DECLARATION

This is dissertation is my original work and has not been submitted for a degree in any other university.

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DEDICATION

In memory of my late my father, Philip Motanya for his support and encouragement throughout my studies, but who passed on before I completed the programme.

This dissertation is also dedicated to those patients with soft tissue sarcomas who participated in my study.

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TABLES AND FIGURES

LIST OF ABBREVIATIONS

1. AIDS=Acquired Immune Deficiency Syndrome
2. AJCC = American Joint Committee on cancer
3. Cm= Centimetres
4. CT scan = Computed Tomography (Imaging) Scan
5. CTX = Chemotherapy
6. DFSP= Dermatofibrosarcoma protuberans
7. EBV=Ebstein Barr Virus
8. FFCC=French Federation of Cancer Centres
9. FNAC= Fine Needle Aspiration for Cytology
10. FS= Fibrosarcoma.
11. GIST=Gastrointestinal Stromal Tumour
12. Gy = Gray
13. HIV=Human Immunodeficiency Virus
14. ICU= Intensive Care Unit
15. K Sh= Kenya Shillings
16. KNH= Kenyatta National Hospital
17. KS=Kaposi's sarcoma
18. LMS= Leiomyosarcoma.
19. LS= Liposarcoma.
20. MRI = Magnetic Resonance Imaging
21. MSKCC= Memorial Sloan-Kettering Cancer Center.
22. NF=Neurofibromatosis
23. NFS= Neurofibrosarcoma.
24. RMS= Rhabdomyosarcoma.
25. Rx = Treatment
26. SPSS = Statistical Programme for Social Scientists
27. STS = Soft Tissue Sarcoma
28. UICC = International Union against Cancer

29. US= Ultrasound [scan]

30. XRT= Radiotherapy

ABSTRACT

Background

Soft tissues sarcomas are the most frequent sarcomas. They represent a rare group of solid mesenchymal tumours with high rates of morbidity and mortality that are influenced by patient, tumour, and treatment factors.. Large series report recurrence rates of between 20-25 %, usually within 2-3 years after surgical treatment. In Africa, many of the patients present late, and have to travel long distances to treatment centres. Access to adjuvant therapy is not guaranteed either. Consequently, the patterns and rates of recurrences may differ from quoted literature.

Purpose/aim of study

To determine the pattern and factors associated with recurrence in patients treated surgically for soft tissue sarcomas at the Kenyatta National Hospital.

Study design

A five and a half years retrospective study between January 2003 and June 2007 and a six months prospective follow-up arm between July 2008 and March 2009.

Patient and methods

Retrospectively, as well as prospectively collected data from a population of patients selected from all those surgically treated at the Kenyatta National Hospital, between January 2003 and March 2009, for soft tissue sarcomas were reviewed. Primary data included demographic variables (age and sex), clinical variables (duration of symptoms, anatomical distribution, radiological tests undertaken, adjuvant therapy given) and pathological variables (tumour type, size, grade stage and surgical margins status). The outcome variables were tumour recurrence and death.

The variables that were studied to determine a relationship with recurrence were: patient age, tumour site, grade, histological type, microscopic involvement of surgical

margins by tumour and whether or not adjuvant chemotherapy and / or radiotherapy were instituted.

Data Analysis

Univariate analyses were used to determine the influence of each variable on the outcome. $P<0.05$ was considered significant.

Results

Mean age was 32.52±18.17 years. The age group distribution was bimodal with peaks at 10-19 years and 40-49 years. The male/ female sex ratio was 0.97:1. The mean duration of symptoms was 110.87±18.75 months. The extremities had the most number of cases (62%). Fibrosarcoma was the most common histological type (36.0%) and the mean tumour size was 13.0 ±7.36 cm. Most (44.7%) patients presented with high grade tumours and 78.0 % of the patients presented with a recurrence. Most of the recurrences (71.7%) occurred within the first year of treatment.

Failure to get adjuvant therapy ($p<0.001$), tumour size >5cm ($p=0.02$), advanced stage (III and IV) ($p<0.001$), and positive microscopic margins ($p<0.001$) were adverse prognostic factors for getting a recurrence. Presentation with a recurrent tumour ($p<0.027$), failure to receive adjuvant therapy ($p<0.001$), advanced stages (III and IV) ($p<0.001$), positive microscopic margins ($p<0.001$), and high grade tumours ($p<0.001$), were all adverse prognostic factors for death. Patients who underwent wide, radical excisions or amputations were less likely to die than those who underwent intra-lesional or marginal excisions ($p=0.05$). For patients who received adjuvant therapy, chemotherapy, compared to radiotherapy, was an adverse factor for death ($p=0.003$). Intralesional and marginal excisions, versus amputations/wide or radical excisions ($p=0.05$) and distant recurrence in the lungs/chest were also adverse factors for death ($p=0.001$).

Conclusions

Advanced stages of soft tissue sarcomas, higher histological grades, positive microscopic surgical margins, and failure to receive adjuvant treatment influenced both recurrence and mortality after surgical treatment. In addition a tumour > 5cm was a negative prognostic factor for recurrence, while presentation with a primary recurrent tumour and intralesional or marginal tumour excisions were negative prognostic factors for death. Better outcome results from surgical treatment of soft tissue sarcomas may be achieved if efforts to treat them earlier were to be a reality.

INTRODUCTION

Soft tissues sarcomas are the most frequent sarcomas. [1] They are an uncommon, biologically and histologically heterogeneous group of malignant tumours of mesenchymal origin.[2] They comprise about 1-3 % in adults [3] and 12-15 % in children [4], of all malignant tumours. Their tissue of origin may be muscle (rhabdomyosarcoma), fat (liposarcoma), and fibrous tissue (fibrosarcoma). Other tissues of origin include blood vessels (angiosarcoma), lymphatic vessels (lymphangiosarcoma) and skin fibrous tissue (dermatofibrosarcoma). More than 50 different histological subtypes of soft tissue sarcoma have been identified. [1]

In 2002, approximately 8300 new cases of soft tissue tumours were expected to occur in the United States, with 3900 deaths, underscoring the relatively high overall mortality associated with this malignancy. [3] The commonest areas of distribution in the body are the extremities (upper and lower limbs) and the intra-abdominal and retroperitoneal regions. The head and neck is the least involved region. [5, 6]

The diagnosis may be established using a combination of radiological and histological investigations. The radiological tests carried out to obtain a diagnosis may include plain radiographs, ultrasound scans, computed tomography (CT) scans or magnetic resonance imaging (MRI) scans. Depending on the type of radiological test done, tumour site, size, extent or the presence of calcification may be defined. In some cases, the radiologist may describe the probable tissue of origin from the radiological appearance of the tumour. [7, 8]

A tissue diagnosis may be obtained from fine needle aspiration for cytology (FNAC), incisional or excisional biopsy. The clinical picture will usually dictate the type of investigation chosen. The tumour grade may then be determined from histopathological examination of the specimen.[9, 10, 11] Treatment is usually surgical. Radiotherapy is often given in addition to surgery.[12] In some situations, especially palliation, radiotherapy may be given as the only mode of treatment. In other instances, radiotherapy, chemotherapy or

both may be administered pre-surgically to shrink the tumour. [12] Except for rhabdomyosarcomas and Ewing's sarcomas, the use of adjuvant chemotherapy generally does little to influence the natural history of the disease. [13]

Most adequately treated soft tissue sarcomas will result in a cure.[14, 15, 16] However, patients treated may end up with recurrences, necessitating re-treatment. A recurrence may even result in death. Most large series report recurrence rates of between 20 and 25 %, usually 2-3 years after the primary treatment and two thirds of recurrences develop within 2 years of primary treatment. [17] In Africa, patients with soft tissue sarcomas present late and have to travel long distances to treatment centres. Many do not benefit from radiotherapy and chemotherapy after the surgical procedure due to inadequate resources. As such recurrence rates may be much higher than the reported rates. [18] Several other factors that may influence recurrence after treatment, include the age of the patient, the primary tumour site and size, the histological cell type, grade and the tumour resection margins. [17]

In Africa, only a few descriptive studies on soft tissue sarcomas have been published. Adigun *et al.*(2007) examined the pattern, distribution and management dilemma in 209 black African patients with soft tissue sarcomas (STS) in a tertiary health institution in Nigeria, between 1985 and 2004. [18] Buhari *et al* (2009) undertook a retrospective descriptive study of the histological pattern, age, sex and behaviour of soft tissue sarcomas of the head and neck at the University of Ilorin Teaching Hospital in Nigeria, between 1985 and 2006. Here again, no outcomes were evaluated. [6]

There are no published studies that have analyzed the relationship between various patient, tumour and treatment variables and recurrence, survival or death after treatment. The current study evaluated the recurrence pattern in relation to the tumour, patient and treatment variables at the Kenyatta National Hospital in Nairobi.

LITERATURE REVIEW

Demographic and Aetiological Characteristics

Soft-tissue sarcomas account for only about 1 percent of all adult cancers and about 15 % of all paediatric malignancies.[3] Approximately 8700 new cases of soft-tissue sarcoma are diagnosed each year in the United States (US) [3] and about 1500 in the United Kingdom. The mortality rate in the US is about 50%. In Kenya, no studies have been undertaken to establish the incidence. The relative frequency and response of each sub- type varies according to age. For example, soft-tissue sarcomas in children, particularly rhabdomyosarcomas, more often respond to chemotherapy than do those in adults.[20] The overall incidence of soft-tissue sarcoma has been increasing,[15] perhaps as a result of the increase in Kaposi's sarcoma, which is often associated with the acquired immunodeficiency syndrome (AIDS), [21,22] as well as improved recognition and diagnosis.

Most soft-tissue sarcomas are sporadic; few have an identifiable cause. There is an association between certain viral infections (notably Epstein Barr virus in those with AIDS) and leiomyosarcoma.[23]

Sarcoma may develop 3 to 15 years after therapeutic irradiation for lymphoma, cervical cancer, testicular tumour, or breast cancer.[24] The risk of the STS developing is dose dependent. The risk of postradiotherapy sarcomas therefore appears to augment with increasing dosage. However the benefits of radiotherapy in such circumstances outweigh the minimally increased risk of sarcoma. [25, 26.]

Chronic lymphoedema-associated angiosarcoma (Stewart-Treves syndrome) usually occurs as a rare complication of treatment for breast cancer. Typically, the angiosarcomas develop in women who have undergone radical mastectomy for breast carcinoma and have had chronic lymphoedema for many years. Angiosarcomas may also develop in the

legs of patients as a consequence of radical inguinal lymphadenectomy for metastases from malignant melanoma (Kettles syndrome).[26]

Chronic lymphoedema occurring on a congenital, idiopathic, traumatic, or infectious basis also predisposes to angiosarcoma. The rationale for this association is the status of immunologic privilege of a lymphoedematous region. [26]

Tumour suppressor genes play a critical role in cell growth inhibition and can suppress the growth of cancer cells. However, these genes can be inactivated by hereditary or sporadic mechanisms and some genetic disorders have been associated with soft-tissue sarcomas. [5] For example, neurofibromatosis type 1, resulting from disruption in the function of the *NF1* tumour suppressor gene, carries a 10 per- cent lifetime risk of malignant tumours of the peripheral-nerve sheath. [27] Children with hereditary retinoblastoma (owing to a germ-line mutation in the *Rb1* tumour-suppressor gene) face an exceptionally high risk of osteosarcoma and soft-tissue sarcomas, which is further increased by the receipt of radiotherapy.[28] Sarcoma has also been reported in patients with the Li-Fraumeni syndrome, which is caused by a germ-line mutation in the *p53* tumour- suppressor gene. [5, 29, 30.]

Clinical and radiological features

The clinical symptoms accompanying the diagnosis of soft-tissue sarcoma are non-specific. The most common finding at presentation is a painless, gradually enlarging mass. The size of the tumour at diagnosis varies according to the site; tumours of the distal limbs and head or neck are usually smaller because they are likely to be noticed earlier, whereas tumours of the thigh and retroperitoneum may become huge before they are detected.[1, 5] Soft-tissue sarcomas expand in a spherical fashion but infiltrate the tumour pseudocapsule and, occasionally, adjacent structures. Accordingly, patients with these tumours may present with site-dependent symptoms of increased pressure, such as paraesthesia, distal oedema, or bladder symptoms.[13]

Pre-treatment radiological imaging is critical for defining the local extent of a tumour, staging the disease, guiding biopsies, and aiding in diagnosis. Imaging studies are also crucial in monitoring tumour changes after treatment, especially after preoperative chemotherapy or radiation therapy, and in detecting recurrences after surgical resection. Each imaging modality, however, has a particular place in patients with soft tissue sarcomas. [5]

Plain radiographs may be used to rule out bone neoplasms and detect calcifications characteristic of soft tissue osteosarcomas or synovial sarcomas. [13] In most cases however, they are not useful for evaluating soft tissue tumours of the extremities.

A chest radiograph is essential in patients with primary sarcoma to look for lung metastases although preoperative computed tomography (CT) of the thorax is preferable for detecting metastases. [5] Computed Tomography (CT) and magnetic resonance imaging (MRI) scans are used to image the primary tumour; neither offers an overall advantage. CT is usually performed to identify intra-abdominal tumours, such as liposarcoma, the most common retroperitoneal tumour. The multiplanar images and better anatomical definition possible with the use of MRI are its key advantages and this approach is preferred for the diagnosis of soft-tissue sarcoma of the limbs. Advances in these two approaches now permit faster acquisition of images and better spatial resolution. [8]

Pathology

With few exceptions, histological examination of a tumour specimen is required before treatment is initiated. A biopsy is preferred for the diagnosis and grading of soft tissue sarcomas, and should be performed by an experienced surgeon or radiologist. The biopsy can be accomplished by core needle or open incisional techniques. An endoscopic or needle biopsy may be indicated for deep thoracic, abdominal or pelvic sarcomas. [1]

Percutaneous core needle biopsy is safe and effective [10, 11] and can be performed with the use of local anaesthesia, on an outpatient basis, for palpable tumours of the upper and

lower limbs. The biopsy site should be chosen so that it will lie within the area of a possible subsequent en bloc resection of the tumour. The subtype and grade of the tumour can be determined in 80 percent of core needle biopsies, [10, 11] and pathologists experienced in examining soft tissue sarcomas have a diagnostic accuracy of 95 to 99 percent. [13, 5]

An open incisional biopsy requires at least a day-case admission and often a general anaesthetic. The disadvantages of incisional biopsy are that the scar may be inappropriately placed with reference to the incision required for wide surgical clearance.[4]

Incisional biopsies have a higher rate of complications than core needle biopsies and thus should be performed only in exceptional circumstances, ideally by the surgeon planning the definitive resection. If the incision is done in a cosmetically pleasing transverse skin crease incision, it will make it very difficult to make an appropriate longitudinal incision for a wide or compartmental resection. [5] Furthermore, the incision may be placed over the dome of the tumour where skin vascularity is most likely to be impaired and consequently the incision may fail to heal or become infected .[9] Subsequent tumour fungation through the wound from the incision biopsy may occur. Even though the biopsy is not a technically challenging procedure, the surgeon should adhere to certain guidelines (**APPENDIX 2).**

Fine-needle aspiration biopsy is an acceptable method for the diagnosis of most soft tissue sarcomas, particularly when it is performed in conjunction with clinical and imaging studies. If tumour grading is essential for treatment planning, fine-needle aspiration biopsy has limitations.[5] If the cytologic findings and interpretations are not consistent with the clinical and radiographic findings and a malignancy is suspected, then open biopsy or core needle biopsy is indicated. [31] In the setting of an adequate fine needle aspiration specimen, approximately 86% of soft-tissue sarcomas can be correctly identified as sarcomas, and approximately 54% can be properly classified into their

histological subtype. [31] Cytological analyses of fine-needle aspirates alone can be used to diagnose recurrent tumour or nodal metastases. [32]

If imaging suggests a retroperitoneal tumour, biopsy should not be performed, given the potential for transperitoneal spread and track implantation.[33] A biopsy should be considered if a gastro-intestinal stromal tumour (GIST) is suspected on radiological grounds, [34] if metastatic disease is suspected, or if the tumour is unresectable.

Pathologists with sarcoma expertise should review pathology assessment of biopsies and resected specimens, especially for initial histopathological classification. Margins must be thoroughly evaluated in these specimens. Because identification of the histopathological type of a sarcoma is often difficult, pathologists should have access to optimal cytogenetic and molecular diagnostic techniques. Molecular and cytogenetic analysis can be useful for establishing the diagnosis of synovial sarcoma, clear cell sarcoma, GIST and liposarcoma. [1] The World Health Organization (WHO) [35] has defined approximately 50 tumour subtypes relevant to soft-tissue sarcomas; these are named largely according to the tissue they most closely resemble.

Staging

Two staging systems are available — the Musculoskeletal Tumour Society (MSTS) or Enneking staging system and the American Joint Commission on Cancer (AJCC) grade, tumour, nodes, metastases (GTNM) staging system. Both of these systems define the extent and severity of the tumour. The MSTS system [36] is based on three components, including the grade of the tumour (G1 is low-grade, G2 is high-grade), the anatomic location (T1 is within a compartment, T2 is extracompartmental), and absence (M0) or presence (M1) of metastases.

The definition of "a compartment" is a central and crucial concept related to the Enneking staging system. In general, a compartment may be defined as any clearly identified fascially enclosed space (e.g. the anterior compartment of the lower leg). Many of these

compartments are the same ones that a surgeon would release in the setting of compartment syndrome. [37]

The tumours are thus defined as stage IA (G1,T1, M0) or stage IB (G1,T2, M0) or stage IIA (G2,T1, M0) or stage IIB (G2,T2, M0). Stage III (any G, any T, and M1) indicates the presence of a metastatic focus.

The second protocol for staging is the GTNM system, which is described by the American Joint Commission on Cancer and the International Union against Cancer (UICC) [34] This system requires the grade (G1, G2, G3 or G4), the size and depth of the primary tumour (less than 5 cm in greatest diameter is T1 and greater than 5 cm in diameter is T2, superficial tumour –a and deep tumour -b), and the absence or presence of regional lymph node involvement (N0 or N1) or distant metastases (M0 or M1). Stage IA is G1,2, T1, N0, M0, stage IB is G1,2, T2a, N0, M0, stage IIA is G1,2, T2b, N0, M0, stage IIB is G3,4, T1, N0, M0, stage IIC is G3,4, T2a, N0, M0 stage III is G3,4, T2b,N0, M0, stage IV is any G, any T, N1 and/or M1. (See details in APPENDIX 3)

The three-step grading system was devised by the French Federation of Cancer Centres (FFCC) Sarcoma Group [38], is widely used and takes into account the degree of differentiation, the mitotic count, and the extent of necrosis. Four- step grading systems are also in use. [34] The staging system devised by the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC) [34] combines the most important determinants of survival in localized soft-tissue sarcomas of the limbs: the grade, depth, and size of the tumour. For the purposes of this study, the AJCC/UICC staging system was used.

Large series confirm that grade and size are of similar prognostic importance. [39, 40] Five-year survival rates for stages I, II, III, and IV are approximately 90, 70, 50, and 10 to 20 percent, respectively, and are further modified by the type and site of the tumour and other factors.[17] For retroperitoneal tumours, a method based on grade, the completeness of resection, and the presence or absence of metastases can be used to identify groups

with different outcomes. [41] For localized gastrointestinal stromal tumours (GIST), relevant risk factors include tumour size and mitotic count. [42]

Treatment

Surgery is the standard primary treatment for most soft tissue sarcomas. Surgery, supplemented when necessary by adjuvant radiotherapy is often curative for localized soft-tissue sarcomas. Treatment is best planned in a multidisciplinary setting, which facilitates consideration of the need for pre- operative induction treatment, discussion of reconstructive strategies, and planning for rehabilitation. Although local treatment of primary soft-tissue sarcoma of the limbs influences the likelihood of local recurrence, the metastatic potential is mainly determined by the grade and size of the primary tumour. [13, 43] There is little evidence that local recurrence increases the likelihood of metastatic spread. [40, 44] Except for rhabdomyosarcomas and Ewing's sarcomas, the use of adjuvant chemotherapy generally does little to influence the natural history of the disease. [13]

Surgery

The type of surgical resection is determined by several factors, including tumour location, tumour size, the depth of invasion, the involvement of nearby structures, the need for skin grafting or autogenous tissue reconstruction, and the patient's performance status. Local therapy consisting of surgery, either alone or in combination with radiation therapy when wide pathologic margins are limited by anatomic constraints, is the approach taken in patients with small (less than 5 cm) primary tumours with no evidence of distant metastatic disease. Wide local excision is the primary treatment strategy for extremity sarcomas, with the goal to resect the tumour with a 2-3 cm margin of surrounding normal soft tissue. The biopsy site or tract (if applicable) should also be included en bloc with the resected specimen. [13]

Approximately one third of patients with a low- or intermediate-grade tumour and wide resection margins will not require further treatment (including radiotherapy). It is rarely necessary to reconstruct major vessels or to resect major nerves unless they are encased

by tumour. However, resection of some major nerves generally results in surprisingly little disability; therefore, resection should be considered if amputation is the alternative.[45] If it is safe from an oncological perspective, then preserving one innervated muscle in any compartment results in better function than a more radical approach. [46] Although tumours are usually smaller in the distal limbs than in the proximal limbs, it is more difficult to preserve function in the distal limbs, especially the forearms and hands. Preoperative induction treatment may reduce the size of tumours of distal limbs and facilitate better functional results. [13]

Amputation is ultimately required in 5 to 10 per- cent of patients with sarcoma of the limbs, usually after previous limb-salvage operations. [47] In such cases, major amputations (forequarter, hindquarter, or through-hip amputation) are often necessary, because recurrences are generally proximal. [48] Other indications for amputation include patient preference or if the tumour has the following characteristics: extensive soft tissue mass and/or skin involvement, major arterial or nerve involvement, extensive bony involvement that requires whole bone resection, failure of preoperative therapy or recurrence following prior adjuvant radiation.[1]

Surgery is also the mainstay of treatment for soft tissue sarcomas of the retroperitoneum (15 percent of soft-tissue sarcomas). En bloc resection of adjacent viscera is frequently required, but complete tumour resection (with negative histological margins) is difficult, owing to the proximity of vital structures. Retroperitoneal sarcoma remains an insidious disease, with a generally inexorable course. Most of these tumours will recur, eventually causing death, underscoring the need for better control. [50, 51, 52]

Radiotherapy

The cytotoxic effects [53] and therapeutic role [27] of radiotherapy (XRT) in treating soft-tissue sarcomas are well described. Radiotherapy should be considered for high-grade tumours of the limbs (unless margins are very wide) and for intermediate-grade tumours of the limbs with close or positive histological margins. [16] Radiotherapy has little role in

primary low-grade soft-tissue sarcoma, although it should be considered for a recurrence.[13]

Radiotherapy is delivered as either external-beam therapy or brachytherapy. The latter involves the insertion of radioactive "seeds" or wires (usually iridium-192) into surgically placed catheters traversing the tumour bed. Brachytherapy has theoretical advantages postoperatively, given the hypoxic nature of the wound and the radiobiologic characteristics of the inverse-square law (local doses are high, but the dose decreases proportionally with increasing distance from the tumour). These advantages are even more important in patients who have already undergone external-beam radiotherapy. [54]

Radiotherapy alone is considered when surgery is inappropriate or declined by the patient; it achieves rates of local control of 30 to 60 percent. [55] More commonly, operative treatment is coupled with adjuvant radiotherapy on the basis of evidence demonstrating similar survival rates after limb-conserving surgery with radiotherapy and after amputation. [45, 56] Optimal timing remains unclear. A lower total dose of radiotherapy (50 Gy) is required when it is delivered preoperatively.

Postoperative radiotherapy has been used to improve local control in patients with high-grade extremity soft tissue sarcomas with positive surgical margins.[33] When surgical resection is the initial therapy, postoperative XRT choices include intraoperative radiation therapy (IORT), brachytherapy or external beam XRT. Radiotherapy is not a substitute for suboptimal surgical resection, and re-resection may be necessary. If the patient has not previously received XRT, one could attempt to control microscopic residual disease with postoperative XRT if re-resection is not feasible. [1] Postoperatively, a total of 60 to 66 Gy is usually delivered to maximize killing of hypoxic tumour cells. [57]

Chemotherapy

Whereas the goal of surgery and radiotherapy is local control of the tumour, the aim of chemotherapy is systemic control, which may be therapeutic, adjuvant, or palliative.

Although some subtypes of soft-tissue sarcoma are sensitive to chemotherapeutic agents, the outcome of therapeutic chemotherapy is unsatisfactory overall, and the use of adjuvant chemotherapy is controversial. [58] Cyclophosphamide , ifosfamide, vincristine, doxorubicin, dactinomycin, and etoposide have all been used to treat these tumours. [59]

Follow-up

Post-treatment surveillance (by means of clinical examination and chest radiography or CT) is recommended to detect treatable recurrence and metastasis. [60] Patients with low-grade tumours that have been successfully resected should have a follow-up physical examination with imaging (chest/abdominal/pelvic CT) every 3-6 months for 2-3 years and then annually. Patients with high-grade tumours that have been successfully resected need more frequent surveillance. They should have a follow-up physical examination with imaging (chest/abdominal/pelvic CT) every 3-6 months for 2-3 years, then every 6 months for the next 2 years, and then annually. Chest imaging should be considered in both cases. [1]

Recurrence

Recurrence is the appearance of new disease after successful treatment of the primary tumour by surgery with or without any other modality, such as radiotherapy and/or chemotherapy. Recurrence may be local or distant.

Because soft-tissue sarcomas expand spherically and along tissue planes, their centrifugal growth creates a false capsule, or pseudo-capsule, of compressed surrounding tissue. Malignant cells penetrate this pseudocapsule. [14] Simple removal of visible tumour in this plane without the pseudo-capsule and a margin of 2-3 cm leaves microscopic disease in situ, and 90 percent of tumours recur unless there is further treatment.[13] Patients with microscopically positive surgical margins are at increased risk of local recurrence. Indeed, margin status after surgical resection is an independent prognostic factor for local recurrence.[1, 15, 40]

Over 30 percent of STSs will still recur even after further excision of the tumour bed, [31] and the subsequent use of radiotherapy does not compensate for the presence of unplanned positive histological margins. [46] (In contrast, leaving a carefully considered positive margin adjacent to a critical structure to facilitate limb preservation results in rates of local recurrence of only approximately 4 per cent when planned irradiation is carried out. [45]).

Various patient, tumour, and pathological characteristics are related to local recurrence. Advanced patient age greater than 50 years, [40] high histological grades, the tumour histologies fibrosarcoma, malignant peripheral nerve tumour and dermatofibrosarcoma protuberans (DFSP) have a higher risk for local recurrence. Microscopically positive surgical margins and recurrent disease at presentation increase the risk of local recurrence after a subsequent re-excision. [49]

Pisters *et al* (1996) in a prospective collected series of over 1,041 patients characterised the risk factors for outcome in patients with extremity soft tissue sarcoma. Significant independent adverse prognostic factors for local recurrence were age greater than 50 years (p=0.001), recurrent disease at the time of presentation (p=0.0001), microscopically positive surgical margins (p=0.0001), and the histological subtypes fibrosarcoma (p=0.006) and malignant peripheral nerve tumour (p=0.0001). For distant recurrence, large tumour size (p=0.03 for size greater than 10cm and p=0.0001 for size greater than 5cm), deep location (p=0.0001), high histological grade (p=0.0001), recurrent disease at presentation (p=0.015), and leiomyosarcoma (p=0.024) and non-liposarcoma histology (p=0.003) were all independent adverse prognostic factors, as was depth (p=0.0001). [40]

Patients with microscopically positive margins, either deliberately because of the site involved, or inadvertently, have lower rates of recurrence when offered adjuvant therapy. This may be in the form of radiotherapy or even chemotherapy if the tumour has been proven to be chemosensitive. [59] In some situations, both adjuvant therapies are offered to increase the chances of more effective treatment.

Soft tissue sarcomas most commonly metastasize to the lungs; tumours arising in the abdominal cavity more commonly metastasize to the liver and peritoneum. Liposarcomas of the lower extremity also often metastasize to the intra- abdominal organs. The dominant pattern of metastasis is haematogenous. Lymph node metastasis is rare (<5%) except for a few histological subtypes such as epitheloid sarcoma, rhabdomyosarcoma, synovial sarcoma, clear cell sarcoma and angiosarcoma. [5]

STUDY JUSTIFICATION

In black Africans, there is paucity of information on soft tissue sarcomas (STS). In Nigeria, the National Cancer Registry shows that this tumour is increasing in incidence.[18] Most patients present late with advanced disease hence the higher likelihood of recurrences in less developed countries.[18]

Data available from the medical records and pathology departments at the Kenyatta National Hospital depict an increasing prevalence of the disease (Table 1). The high incidence of HIV/AIDS in the Kenyan population may also be responsible for the increase, [21] perhaps as a result of the increase in Kaposi's sarcoma, which is often associated with the acquired immunodeficiency syndrome (AIDS),[21, 22] as well as improved recognition and diagnosis in patients with soft tissue sarcomas.

This combined prospective and retrospective study evaluated the influence of various patient and tumour characteristics on the rates of recurrence among patients treated for primary STS. Unlike common malignancies, where adverse outcomes after treatment, such as recurrence can be investigated with large prospective randomized trials, such an endeavour has been hampered with soft tissue sarcomas due to its rarity.[4] It has been estimated that, to detect differences of approximately 10% for a given end-point, such as recurrence free-survival or overall survival, it would require around 900 patients. [4] Certainly, getting this numbers at the KNH would be very difficult, if not impossible, and more so for patients treated surgically.

Studies done in other parts of the world have established that recurrences after surgical treatment are closely related to the tumour anatomical site, the size of the tumour and tumour microscopic margins after resection. There are currently no published local studies to establish the local recurrences after surgical treatment. This study sought to fill this gap. [17, 40]

Patients' records in at the Kenyatta National Hospital indicate that different patients undergo different treatment modalities and protocols for soft tissue sarcomas, depending on the surgeon's preference. This could have a bearing on the treatment outcomes such as the recurrence rates.

THE STUDY SETTING

This study was conducted at the Kenyatta National Hospital (KNH). Kenyatta National Hospital is the oldest and main referral and teaching hospital in Kenya. It was built 107 years ago. The Hospital currently provides a rich medical research environment. It covers an area of 45.7 hectares and within its complex are the College of Health Sciences (University of Nairobi); the Kenya Medical Training College (KMTC), Kenya Medical Research Institute (KEMRI) and the National Public Health Laboratory Service (Ministry of Health), among other institutions.

Kenyatta National Hospital is the sole public hospital with specialist oncology, neurosurgical, paediatric, cardiothoracic and plastic surgical units, in the country. It has 50 wards, 20 out-patient clinics, 24 theatres (16 specialised) and a modern Accident and Emergency Department. The hospital offers a wide range of diagnostic services such as Laboratories, Radiology and Imaging and Endoscopy. It also offers other specialised services like medical and radio-oncology. It has a bed capacity of 1800. The average bed occupancy rate can go up to as high as 300%. At any given day, the hospital hosts in its wards between 2500 and 3000 patients. On average the hospital caters for over 80,000 in-patients and over 500,000 out-patients annually.

OBJECTIVES OF THE STUDY

Broad Objective.

The aim of this study was to determine the pattern and factors influencing recurrence after primary surgery for soft tissue sarcoma at the Kenyatta National Hospital.

Specific Objectives

1. To determine the pattern of presentation among patients who were surgically treated.
2. To determine the rates of local and distant recurrence after primary surgery.
3. To determine the influence of various patient and tumour factors on recurrences.
4. To determine the influence of adjuvant treatment on recurrence.
5. To determine the time interval between treatment and the outcomes recurrence and death.

PATIENTS AND METHODS

Study Population

Between 2002 and 2007, 436 cases of STS were recorded in the KNH pathology department (Table 1). Out of these, all patients who underwent resection with curative intent at various units at the KNH were included in the study. The patients must have had negative gross surgical margins at completion of surgery. They had to have their full medical records available. All age groups were included in this study. The recurrence rate was determined by dividing the number of patients who presented with recurrences by the total number of patients treated surgically during the study period.

Table 1: Soft Tissue Sarcoma cases in KNH with a histological diagnosis

Year	Number of STS cases with histology seen
2002	62
2003	66
2004	70
2005	73
2006	80
2007	85
TOTAL	**436**

Patients with the following were excluded from the study:

1. Patients with tumours of bone origin.
2. Patients whose records were not available or those whose records were incomplete.
3. Patients with gross involvement of the resection margins
4. Patients who had other primary treatment modalities other than surgery.

Study Design and Duration

This was a five and a half years retrospective descriptive study between January 2003 and June 2008. A six month prospective arm was added to the study and sixteen consecutive patients were recruited between July 2008 and September 2008 and followed up for 6 months.

Sample size

All patients, whose records were available during the study period, were included. In the prospective arm, all consecutive patients treated surgically, were enrolled and followed up for 6 months.

Data collection

Files of all the patients seen in various units were perused and their details entered in the study questionnaire before analysis. The files were obtained from the records department at the Kenyatta National Hospital. Demographic data included age and gender of the patient. Clinical data included the duration of disease symptoms, the body region involved, radiological diagnostic tests done, the nature of surgical treatment offered, and the use of adjuvant therapies. Pathological data included the histological type, tumour size, grade, stage, and the microscopic margin status. Follow-up information included the site of recurrence, follow-up period and status (alive, dead, and lost to follow-up) at last follow-up.

Data Analysis

Data was analyzed using the SPSS version 11.1, and results presented in tables and graphs. Univariate analyses were used to obtain relationships between various patient and tumour variables and recurrence. The Chi square test was used to compare the proportions of different variables for outcomes..To generate the Chi square statistics, 2 X 2 tables were employed. The independent t-test was used to determine the relationship between means of various continuous variables and the outcomes recurrence and death. The level of statistical significance was set at $p < 0.05$. Other data were summarized in the form of descriptive statistics (means, standard deviations and frequencies) and presented in the form of tables and graphs.

Ethical Considerations

The approval of the KNH Ethics and Research Committee was sought and granted before the study was undertaken.

Definitions

Upper limb tumours: Tumours at or distal to the shoulder joint.

Lower limb tumours: Tumours at the groin or distal to the hip joint.

Tumour size: The maximum diameter of the tumour at pre-operative radiographic imaging, intra-operative assessment or at gross pathological assessment. The size was given in centimetres (cm).

Surgical margins: Macroscopic (gross) margins were assessed at the time of surgery while microscopic margins were determined at histology of excision specimens.

Grossly positive margins: When the surgeon or pathologist could identify tumour at the margins of resection, on gross examination.

Microscopic margins: Microscopic margins were defined as positive if the tumour was present at the surgical margin and negative if the surgical margin was uninvolved by tumour, after excision on microscopic examination.

Complete surgical resection: Complete surgical resection was defined as the absence of gross residual disease following surgical excision of the tumour, as indicated by the surgeon in his/her operation notes.

Intralesional excision: This was tumour resection within the pseudocapsule.

Marginal resection: The tumour was shelled out within the surrounding reactive zone.

Wide resection: The tumour was resected through normal tissue outside the reactive zone, with a margin of 2-3 centimetres, removing at least one uninvolved tissue plane circumferentially.

Radical resection: The entire compartment, in which the tumour was located, was resected.

Amputation: The limb was cut off proximal to the lesion, with a wide margin between the lesion and the amputation site.

Forequarter or hindquarter amputations: Forequarter or hindquarter amputations involved removal of part of the limb girdle, when the tumour site was very close to or involving the joint and therefore precluded an amputation or disarticulation.

Disarticulation: The limb was dismembered through a joint at a level just proximal to the lesion.

RESULTS

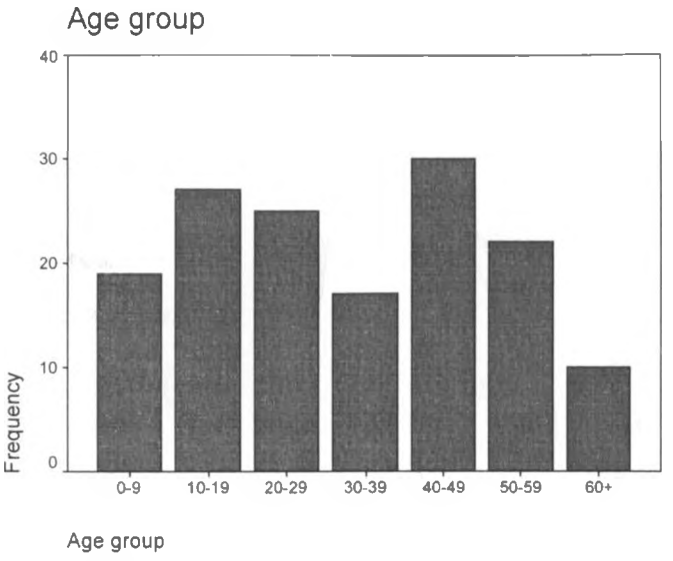
Demographic characteristics

The mean age was 32.52 ±18.17 years and the median age was 32.0 years. The age range was from 0.5 to 75 years. All age groups were affected (Table 2 and Fig. 1)

Table 2: Age group distribution

Age Group/Years	Frequency	Percentage
0-9	19	12.7
10-19	27	18.0
20-29	25	16.7
30-39	17	11.3
40-49	30	20.0
50-59	22	14.7
60+	10	6.7
Total	**150**	**100**

Figure 1: Bar chart of age group distribution



There were 74 males (49.3%), and 76 females (50.7%).

Symptom Duration

The duration of symptoms ranged from 0.5 to 144 months. The mean duration was 10.87±18.75 months, while the median duration was 6.0 months. In one patient, the tumour was discovered incidentally when a routine obstetric ultrasound was done during pregnancy.

Tumour Distribution in the Body

Most of the STS were distributed in the extremities (62.2%) and the abdominal/retroperitoneal regions (15.3%). Together, 77.3 % of the tumours were found in these regions.

Table 3: Body Region Distribution of the Soft Tissue Sarcomas at KNH

Body Region	Frequency	Percentage
Head and Neck	11	7.3
Thoracic Region	9	6.0
Abdominal Trunk	14	9.3
Intra-abdominal or retroperitoneal	23	15.3
Upper limbs	28	18.7
Lower limbs	65	43.3
Total	**150**	**100**

Pathological Characteristics

Histological Type

Fibrosarcoma was the most common soft tissue sarcoma with 54 cases (36.0%). The frequency of the other types was rhabdomyosarcoma 39 (26.0%), liposarcoma 11 (7.3%), leiomyosarcoma 10 (6.7%), malignant fibrous histiocytoma (MFH) 10 (6.7%), dermatofibrosarcoma protuberans (DFSP) 8 (5.3%), and synovial sarcoma 7 (4.7%). The remaining tumour types comprised 11 (7.4%) of the cases. These included neurofibrosarcoma 4 cases, alveolar soft part sarcoma, myxofibrosarcoma, haemangiosarcoma, haemangiopericytoma, pleomorphic sarcoma, primitive neuro-ectodermal tumour (PNET) and malignant peripheral nerve sheath tumour (1 case each).

Table 4: Histological Types for Patients with Soft Tissue Sarcomas

Histological Type	Age less than 20		Age ≥ 20	
	Frequency	%	Frequency	%
Fibrosarcoma	10	19.6	44	44.4
Rhabdomyosarcoma	29	56.9	10	10.1
MFH	5	9.8	5	5.1
Liposarcoma	0	0.0	11	11.1
Leiomyosarcoma	0	0.0	10	10.1
DFSP	1	2.0	7	7.1
Synovial Sarcoma	1	2.0	6	6.1
Other	5	9.8	6	6.1
Total	**51**	**100.0**	**99**	**100.0**

Patients less than 20 years comprised 34% of all those resected (Table 4). The most common histological type was rhabdomyosarcoma (RMS) with 29 cases (56.9 %), followed by fibrosarcoma (FS) with 10 cases (19.6%). There were no patients with liposarcoma or leiomyosarcoma in this age group. Synovial sarcoma and DFSP (1 patient each) had the least proportion of patients (2% for each).

There were 99 patients (34%) aged 20 years and above with soft tissue sarcomas. Fibrosarcoma (44.4%) was the commonest histological type in patients over 20 years with 44 cases, followed by RMS with 10 cases (10.1%), liposarcorma 11 cases (11.1%) , leiomyosarcoma 10 cases (10.1%), DFSP 7 cases (7.1%), synovial sarcoma 6 cases (6.1%) and MFH with 5 cases (5.1%).

Extremity lesions were the most common.(41.9%). Of these, fibrosarcoma had 39 cases. The frequencies of the other types were rhabdomyosarcoma 23 (24.7 %), liposarcoma 10 (10.8 %), malignant fibrous histiocytoma (MFH) 6 (6.5%), dermatofibrosarcoma protuberans (DFSP) 4 (4.3%), and synovial sarcoma 6 (6.5 %). Leiomyosarcoma had none. The remaining tumour types comprised 5 (5.4%) of the cases.

Tumour Size

Patients presented with tumour sizes ranging from 2 to 46 centimetres (cm). The mean STS size was 13.0±7.36cm.

Tumour Grade

Most of the patients, 67 in number (44.7%), presented with poorly differentiated tumours, followed by 51 (34.0%) with moderately differentiated STS. There were 32 patients (21.3%) with well differentiated STS at presentation. None of the patients had undifferentiated tumour grade (grade 4) in their histology reports.

AJCC Stage

The American Joint Committee on Cancer (AJCC) / International Union against Cancer Staging was as follows:

Table 5: Distribution of Patients according to AJCC Stage

AJCC Stage	Frequency	%
I	5	3.3
II	70	46.7
III	71	47.3
IV	4	2.7
Total	**150**	**100.0**

Five patients (3.3%) presented with stage I tumours whereas stages II, III, and IV had 70 (46.7%), 71(47.3%) and 4(2.7%) patients respectively.

Evaluation and treatment

Radiological Investigations

The types of radiological tests done and their distribution are as follows:

Table 6: Radiological Investigations

Radiological Test	Frequency	%
X-Ray	95	63.3
USS	24	16.0
CT Scan	25	16.7
MRI Scan	6	4.0
Total	**150**	**100**

Table 7: Surgical Excision Types

Type of surgery	Frequency	%
Intralesional/Marginal excision	4	2.7
Wide /radical excision	111	74.0
Amputation/disarticulation	35	23.3
Total	**150**	**100.0**

Most of the patients underwent radical operations. One hundred and forty six patients (97.3%) underwent either a wide or radical excision or an amputation or disarticulation. Only 4 patients underwent an intralesional or marginal excision.

Surgical Margins

After surgical extirpation of their tumours, and upon histopathological examination, 66 (44.0%) patients had negative histological surgical margins at their excision sites, whereas 84 patients (56.0%) had positive histological margins. The respective mean sizes of the tumours with positive and negative microscopic margins were 14.1 and 11.6 cm respectively. This difference was statistically significant (p value 0.037)

Adjuvant Therapy

Adjuvant treatment was given to 87 (68%) patients while 63 (42%) patients received none. Out of these, 27 (18.0 %) received radiotherapy, 43 (28.7 %), received chemotherapy, and 17 (11.4%) were given both chemo and radiotherapy.

Recurrence

One hundred and seventeen patients (78.0 %) had recurrence of their tumours after primary surgical treatment. Thirty three patients (22 %) had no recurrence.

In the retrospective arm of the study, out of 134 cases, 113 (84.3 %) patients developed recurrence whereas 21 (15.7 %) patients had no recurrence after a mean follow-up of 1.6 years.

In the prospective arm, 4 patients (26.7%) developed recurrences while 12 patients did not present with a recurrence during the six month follow- up period (mean follow up 6 months) of the study.

Sites of Recurrences

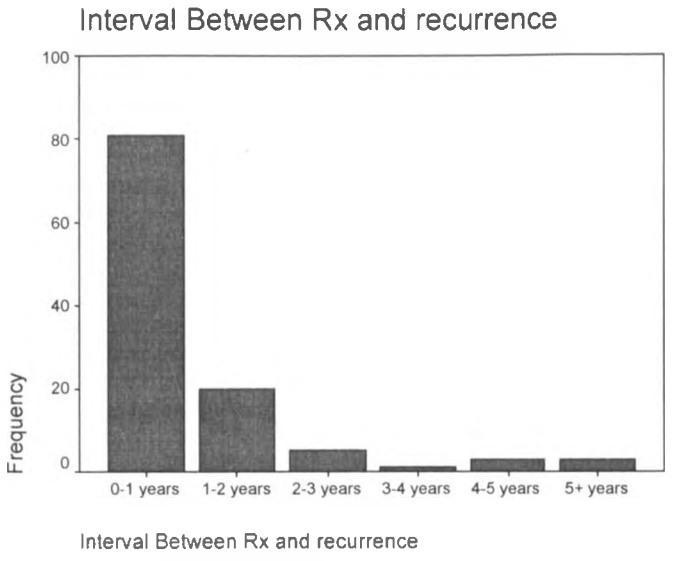
The primary sites were the areas of recurrence in 77 (51.3 %) patients, while the lungs or chest regions were the sites of recurrence in 26 (17.3 %) patients. Other sites of recurrence represented 14 (9.3 %) cases. These included regional lymph nodes, the brain or central nervous system and other regions other than the primary.

Duration between Treatment (Rx) and Recurrence (Relapse Free Survival)

The mean duration between treatment and recurrence was 1.32±1.67 years while the median was 0.7 years. This analysis was done in patients who had recurrences and in the retrospective arm of the study only.

Between 0 to 1 years, 81 (71.7 %) patients presented with a recurrence. The numbers were 20 (17.7 %), between 1 and 2 years, 5 (4.4 %) between 2-3 years, 1 (0.9%) between 3-4 years, and 3 (2.7 %) between 4-5 years respectively. Three cases presented with recurrences after 5 years (2.7 %). This analysis was done for the retrospective arm only in patients with recurrences.

Figure 2: Bar Chart for Interval between Treatment and Recurrence



Status at Last Follow Up

By the time of the last follow up, 75 (50.0 %) patients were alive, 69 (46.0 %) were dead and 6 (4.0%) patients had been lost to follow up.

Table 8: Status at Last Follow Up

Status at Last Follow-up	**Frequency**	**%**
Alive	75	50.0
Dead	69	46.0
Lost to follow-up	6	4.0
Total	**150**	**100.0**

Mortality

Time between Primary treatment and death (Disease Specific Survival)

For cases that ended up with deaths, the, mean duration between treatment and death (the disease specific survival) was 0.93±0.84 years while the median was 0.80 years. The range was 0.1 to 3.5 years.

Table 9: Demographic and Pathological Variables: 2X2 Tables

Variable	OUTCOME					
	Recurrence			Death		
	Yes	No	P value	Alive	Dead	P value
Age 0-20 yrs	40	11	0.927*	20	28	0.109*
Age >20 yrs	77	21		55	41	
Age<50 years	95	28	0.723*	62	56	0.844*
Age >50 years	22	5		13	13	
Male	60	14	0.369*	38	34	0.868*
Female	57	19		37	35	
Head & Neck	9	2	0.782*	3	7	0.147*
Other Regions	91	31		72	62	
Head, Neck & Abdomen	26	8	0.807*	11	19	0.057**
Other Regions	91	25		64	50	
Fibrosarcoma Histology	41	13	0.56*	33	20	0.062**
Other Histologies	76	20		42	49	
Primary Local Tumour	99	30	0.57*	60	64	0.027***
Recurrent Tumour	18	3		15	5	
Tumour <5cm	10	7	0.02***	9	7	0.723*
Tumour>5cm	107	26		66	62	

Table 10: Pathological and Treatment Variables: 2X2 Tables

Variable	OUTCOME					
	Recurrence			Death		
	Yes	No	P value	Alive	Dead	P value
Grade I & II	57	26	0.002***	60	17	<0.001***
Grade III	60	7		15	52	
Stages I & II	48	27	<0.001***	59	14	<0.001***
Stages III & IV	69	6		16	55	
Positive Margins	78	6	<0.001***	29	50	<0.001***
Negative Margins	39	29		46	19	
Wide/Radical Excision	87	24	0.614*	60	45	0.142*
Amputation/Disarticulation	26	9		15	20	
Intralesional/Marginal Excision	4	0	0.576*	0	4	0.05***
Wide/Radical Excision/Amputation	113	33		75	65	
Adjuvant Therapy	56	31	<0.001***	61	23	<0.001***
No Adjuvant Therapy	61	2		14	46	
Adjuvant XRT Only	14	13	0.085**	24	3	0.003***
Adjuvant CRT Only	31	12		22	18	
Recurrence at Primary Site				41	31	<0.001***
Lung/Chest Recurrence				0	26	

Note:

*-Result Not Statistically Significant

**-Result Near Statistically Significant

***-Result Statistically Significant

Age and Recurrence

Patients >20 years had a higher proportion of recurrences than those < 20 years. However this was not statistically significant (p=0.927). The difference in recurrence rates between patients of age < 50 years and those > 50 years was also not statistically significant (p=0.723).

Head and Neck Tumours versus Other regions and Recurrence

There was no statistically significant difference between recurrence in head and neck tumours versus those from other regions, (p=0.782). For recurrences between the head neck and abdominal regions versus the other body regions, the difference in the rates of recurrence were also not significant, (p=0.807).

Grade and Site of Recurrence

High grade tumours were more likely to metastasize to the chest or lungs compared to low (Grade I) and medium grade (III) tumours (p=0.003).

Table 11: Grade and Site of Recurrence

Grade	Site of Recurrence		p-value
	Primary	**lung /chest**	
Grade I and II	46 (86.8%)	7 (13.2%)	**0.003*** **
Grade III	28 (60.9%)	18 (39.1%)	

Age and Mortality

The differences in mortality rates between the age groups >20 years and < 20 years (p=0.109) and the age groups >50 years and < 50 years (p=0.844) were also not statistically significant.

The mortality rate between the head and neck tumours versus other regions was also not significant, (p=0.147).

A shorter mean duration of symptoms was a negative prognostic factor for death (p=0.004):

Table 12: Mean Duration of Symptoms and Mortality Outcome

Status at last follow-up	N	Mean Duration of Symptoms in months	p-value
Alive	75	15.4	0.004***
Dead	69	6.3	

This probably suggests that patients who died had more aggressive tumours.

Mean tumour size had no prognostic significance on the mortality outcome (p=0.867).

Table 13: Mean Tumour Size and Mortality Outcome

Mortality Outcome	N	Mean Tumour Size in cm	p-value
Alive	75	12.64	0.867*
Dead	69	12.84	

Table 14: Mean age and Tumour Grade

Grade	No	Mean age	p-value
Grade I & II	64	35.647	0.013***
Grade III	64	27.685	

Patients with a lower mean age were significantly more likely to present with high grade tumours (p=0.013).

Discussion

All age groups were affected. The mean, median and mode ages for patients enrolled in the study were 32.5, 32.0 and 29.0 years respectively. There were 51 (34%) patients who were less than 20 years, 99 patients (66 %) were above 20 years and 21.4% were over 50 years. In a review article by Lahat *et al* (2008) based on studies in North America, [61] the median age at diagnosis was 56 years and 10.4 % of the patients were under 20 years while 52.2% of the patients were over 55 years. According to findings from this study however, patients with soft tissue sarcomas are of a younger age group. This is likely because of differences in demographics between our third world set-up and the western set-up. Most of our general population comprises of the younger age group, and this also seems to be reflected in our distribution of the soft tissue sarcomas.

There was a bimodal distribution in the age groups distribution pattern. The peaks were in the 10-19 years group (18.0 %) and in the 40-49 years age group (20.0 %). As it will be shown later in the discussion, the tumour type distribution in these age groups was also different. Neither an age of less than 20 years nor greater than 50 years conferred a negative prognostic factor for recurrence. Patients with high grade tumours had a significantly lower mean age (27.7years) compared to those with low and medium grade tumours (27.7 years): the p value was 0.013. Pisters *et al* (1996) in an analysis of prognostic factors in 1,041 patients [40], found than age over 50 years was an independent prognostic factor for recurrence. The reasons given were that patients of this age group presented relatively later with larger tumours than younger patients. In this study at the KNH, this was not the case because perhaps most patients across all age groups, presented with large, high grade tumours and therefore age as a single variable did not confer a negative prognosis on recurrence.

There were almost equal proportions of males and females affected in this study. There were 74 males (49.3 %), and 76 females (50.7 %). The male to female ratio was 0.97:1. Guerney JG *et al* [62] in a population based study, found that rates among males tended to be higher than rates for females within all age groups although the overall difference was slight (11.8 per million males versus 10.3 per million females) for the younger than 20

year old population. In a Nigerian study involving all age groups by Adigun [18] *et al* (2007), males comprised 55% while females were 45% of the patients. The sex distribution in this study is therefore almost similar to that in other published studies from different parts of the world. Soft tissue sarcomas usually affect males and females equally as there are no sex genetic or hormonal factors associated with their pathogenesis or development.

There was a wide range in the duration of symptoms before patients presented to hospital (0.5-144 months).The mean was 10.87±18.75 months while the median was 6 months. This means that patients had the tumours for a long time before they sought medical attention. Another likely factor is that surgical services are not readily available in peripheral hospitals necessitating referral of these patients. Where surgical services were available, the patients were still referred so that they could benefit from oncology services. These delays resulted in patients presenting late with large tumours, which provided enormous challenges in their surgical treatment. This may have resulted in the high rates of positive margins, recurrences and death observed.

The extremities were the most common anatomical sites with a total of 93 cases (62.0 %). The upper limbs had 28 cases (18.7%); the lower limbs 64 cases (43.3%), the head and neck 11 cases (7.3%), the thoracic trunk 9 cases (6.0%) and the intra – abdominal and retroperitoneal regions 23 cases (15.3%). This distribution is closely similar to that of Clark MA *et al* (2005) [13],who in a review article gave the distribution as lower limb girdle 40%, upper limbs and girdle 20%, retroperitoneal and intra-peritoneal sites 20 %, trunk 10% and head and neck 10 %. The body tumour distribution pattern was therefore similar to that in other published series.

All patients usually have either a CT or MRI scan to help in planning for surgery. [8] In this study, only 31% of patients underwent CT or MRI scanning before surgery, and for those who had them done, it was more often than not a secondary imaging modality, usually after an initial X-ray film or an ultrasound scan. This essentially implies that only 31% of the patients had the appropriate radiological investigations before surgery. This may have

impacted negatively on planning for surgery. This may in turn have had an adverse effect in form of the poor outcomes observed in this study. Despite the availability of a CT scan at the KNH during the entire study period, and an MRI scan later, it was possible their high costs made it difficult for patients to access the tests. Moreover, it is also possible that even when a patient was able to afford, other emergent situations precluded patients with STS, getting the scans done.

Fibrosarcoma was the most common STS with 54 cases (36.0%). The incidence of the other types was rhabdomyosarcoma 39 (26.0%), liposarcoma 11 (7.3%), leiomyosarcoma 10 (6.7%), malignant fibrous histiocytoma (MFH) 10 (6.7%), dermatofibrosarcoma protuberans (DFSP) 8 (5.3%), and synovial sarcoma 7 (4.7%). The remaining tumour types comprised 11 (7.4%) of the cases. These included malignant peripheral nerve sheath tumour (MPNT), alveolar soft part tumours, myxofibrosarcoma, haemangiosarcoma, primitive neuroectodermal tumour and haemengiopericytoma. Koea *et al* (2003) [63] in a study of 951 patients with primary localized sarcoma of the extremities found the distribution as follows: MFH 33 %, liposarcoma 31 %, synovial sarcoma 15 %, leiomyosarcoma 10 %, fibrosarcoma 53 %, and MPNT 5 %.

Adigun *et al* (2007) in a study of 209 patients in Nigeria, [18] over a period of 20 years, found fibrosarcoma the most common histological type with 36.4 % of the cases, followed by MFH with 34.9%. Others were RMS 10.0%, LS 10.0%, LMS 7.7%, and NFS with 1%. In a study by Gutierrez *et al* (2007) at the Florida Cancer Data System, between 1981 and 2004, records of a total of 8,249 patients were examined. [64] The tumour histologies among these patients were leiomyosarcoma and gastrointestinal stromal tumour (LMS/GIST) (43.5%), malignant fibrous histiocytoma (MFH) (31.5%), liposarcoma (19.0%), and fibrosarcoma (6.0%). Tumours were situated in the extremities (30.7%), truncal or visceral locations (50.4%), retroperitoneum (11.7%), and head or neck (7.2%). This pattern is different from the one found in this study. Apart from the similarities of fibrosarcoma being the most common histological type in this study and that of Adigun et al (2007) in Nigeria, the distribution of the other histological types was different. It is possible that differences in the patterns were due to the different

geographic regions with their different demographics and patterns of diseases. This study also had the bias of including only patients who underwent surgery. In this study, fibrosarcoma histology did not confer negative prognostic status for recurrence. The most likely reason for this observation was because most of the fibrosarcomas were in the extremities and were therefore amenable to surgery.

Patients presented with tumour sizes ranging from 2 to 46 centimetres (cm) with a mean tumour size of 13+7.37 cm. Patients with tumours that had a larger mean tumour size were more likely to have positive microscopic surgical margins (p=0.037). A tumour size greater than 5cm was an adverse prognostic factor for recurrence (p=0.02). However a tumour size greater than 5 cm was not an adverse prognostic factor for death (p=0.723). Fiore M et al (2007) [65] on the other hand, in a study involving three hundred twenty-nine patients, with localized myxoid/round cell or pleomorphic liposarcoma who underwent surgery at the Istituto Nazionale per lo Studio e la Cura dei Tumori (Milan, Italy) over 25 years, found that tumour size (>10 cm), was an independent predictor of death. Stojadinovic A et al (2002) [17] analysed 2,123 patients with completely resected localized primary STS treated from 1982 to 1999 at the Memorial Sloan-Kettering Cancer Center, New York, NY. They found that a tumour size bigger than 5 cm (p<0.001) was a negative prognostic factor for tumour related mortality for retroperitoneal, head and neck, thoracic and visceral STS. In a retrospective study involving 209 patients in Nigeria, Adigun et al (2007) [18] found that most patients presented late with huge tumours, sometimes in the range of 15-30 cm, more so, for tumours of the extremities.

This relationship between tumour size and positive surgical margins explains why the recurrence and mortality rates in this study were high; most patients presented with large tumours. It is possible that large tumours are locally aggressive and therefore difficult to completely resect at surgery since they are likely to have spread beyond their gross surgical margins and compartments of origin. The results after surgery are therefore likely to be positive histological margins with high chances of recurrence. As for mortality outcomes, a tumour greater than 5 cm was not a negative prognostic factor for death. It is possible that whereas large tumours are locally aggressive and therefore more

likely to recur than small tumours, patients usually die from metastasis or distance recurrences. It is likely than the inherent biology of the tumour is a factor in distant spread. [5]

Thirty five patients (23.3%) underwent an amputation or disarticulation for local control of extremity tumours. The most frequent type of surgery was wide or radical excision which was carried out in 111 patients (74%). Only 4 patients (2.7%) had their tumours treated by intralesional or marginal excisions. Clark *et al* (2005) [13] in a review article, and in a study in 2003 on amputation for soft tissue sarcomas [47] found the rates of amputation for soft tissue sarcomas to be between 5 and 10 %. The amputation/disarticulation rate in this study (23.3%) was higher than the previously documented series, probably because many patients presented with extremity tumours that were large, ulcerated and fungating and which were probably also bleeding and infected. In these situations, an amputation or disarticulation was the only option. In this study, an amputation or disarticulation did not offer a patient protection from recurrence ($p=0.614$) and death ($p=0.142$). It is possible that since most patients presented with large and aggressive tumours, surgery resulted in close or positive margins with the propensity for local, distant recurrence and death. This may have been made worse with the low rates of adjuvant treatment.

In this study, patients who received adjuvant treatment in the form of radiotherapy, chemotherapy or both, were less likely to get a recurrence ($p<0.001$) as opposed to patients who did not receive any adjuvant therapy. On the same note, patients who received adjuvant treatment were also less likely to die, compared to those who received no treatment ($p<0.001$). Khatri VP *et al* (2005) [4] reported on a clinical trial conducted at the surgery branch of the National Cancer Institute. Patients in a group who received chemotherapy had a significantly lower recurrence rate ($p<0.001$). Clark *et al* (2005) [13] reported the cytotoxic effects and therapeutic role of radiotherapy (XRT) in treating soft tissue sarcomas. Hueman MT (2008) [66] *et al* wrote that XRT can be used to achieve local tumour control after surgery. However, this is most beneficial when the surgical margins are negative. According to Dickey ID *et al* (2007) [67] local recurrences may occur in up to 60% of cases, of the fibrosarcoma histological type, and is the reason why

postoperative radiation, preoperative radiation, or both are often recommended. Local recurrence is reduced to about 25% when postoperative irradiation is used.

In this local study, there was a clear benefit of adjuvant therapy, as it was protective against both recurrence and death. A comparison of the use of adjuvant radiotherapy alone versus the use of adjuvant chemotherapy alone found that radiotherapy had a significant benefit against death (p=0.003) but not against recurrence (p=0.085). Despite this, and a number of other studies proving the immense benefit provided by adjuvant radiotherapy, only 44 (29.3%) patients received XRT. The reasons seemed to be logistical and financial shortcomings, as opposed to the western world where the reasons for not receiving adjuvant radiotherapy are: wound complications, old age and complicating additional disease.[5] Since a significant number of patients were referrals, it meant that many of them were unable to keep their appointments for adjuvant treatment. The fact that less than a third of the patients received radiotherapy may have contributed to the high recurrence rates in this study. The use of chemotherapy alone as adjuvant therapy is limited to a few select tumours that are chemosensitive like rhabdomyosarcomas and Ewing's sarcomas. [58, 59]

This study at the KNH, found that positive microscopic surgical margins were an adverse prognostic factor for both recurrence (p<0.001), and death (p<0.001). Stojadinovic *et al* (2002) in a study at the Memorial Sloan-Kettering Cancer Center, in New York, involving 2,084 patients with localized primary soft tissue sarcoma (all anatomic sites) treated from 1982 to 2000, found that after primary resection, 1,624 (78%) patients had negative and 460 (22%) had positive resection margins. [68] They also found that having positive margins nearly doubled the risk of local recurrence and increased the risk of distant recurrence and disease-related death. Resection margin remained significantly associated with distant recurrence-free survival and disease-specific survival across all subsets after adjusting for other prognostic variables. The overall 5-year disease-specific survival rates for negative and positive margins were 83% and 75%.

In contradistinction, in this study, 66 (44.0%) patients had negative histological surgical margins at their excision sites, whereas 84 patients (56.0%) had positive histological margins. The risk of recurrence in patients with positive margins versus those with negative margins was similar to that of Stojadinovic *et al* (2002). It was 78 patients-(66.3%) for positive margins and 39 patients (33.3%) for negative margins. The risk of death in patients with positive margins in this study was 2.6 fold. This may have contributed to the high rates of recurrences (78%) and deaths (46%) observed. Most patients also presented late with large tumours that made it difficult to achieve negative microscopic margins after excision. The relatively small proportion of patients who underwent CT or MRI scans, also made adequate planning for the resections difficult. So far no local or African study on the rates of microscopic surgical margins has been published for comparison.

High (grade III) tumours were an adverse prognostic factor for distant recurrence in the lungs and chest ($p=0.003$) and for death ($p<0.001$). High grade tumours were also more likely to recur, compared to low and medium grade tumours ($p=0.002$). Since most of the patients in this study had high grade tumours (44.7%), this may have been a factor in the high rates of recurrences and deaths. Hueman MT *et al* (2008) in a review article on Management of Extremity Soft Tissue Sarcomas, reported that histolological grade was the most important factor in predicting risk for distant metastasis and tumour related death.[66] High tumour grade confers an inherent aggressive biological behaviour on the tumour which increases the risk for both local and distant recurrence and death. [43]

In this study, primary presentation with a recurrent tumour was an adverse prognostic factor for death ($p=0.027$), after re-resection compared to patients who presented with soft tissue sarcomas for the first time. However, surprisingly, it was not an adverse factor for local recurrence ($p=0.570$). The occurrence of local relapse per se might favour the systemic spread of disease and, therefore, directly affect survival, or it might simply be a marker of biological tumour aggressiveness. [5]

Study Limitations

Not all the records of the patients were readily available during the study period. Some patients were not available for follow up; whereas patients who had been recently treated had not been followed up for a significant duration of time, and therefore their outcomes had not been observed. Moreover, all patients were not followed up for a similar duration of time.

Some of the patients were referrals, having been treated in other institutions. Their initial treatment records were therefore not available for use in the study.

Various patients were managed by surgeons or surgical teams with varying expertise and experience and management protocols. This may have had an impact on the outcomes. Moreover the expertise or experience of the surgeon was not a variable in this study.

The sample in this study may have had a bias since it included only patients who were chosen to undergo surgery. This may have contributed to some of the differences observed between results of this study and studies done in other centres.

CONCLUSIONS

Most of the patients presented late with large tumours and had had the tumours for long. This was probably a factor that contributed to the high proportion of patients with positive margins, recurrence and death in this study. Most patients did not receive adjuvant treatment and this may have also had a negative bearing on the outcomes.

This study found that there were various patient, tumour and treatment factors that influenced recurrence and mortality outcomes. Positive surgical microscopic margins, tumour size greater than 5 cm, high grade tumours, AJCC stages III and IV and lack of adjuvant treatment were negative prognostic factors for recurrence. A recurrent tumour at presentation was not a negative prognostic factor for recurrence after re-resection.

The negative prognostic factors for death were high grade tumours, AJCC stages III and IV, presentation with a recurrent tumour, intralesional and marginal tumour excisions, positive microscopic margins after surgery, tumour recurrence in the lungs or chest after surgery, presentation with a recurrent tumour and failure to receive adjuvant therapy. Radiotherapy was more beneficial as adjuvant therapy compared to chemotherapy in protecting the patient from death.

Patient age less than 20 years or greater than 50 years were not negative prognostic factors for both recurrence and death. The gender of the patient, head neck and abdominal location of tumours and fibrosarcoma histology were also not negative prognostic factors for recurrence and death. The rates of amputations and disarticulations were higher than those in reported series (5-10%) [5,47].However, amputations, disarticulations and radical excisions did not confer protection against recurrence.

In our own environment, delayed and advanced stages of the disease are the rule. Modern imaging techniques such as computed tomography (CT) and, magnetic resonance

imaging (MRI) are not commonly available-and where they are available, they are usually not affordable for the majority of our patients.

Recommendations

1. Thorough preoperative multidisciplinary planning should be done, taking into consideration a variety of neo-adjuvant, surgical and adjuvant therapeutic options that may be available. An inappropriate initial surgical procedure has been demonstrated to compromise the outcome

2. All patients need to undergo a CT or MRI scan of the tumour before surgery, to enable define the extent of the tumour and allow appropriate planning for the surgical treatment. The preoperative evaluation should include CT of the chest to rule out metastasis to the chest, the most common site. Other potential sites of spread like the lymphatics and bone should also be evaluated both clinically and radiologically.

3. Patients who have unknown or positive microscopic margins, should be considered for re-excision to achieve negative margins where possible. In addition, these patients should receive adjuvant radiotherapy. There is also room for neoadjuvant radiotherapy, since patients generally present with large tumours and the ability to achieve negative surgical margins is not possible. This is likely when the tumour is in close proximity to bone, joints or neurovascular structures.

4. Patients with high grade tumours and those with unknown or positive margins should be considered for adjuvant radiotherapy. Those with chemosensitive tumours like rhabdomyosarcomas should receive chemotherapy.

5. Adequate post operative follow-up should be offered to the patients to ensure wound healing and to look for features of local or distant recurrence. There is need to document post surgical and adjuvant therapy morbidity status. This will be a guide as to whether limb saving procedures should be undertaken, particularly for extremity soft tissue sarcomas.

6. Tumours previously classified as leiomyosarcomas of the gastrointestinal tract (GIT), whose origin are the interstitial cells of Cajal, need to be reclassified as gastrointestinal stromal tumours (GIST). Currently different pathologists classify them as separate histological types, when indeed the standard current histological classification is GIST. Genetic and molecular studies may assist in this reclassification

7. There is need to seek immunohistochemistry services to aid in the diagnosis of tumours whose primary tissue of origin is not clear. It may also aid in the confirmation in select histological types.

8. Large prospective randomized studies are needed to further evaluate the prognostic factors for recurrence and death. These studies can be done in a single institution or they can be multi-institution based. Multivariate analyses of various prognostic variables found to be adverse, should also be done, since two or more variables may act in concert to produce an adverse effect.

9. There is need for limb preserving procedures in a select group of patients, since amputation is not necessarily protective against subsequent metastasis and death.

10. We need to establish good interdisciplinary relationships among the managing physicians and educate our patients on early presentation to the hospital.

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APPENDIX 1: Data Sheet

Demographic Data

1. Study code

2. Inpatient number

3. Age _____

4. Age group
   - ☐ 0-9……
   - ☐ 10-19….
   - ☐ 20-29….
   - ☐ 30-39….
   - ☐ 40-49….
   - ☐ 50 and above…..

5. Gender
   - ☐ Male-
   - ☐ Female-

Clinical Data

6. Duration of main symptom (Time)…..

7. Body region involved (at time of initial presentation)
   - ☐ Head and Neck
   - ☐ Thoracic Trunk
   - ☐ Abdominal Trunk
   - ☐ Intra-abdominal or Retroperitoneal
   - ☐ Upper limbs
   - ☐ Lower limbs

8. Diagnostic Tests

- ☐ X-ray
- ☐ Ultrasound Scan
- ☐ CT Scan
- ☐ MRI Scan
- ☐ Other

Pathological Data

9. Histological Type _____

10. Tumour size (in cm) _____

11. Tumour grade (FFCC)

- ☐ Well differentiated
- ☐ Moderately differentiated
- ☐ Poorly differentiated

12. Surgical margins status

- ☐ Free
- ☐ Not free

13. Stage (AJCC)

- ☐ Stage I
- ☐ Stage II
- ☐ Stage III
- ☐ Stage IV

Follow-up information

14. Site of recurrence

- ☐ Primary site
- ☐ Other

15. Duration between treatment and recurrence

- ☐ 0-1 years
- ☐ 1-2 years
- ☐ 2-3 years
- ☐ 3-4 years
- ☐ 4-5 years

16. Status at last follow-up.

- ☐ Alive
- ☐ Dead
- ☐ Lost to follow up

17. Post surgery treatment given

- ☐ Radiotherapy
- ☐ Chemotherapy
- ☐ Both radio- and chemotherapy
- ☐ Other (specify)
- ☐ None

APPENDIX 2: Principles of performing incisional biopsy for extremity soft tissue Sarcomas

- _Small longitudinal incision
- _Avoid flaps
- _Neurovascular structures should not be exposed
- _Sample the periphery of tumour which is the most viable, representative and diagnostic portion
- _Avoid crushing the specimen with forceps
- _Obtain frozen section to determine adequacy of sample
- _Meticulous hemostasis
- _Avoid suction drains
- _Close carefully to prevent necrosis or ulceration of wound
- _ Biopsy tract should NOT traverse normal anatomical musculoskeletal compartment

APPENDIX 3: AJCC Staging System for Soft Tissue Sarcoma

Classification

Primary Tumour (T)

T1- Tumour <5 cm

- T1a -Superficial tumour
- T1b- Deep tumour

T2- Tumour ≥5 cm

- T2a- Superficial tumour
- T2b- Deep tumour

Regional Lymph Nodes (N)

N0-No regional lymph node metastasis

N1- Regional lymph node metastasis

Distance Metastasis (M)

M0-No distant metastasis

M1- Distant metastasis

Histologic Grade (G)

G1- Well differentiated

G2- Moderately differentiated

G3- Poorly differentiated

G4- Poorly differentiated or undifferentiated

Stage Grouping

Stage IA is G1, 2, T1, N0, M0,

Stage IB is G1, 2, T2a, N0, M0,

Stage IIA is G1, 2, T2b, N0, M0,

Stage IIB is G3, 4, T1, N0, M0,

Stage IIC is G3, 4, T2a, N0, M0

Stage III is G3, 4, T2b, N0, M0,

Stage IVA is any G, any T, N1 and/or M1.

Modified from American Joint Committee on Cancer, 6th ed. [34]

APPENDIX 4: AJCC TNMG Staging Table

Stage

	T1a T1b	T2a	T2b
G1 or G2	IA	IB	IIA
G3 or G4	IIB	IIC	III
N1	IV		
M1			

APPENDIX 5: Work Plan Table

ACTIVITY	DURATION [WEEKS]	APPROXIMATE DATES
Writing of Proposal	4	May 2008
Corrections and submission To Ethical committee	4	June 2008.
Time taken with ethical Committee	4	July-August 2008
Data collection	12	September-November 2008
Data analysis	4	December 2008- January 2009
Compiling of work	2	February 2009
Final corrections and Submission	4	March 2009

APPENDIX 6: Study Budget & Justification

ITEM	BUDGET ESTIMATE IN KSH
Internet Surfing and literature review	10,000
Typing and printing services	15,000
Ethical committee	1,000
Data analysis [software and statistician]	15,000
Document handling and binding	5,000
Contingency 10%	4,600
TOTAL	50,600

Most of the study was done retrospectively, and was therefore not costly. The main elements of the cost were related to typing, printing services and the analysis of the data.