surgery

Amputation: 4 patients had amputations. Of these 2 had lesions on the hand and underwent their surgery prior to their referral to Hillbrow Hospital. One midcalf amputation was performed for complications following local excision. Two of the patients who had amputations are alive with no evidence of disease, one patient developed a stump recurrence and one died of metastatic disease.

Surgical Margins: 6 patients had no surgery or incision biopsy only (5 high grade), 58 had microscopically incomplete excisions (35 high grade), 2 had macroscopically incomplete excisions (both high grade) and 20 had microscopically complete excisions (11 high grade). There was no significant decrease in disease free survival in patients with microscopically incomplete excisions compared with those with complete excisions ($p < 0,5$). Patients who had no excision or grossly inadequate excision had a very poor survival.

Chemotherapy

46 out of 57 patients with high grade tumours received chemotherapy. 4 patients were medically unfit to receive chemotherapy and 7 patients refused chemotherapy. There was no survival difference between those who received chemotherapy and those who did not ($p < 0,5$).

Radiotherapy 23 patients did not receive irradiation. 9 patients had stage 1A disease, 3 had amputations, 7 absconded and 3 received initial treatment elsewhere. In one patient, radiotherapy was withheld because the patient was very young. 3 patients received preoperative irradiation, 47 received postoperative irradiation and 6 received pre and post operative radiation. Two patients did not complete the prescribed course of radiation. The mean dose given was 59,91 Gy with a range of 18 Gy to 17,6 Gy. The treatment was given over a period ranging from 6 to 150 days, with a mean of 53 days.

COMPLICATIONS

Surgical Complications

Surgical complications included wound sepsis (5 patients) which caused a delay in wound healing. Most cases of postoperative sepsis were treated conservatively with antibiotics and dressings and responded well. Uncommon postoperative complications included oedema (2 patients), seroma (2 patients), limitation of movement due to scar formation (1 patient), nerve palsy (1 patients) and gangrene resulting in amputation (1 patient).

Radiotherapy Complications

Acute complications following radiotherapy included marked erythema (6 patients) and moist desquamation (8 patients) leading to a split in the course of radiotherapy. Late complications were uncommon and in general not severe. They included telangiectasia (4 patients), induration (8 patients), limb oedema (3 patients), fibrosis limiting limb flexion (1 patient), delayed healing of surgical wound (1 patient) and a skin ulcer which healed with conservative management. No patient required amputation as a result of a radiotherapy complication. The functional results were good and no patient developed a useless limb.

Chemotherapy Complications

The most frequent complications associated with chemotherapy were temporary alopecia, and nausea and vomiting. Other complications included leucopenia (WCC < 2,5 x 10^9/l) in 4 patients and, less commonly, thrombocytopenia (platelet count < 150000 x 10^9/l) in 1 patient. These complications led to a delay in administration of the next course of chemotherapy. One patient developed septicaemia due to leukopenia, which required hospital admission. One patient developed clinical cardiac complications following adriamycin. The total dose of adriamycin given to this patient was 510 mg. There were no deaths associated with chemotherapy.

RECURRENCES AND SALVAGE

Low Grade Sarcomas (see table 5)

6 (18%) patients developed local recurrences and 2 (6%) had persistent disease. All these patients had tumours greater than 5 cm in diameter. 6 patients underwent excision of the recurrences and 2 required amputation. 5/8 patients (62%) are alive without evidence of disease. One patient has persistent local disease and one died from lung metastases. One patient developed further local recurrences treated with reexcision and is at present free of diseuse. The five year disease free survival following recurrence is 38%, as shown in fig. 4.

High Grade Sarcomas

Local Recurrence: (see table 6) Of the 57 patients with high grade sarcomas, seven developed local recurrences, and five had persistent local disease. One tumour was less than 5 cm in diameter, while the rest were greater than 5 cm in diameter. Two patients with local recurrence had r lal disease at presentation.

Distant Metastases: (see table 7) 8 patients developed distant metastases, 4 associated with local recurrence. The mean time to development of metastases was 25 months. The most common site of metastases was to the lung (66%). All

patients with metastases had tumours greater than 5 cm. 5/8 patients died of metastastic disease, 2 were lost with metastatic disease and one is disease free at present, 3 months following axillary dissection for nodal metastases.

LOCAL RECURRENCE AND SALVAGE LOW GRADE TUMOURS

STAGE/SITE	INITIAL THERAPY	TIME TO RECURRENCE	TREATMENT OF RECURRENCE	STATUS	DAYS
1B THIGH	SURGERY	20	EXCISION	NED	67
1B UPPER ARM	SURGERY	76	EXCISION + 14 Gy	LOCAL PERS	139
1B THIGH	SURGERY RADIO	28	AMPUTATION	DOD	36
1B UPPER ARM	SURGERY	50	EXCISION + 60 Gy	NED	86
1B UPPER ARM	SURGERY RADIO	50	EXCISION + 60 Gy	NED	66
1B CALF	SURGERY RADIO	0	AMPUTATION	NED	17
1B CALF	SURGERY	10	EXCISION	ALIVE LOCAL RECUR	38
1B UPPER ARM	SURGERY RADIO	0	EXCISION	NED	99

NED:no evidence of disease; DOD:dead of disease

TABLE 5

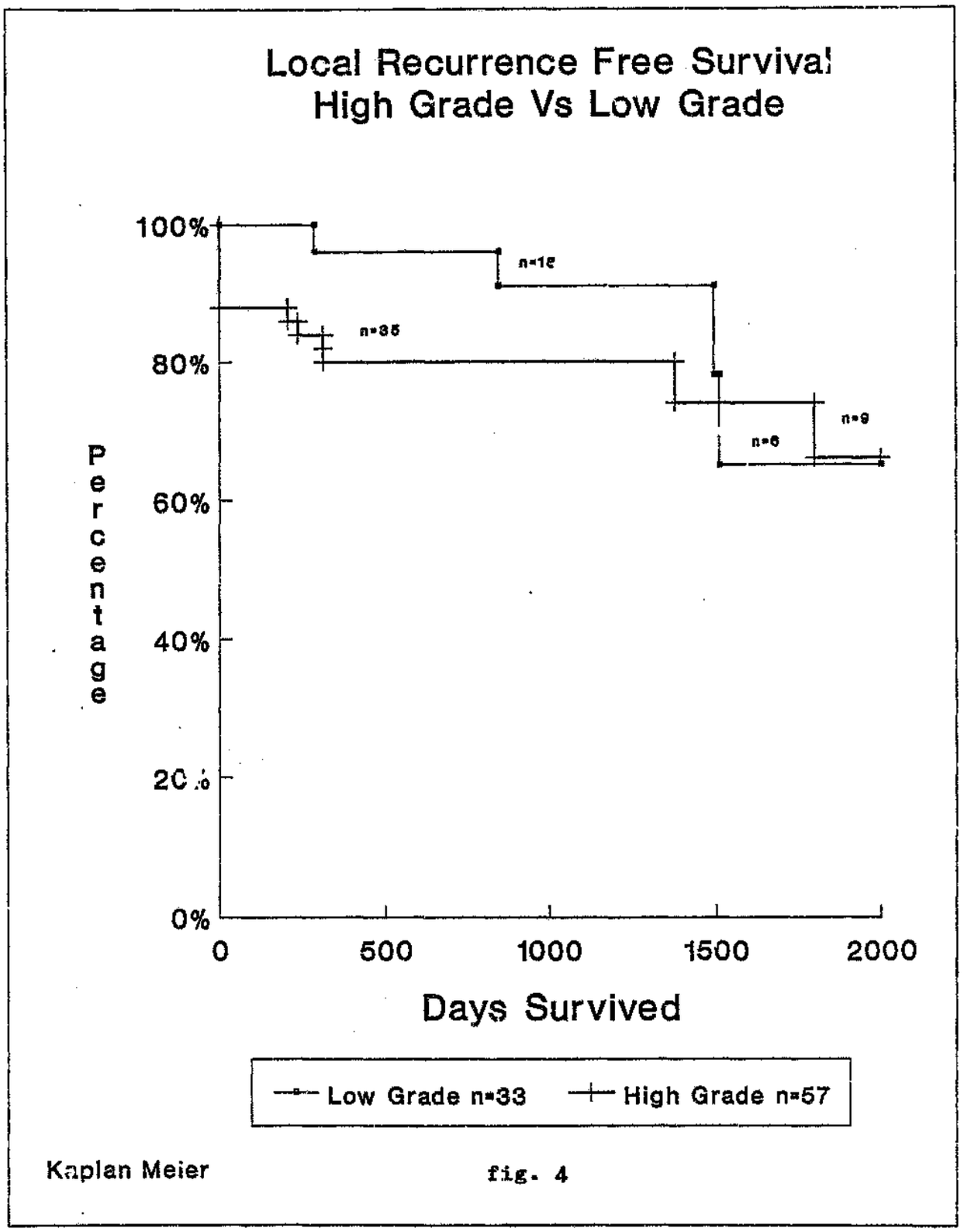

Local Recurrence Free Survival
High Grade Vs Low Grade
100%
80%
60%
40%
20%
0%
Percentage
n=16
n=35
n=9
n=6
0
500
1000
1500
2000
Days Survived
Low Grade n=33
High Grade n=57
Kaplan Meier

fig. 4

TABLE 6

LOCAL RECURRENCE AND SALVAGE
HIGH GRADE TUMOURS

STAGE/SITE	INITIAL CHEMO + RADIOTHERAPY	MONTHS TO METASTASIS	RECURRENCE SITE	TIME	TREATMENT OF RECURRENCE	STATUS	(MO)
3B THIGH	YES	0	LUNG	50	NONE	DOD	50
3B FOREARM	YES	58	NODE	77	EXCISION	NED	78
3B THIGH	NO	8	NONE		EXCISION RADIO CHEMO	NED	34
3B FOOT	YES	10	NONE		AMPUTATION	NED	42
3B ARM	NO	10	LUNG	22	RADIO CHEMO	LWD	24
3C FOREARM	YES	60	NONE		EXCISION CHEMO	NED	76
3B FOREARM	YES	0	LUNG	3	NONE	DOD	17
3A HAND	RADIOTHERAPY	46	NONE		EXCISION	AWD	53
3B THIGH	YES	0	NONE		NONE	LWD	6
3B THIGH	RADIOTHERAPY	0	NONE		NONE	LWD	3
3C FOREARM	YES	0	NODE	27	NONE	DOD	32
4A CALF	YES	7	NONE		EXCISION + RADIOTHERAPY	LWD	9

NED:no evidence of disease; DOD:dead of disease; LWD:lost with disease; AWD: alive with disease

TABLE 7

DISTANT METASTASES ONLY

HIGH GRADE

STAGE/SITE	INITIAL CHEMO RADIOTHERAPY	METASTASIS SITE	TIME	STATUS	(MO)
3B CALF	CHEMOTHERAPY AMPUTATION	LUNG	23	DOD	27
3B THIGH	YES	BONE	12	LWD	26
3A FOREARM	YES	LUNG/ BONE	19	DOD	21

DOD:dead of disease; LWD:lost with disease

DISCUSSION

The soft tissue sarcoma clinic was established with the following goals:

1. Review of all pathological specimens to determine type, grade, and adequacy of surgical excision of the tumours.
2. Emphasis on limb preservation where possible, with the addition of adjuvant radiotherapy in order to decrease local recurrence.
3. Adjuvant chemotherapy for patients with high grade lesions, in order to attempt to decrease the development of metastatic disease, and improve disease free and overall survival.

The data presented confirm the high level of efficacy of high dose irradiation combined with limited surgery in the treatment of soft tissue sarcomas of the extremities. The achievement of local control in 70/90 patients by this combinad modality approach compares with results reported from institutions where radical, often ablative, surgery was used. For example, the local control following radical surgery was 70% in 653 patients treated at The Memorial Hospital and 75% of those treated at the MD Anderson Hospital(27). At the Massachussets General Hospital, out of 250 patients treated with limb sparing surgery and radiation 23 developed local failure which compares with our results obtained using a similar approach.

Complications associated with combined surgery and radiotherapy were mild and reversible in most cases. There were no amputations as a result of radiotherapy complications, although one patient underwent amputation as a post surgical complication. This patient did not receive radiotherapy. The world literature reports a definite wound complication rate associated with the use of irradiation in clinical studies of combination therapy. A series of three hundred patients with extremity soft tissue sarcomas treated with postoperative external beam radiation had a major wound complication rate of 7%(10). Preoperative radiotherapy, in another series of patients with extremity soft tissue sarcomas, resulted in a 27% incidence of wound complications(42). The low incidence of complications in this study is probably attributable to the use of postoperative irradiation in most cases, thereby avoiding the potential problems with wound healing associated with preoperative irradiation. Thus, where the lesion is resectable, postoperative irradiation should be used. Preoperative irradiation is used mainly when resectability is doubtful.

Despite the improvement in local control rates, it has been reported that 40 to 60% of patients with high grade tumours die of metastatic disease within 5 years(21). In most series reported prior to 1982, 5 year survival was in the range of 40% for high grade lesions(8,10,17). Adjuvant chemotherapy has been used with the intention of

eradicating micrometastatic disease and thereby improving survival. Compared with historical controls, pilot studies evaluating adjuvant chemotherapy were encouraging. However, 6 out of 7 randomized trials comparing adriamycin to no adjuvant chemotherapy did not show an improvement in disease free or overall survival(26). The disease free survival varied from 50 to 80% in the observation arms, compared to 50 to 90% in the chemotherapy arms. Of the trials using multiagent chemotherapy, only the trials from the National Cancer Institute and the Mayo Clinic show an improvement in disease free survival. In randomized adjuvant trials using combination adriamycin based chemotherapy, the disease free survival varied from 28 to 67% in the observation arms, compared to 54 to 88% in the chemotherapy arms(26). The 63% 5 year disease free survival and 79% overall survival obtained in patients with high grade lesions in this study is better than in historical series, but compares with survivals recorded in recently reported randomized trials. The extent of the contribution of adjuvant chemotherapy to the good disease free and overall survivals obtained cannot be determined, as there was no control group. Further randomized trials are required to determine the efficacy of chemotherapy. The potential value of adjuvant chemotherapy must be weighed against the toxicity of these regimes.

Of the prognostic factors assessed, tumour size, resection margins, involvement of deeper structures and nodal involvement were found to be significant. In other studies

the above factors were also found to be important. Tumour size was shown to be important in a study by Suit et al where the disease free survival was 67% in lesions less than 5 cm, and 50% in lesions greater than 5 cm(25). Inadequate resection margins are associated with a lower disease free and overall survival, as shown by Collin et al(22). He found a 76% 5 year survival with adequate margins compared to a 52% survival with inadequate margins. He also found that invasion of blood vessels, nerve or bone, and nodal involvement were associated with a poorer prognosis. Although in our study there was no significant difference in disease free survival between low and high grade tumours, there was a significant difference in metastasis free and overall survival. The correlation between tumour grade and survival has been documented in several studies. In a report by Suit et al, the disease free survival was 80%, 51% and 17% for grade 1, 2 and 3 respectively(25). In a review from the Memorial Sloan Kettering Cancer Center, patients with low grade tumours had a 74% 5 year survival and those with high grade tumours had a 46% 5 year survival(22).

In this study tumours were divided into low or high grade only. Hajdu proposed that sarcomas be graded as either high or low grade to facilitate clinical assessment of tumour behaviour, and eliminate the confusion caused by the term "intermediate grade"(22). In a recent review, consensus in the grading of 90 soft tissue sarcomas using a 3 grade

system occurred in only 50% of cases, but in looking at low grade (gradel) vs high grade (grade 2 and 3), consensus occurred in 75% of cases(5). In a report from Costa et al from the National Cancer Institute, grade 1 tumours did significantly better than grade 2 and 3, but there was no significant difference in outcome between grade 2 and 3 lesions(11).

Age, sex, upper vs lower extremity were not found to be significant prognostic factors, which agrees with the findings of other studies(22). However, in studies at the Memorial Sloan Kettering and the Massachussetts General, older patients were found to have a poorer prognosis, possibly related to inadequate surgery(8,25).

Tumour location on the limb and presence or absence of skin involvement, which were not found to be significant prognostic factors in this study, have been reported to be important in a number of other studies(19,25). Suit et al found that 5% of distal lesions recurred locally, compared to 28% of thigh lesions and 48% of upper arm lesions(25). However, disease free survival did not relate to anatomic site, provided results for small and large lesions and for different histological grade were examined separately. Suit et al found that 8/9 patients whose tumour involved the skin developed distant metastases(25).

CONCLUSION

This review of patients treated by the combined soft tissue sarcoma clinic at Hillbrow Hospital demonstrates that with limb sparing surgery and adjuvant radiotherapy, good local control with preservation of limb function can be obtained in the majority of patients. Amputation should be reserved for those few patients with very advanced disease. The good survivals obtained, especially for high grade lesions, may be attributed to the use of adjuvant chemotherapy. However other factors may have played a role, such as improved primary treatment and optimal staging. The role of adjuvant chemotherapy should be evaluated in well designed randomized trials, with stratification according to important prognostic factors.

REFERENCES

1. Perez C.A. Brady L.W. Principles and Practice of Radiation Oncology 1987 JB Lippincott and Company

2. Suit H.D. Role of Radiotherapy in the Management of Patients with Sarcoma of Soft Tissue Refresher Course no 311 30th Annual Scientific Meeting ASTRA 1988

3. De Vita V.T., Hellman S., Rosenburg S.A. Cancer Principles and Practice of Oncology Second Edition JB Lippincott 1985 1243-1291

4. Cora L.R, Fazekas J.T., et al, Postirradiation Sarcoma of the Head and Neck Cancer 1980 47:1982-1985

5. Yarbro J.W. Sarcomas Seminars in Oncology 1989 Vol 16 no 4

6. Davidson T., Westberg G., et al Radiation Induced Soft Tissue Sarcomas Br J Surg 1986 73:308-309

7. Halperin E.C., Greenberg M.S., Suit H.D., Sarcoma of Bone and Soft Tissue following Treatment of Hodgkin's Disease Cancer 1984 53:232-236

8. Shiu M.H., Castro E.B., Hajdu S. Surgical Treatment of 297 Soft Tissue Sarcomas of the Lower Extremity Ann Surg 1975 182:597

9. Chang A.E., Matori Y.L., Dwyer A.G. et al Magnetic Resonance Imaging versus Computed Tomography in the Evaluation of Soft Tissue Sarcoma of the Extremities Ann Surg 1987 205:340-348

10. Lindberg A.D., Martin R.G., Romsdahl M.M. et al Conservative Surgery and Postoperative Irradiation in 300 Adults with Soft Tissue Sarcomas Cancer 1981 47:2391

11. Costa J, Wesley R.A., Glatstein E., Rosenberg S.A., The Grading of Soft Tissue Sarcomas - Results of a Clinicopathological Correlation in a Series of 163 Cases Cancer 1984 53:530-541

12. Mazeron J, Suit H.D. Lymph Nodes as Sights of Metastases from Sarcomas of Soft Tissue Cancer 1987 60:1800-1808

13. Potter D.A., Glenn J., Kinsella T. et al Patterns of Recurrence in Patients with High Grade Soft Tissue Sarcoma J Clin Oncol 1985 3:353

14. Scott S.M., Reiman H.M., Pritchard D.J., Soft Tissue Fibrosarcoma - A Clinicopathologic Study of 132 Cases Cancer 1989 64:925-931

15. Anderson W.A.D., Kissane J.M. Pathology 7th Edition 1977 The CV Mosby Company

16. Rubin P. Clinical Oncology - A Multidisciplinary Approach 6th Edition 1983.

17. Rosenberg S.A. et al The Treatment of Soft Tissue Sarcomas of the Extremities Ann Surg 1982 Sept 305-314

18. Eby C.S., Brennan M., Fine G. Lymphangiosarcoma: A Lethal Complication of Chronic Lymphoedema Arch Surg 1967 94:223-230

19. Lack E.E., Steinberg S.M., White D.E. et al Extremity Soft Tissue Sarcomas: Analysis and Prognostic Variables in 300 Cases, and Evaluation of Tumour Necrosis as a Factor in Statifying Higher-grade Sarcomas J Surg Oncol 1989 41:263-273

20. Sara A.S., Evan L., Malignant Melanoma of the Soft Parts (Clear Cell Sarcoma): A Study of 17 Case with Emphasis on Prognostic Factors Cancer 1990 65: 367-374

21. Russell W.O., Cohen J., Enziger F., et al A Clinical and Pathological Staging System for Soft Tissue Sarcomas Cancer 1977 40:1562-1517

22. Collin C., Goldbold J., Hajdu S., Brennan M., Localised Extremity Soft Tissue Sarcomas: An Analysis of Factors Affecting Survival J. Clin. Oncol. 5. 1987: 601-612

23. Stotter R.T., A'Hern R.P., Fischer C et al The Influence of Local Recurrence of Extremity Soft Tissue Sarcoma on Metastasis and Survival Cancer 1990 65:119-129

24. Ghavimi F., Mandell L.R., Heller G., Hajdu S.I. et al Prognosis in Childhood Rhabdomyosarcoma of the Extremity Cancer 1989 64:2233-2237

25. Suit H.D., Russell W.O., Martin R.G., Sarcoma of Soft Tissue: Clinical and Histopathologic Parameters and Response to Treatment Cancer 1975 35:1478-1483

26. Eilber F.R., Huth J.F., Mirra J., et al Progress in the Recognition and Treatment of Soft Tissue Sarcomas Cancer 1990 65:660-666

27. Cantin J., McNeer G.P., Chu F.C., et al The Problem of Local Recurrence after Treatment of Soft Tissue Sarcomas Ann Surg 1968 168:47-53

28. Enneking W.F., Spanier S.S., Malawer M.M., The Effect of the Anatomic Setting on the Results of Surgical Procedures for Soft Part Sarcomas of the Thigh Cancer 1981 47:1005-1022

29. Rooser B., Gustafson P., Rydholm A., Is there no Influence of Local Control on the Rate of Metastases in High Grade Soft Tissue Sarcomas? Cancer 1990 65:1727-1729

30. Collin C., Hajdu S., Goldbold J. et al Localised Operable Soft Tissue Sarcomas of the Lower Extremity Arch Surg 1986 121:1425-1423

31. Abbatucci J.S., Boulier N., De Ranieri J. et al Radiotherapy as an Integrated Part of the Treatment of Soft Tissue Sarcomas Radiotherapy and Oncology 1984 2:115-121

32. Putnam J.B., Roth J.A., Wesley M.N. et al Analysis of Prognostic Factors in Patients Undergoing Resection of Pulmonary Metastases From Soft Tissue Sarcomas J Thorac Cardiovasc Surg 1984 87:260-268

33. Eilber F.R., Morton D.L., Eckardt J. et al Limb Salvage for Skeletal and Soft Tissue Sarcomas: Multidisciplinary Preoperative Therapy Cancer 1984 53:2579-2584

34. Shiu M.H., Collin C., Hilaris B., et al Limb Preservation and Tumour Control in the Treatment of Popliteal and Antecubital Soft Tissue Sarcomas Cancer 1986 57:1632-1639

35. Shiu M.H., Turnbull A.D., Nori D. et al Control of Locally Advanced Extremity Soft Tissue Sarcomas by Function-saving Resection and Brachytherapy Cancer 1984 53:1385

36. Mills E.E.D., Hering E.R., Management of Soft Tissue Sarcomas by Limited Surgery Combined with Tumour Bed Irradiation using Brachytherapy and Supplemental Teletherapy British Journal of Radiology 1981 54:312-317

37. Ashby M.A., Ago C.T., Harmer C.L., Hypofractionated Radiotherapy for Sarcomas Int J Oncol Biol Phys 1986 12:13-17

38. Tepper J.E., Suit H.D., Radiation Therapy Alone for Sarcomas of Soft Tissue Cancer 1985 56:475-478

39. Pickering D.G., Stewart J.S., Rampling P et al Fast Neutron Therapy for Soft Tissue Sarcomas Int J Rad Oncol Biol Phys 1987 13:1489-1495

40. Cohen L., Hendrickson F., Mansell J., et al Response of Sarcomas of Bone and of Soft Tissue to Neutron Beam Therapy Int J. Rad. Oncol. Biol. Phys 1984 vol 10 821-824

41. Tepper J., Rosenberg S., Glatstein E., Radiation Therapy in Soft Tissue Sarcomas of the Extremity - Policies of Treatment at the NCI Int J Rad Oncol Biol Phys 1982 vol 8 263-273

42. Arbeit J.M., Hilaris B.S., Brennan M.F. Wound Complications in the Multimodality Treatment of Extremity and Superficial Truncal Sarcomas J Clin Oncol S 1987 480-488

43. Owen J.C., Shiu M.H., Smith R., Hajdu S.I. Soft Tissue Sarcomas of the Hand and Foot Cancer 1985 55:2010-2018

44. Kinsella T.J., Loeffler J.S., Fraass B.A. et al Extremity Preservation by Combined Modality Therapy in Sarcomas of the Hand and Foot: An Analysis of Local Control, Disease Free Survival and Functional Result Int J Rad Oncol Biol Phys 1983 9:1115-1119

45. Rosenberg S.A., Chang A.E., Glatstein E., et al The Treatment of Soft Tissue Sarcomas of the Extremities: Prospective Randomized Evaluations of 1. Limb Sparing Surgery plus Irradiation Compared with Amputation 2. The Role of Adjuvant Chemotherapy Ann Surg 1982 vol 96 no 1 306-317

46. Suit H.D., Mankin H.J., Wood W.C. et al Treatment of the Patient with Soft Tissue Sarcoma J Clin Oncol 1988 61:854-862

47. Gottlieb J., Combination Chemotherapy for Metastatic Sarcoma Cancer Chemother Rep 1974 58:265-270

48. Chang A., Kinsella T., Glatstein E. et al Adjuvant Chemotherapy for Patients with High Grade Soft Tissue Sarcoma of the Extremity J Clin Oncol 1988 vol 6 1791-1500

49. Edmonson J.H., Flemming T.R., Ivins J.C. Randomized Study of Systemic Chemotherapy Following Complete Excision of Non-osseous Sarcomas J Clin Oncol 1984 2:1390-1396

50. Budd G.T., Metch B., Balcerzak S.P., et al High Dose Cisplatin for Metastatic Soft Tissue Sarcoma Cancer 1990 65:866-869

51. Mills E.D.D, Adjuvant Chemotherapy of Adult High Grade Soft Tissue Sarcomas J Surg Oncol 1982 21:170-175

52. Elias D.A., Antman K.H., Adjuvant Chemotherapy for Soft Tissue Sarcomas: An Approach in Search of an Effective Regimen Seminars in Oncology 1989 vol 6 no 4: 305-311

53. Gottlieb J.A., Baker H., O'Ryan R.M. et al Adriamycin use Alone and in Combination for Soft Tissue Sarcomas and Bony Sarcomas Cancer Chemother Rep 1975 part 3 6:271-282

54. Yap B.S., Baker L.H., Sinkovics J.V. et al Cyclophosphamide, Vincristine, Adriamycin and DTIC (Cyvadic) Combination Chemotherapy for the Treatment of Advanced Sarcomas Cancer Treat Rep 1980 64:93-98

55. Lerner H.J., Amato D.A. et al ECOG: A Comparison of Adjuvant Doxorubicin and Observation for Patients with Localised Soft Tissue Sarcomas J Clin Oncol 1987 vol 5 no 4 813-617

56. Gottlieb J.A., Benjamin R.S., Baker L.H. et al The Role of DTIC in the Chemotherapy of Sarcomas Cancer Treat Rep 1976 60:199-203

57. Borden P.C., Amato D.A., et al Randomized Comparison of Three Adriamycin Regimens for Metastatic Soft Tissue Sarcoma J Clin Oncol S 1987 5:840-850

59. De Paula U., Suit H.D., Harmon D., Adjuvant Chemotherapy in Clinical Stage M^0 Sarcoma of Soft Tissue Cancer 1988 62:1907-1911

60. Ozella L., Stout A.P., Murray M.R. Cultural Characteristics of Malignant Histiocytomas and Fibrous Xanthomas Cancer 1963 vol.16: 331

61. Baker L.H., Frank J., Fine G. et al Combination Chemotherapy using Adriamycin, DTIC, Cyclophosphamide and ACTD for Advanced Soft Tissue Sarcomas: A Randomized Comparative Trial J Clin Oncol 1987 5:851-861

62. Gherlinzoni F., Bacci G., Picci P. et al A Randomised Trial for the Treatment of High Grade Soft Tissue Sarcomas of the Extremities: Preliminary Observations J Clin Oncol 1986 4:552-558

Author: Krawitz H.E
Name of thesis: A multimodality approach to the management of soft tissue sarcomas of the extremities with emphasis on limb preservation

PUBLISHER:
University of the Witwatersrand, Johannesburg
©2015

LEGALNOTICES:

Copyright Notice: All materials on the University of the Witwatersrand, Johannesburg Library website are protected by South African copyright law and may not be distributed, transmitted, displayed or otherwise published in any format, without the prior written permission of the copyright owner.

Disclaimer and Terms of Use: Provided that you maintain all copyright and other notices contained therein, you may download material (one machine readable copy and one print copy per page)for your personal and/or educational non-commercial use only.

The University of the Witwatersrand, Johannesburg, is not responsible for any errors or omissions and excludes any and all liability for any errors in or omissions from the information on the Library website.