REVIEW ARTICLE

A Review Of Soft Tissue Sarcoma

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Abstract

Background: *Soft tissue sarcomas (STS) are a heterogeneous group of rare tumours that arise predominantly from the embryonic mesoderm. They present most commonly as an asymptomatic mass originating in an extremity but can occur anywhere in the body, particularly the trunk, retroperitoneum, or the head and neck. They account for about 0.7% of all adult malignancies.*

Method: *A review of the literature of STS was undertaken with emphasis on current approach in management.*

Result: *Despite recent advances in the knowledge of the molecular biology of STS, there is yet no identifiable aetiology in most cases. Tru-cut biopsy is a safe, accurate and economical procedure for diagnosing STS. Enough tissue is usually obtained for use in several diagnostic tests such as electron microscopy and cytogenetic analysis.*

With the advent of Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA), tumours can easily be delineated from muscle groups, bone and neurovascular structures.

Surgery remains the main potentially curative therapy for STS. In the last two decades, the role of adjuvant radiotherapy has revolutionized the treatment from a situation where amputation was the standard treatment for extremity STS to the present time where limb sparing surgery is appropriate in more than 90% of patients. Postoperative adjuvant chemotherapy significantly improves the overall and disease free survival for patients with large size and high grade sarcomas.

Conclusion: *Optimal results of treatment require multidisciplinary interaction between the referring practitioner, the treating surgeon, the pathologist, the radiotherapist and the chemotherapist.*

KEY WORDS: *Soft Tissue Sarcoma, Management, Review*

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INTRODUCTION

Soft Tissue Sarcomas (STS) are extremely rare tumours that are infrequently seen in most surgical practice. They arise from mesodermally derived extra skeletal tissues such as connective tissue, lymphatic vessels, smooth and skeletal muscles, fat, fascia, synovial structures and reticuloendothelium. These tissues contribute more than 50% of the body weight. In the developed countries, STS has been the subject of extensive basic and clinical research that has yielded improved understanding and more precise treatment. The situation is different in the developing countries.

The aim of this article is to present an overview of the current understanding of the aetiology, genetics and clinical management of STS so as to re-awaken the interest of the practitioners who manage this clinical condition in our sub-region. Extremity and retroperitoneal STS are included in the discussion, as the management principles for these tumours are similar.

EPIDEMIOLOGY

Soft Tissue Sarcomas are relatively uncommon tumours accounting for about 0.7% of all adult malignancies but up to 15% of childhood malignancies[1]. In the year 2004, approximately 8,680 new cases were expected to be diagnosed in the United States and 3,660 deaths from soft tissue sarcomas are predicted accounting for 0.63% of all cases and 1.15% of deaths from cancer[2]. In Nigeria, there is paucity of information on STS, with a few reports from Ibadan[3], Calabar[4], Lagos[5], Zaria[6], Port Harcourt[7] and Ilorin[8, 9]. The National Cancer Registry shows that this tumour is increasing in incidence. It constitutes 1.3% of all solid malignancies seen at University College Hospital (UCH), Ibadan[10].

The peak incidence is in childhood while a second peak occurs in adult 40-50 years of age[11]. STS can occur anywhere in the body, but most are in an extremity (59%), the trunk (19%), the retroperitoneum (15%), or the head and neck (9%)[12]. Currently, more than 50 histologic types of STS have been identified, but the most common are malignant fibrous histocytoma (28%),

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leiomyosarcoma (12%), liposarcoma (15%), synovial sarcoma (10%) and malignant peripheral nerve sheath tumour (6%)[13]. Rhabdomyosarcoma is the most common STS of childhood worldwide[14] while malignant fibrous histiocytoma (MFH) is the commonest soft tissue sarcoma in adults[15]. The dominant pattern of metastasis is haematogenenous. Lymph node metastasis is rare (less than 5%), except for a few histologic subtypes such as epitheloid sarcoma, synovial sarcoma, rhabdomyosarcoma and angiosarcoma[16].

AETIOLOGY AND GENETICS

There is no identifiable aetiology in most cases of STS. While most tumours arise de novo, a variety of predisposing or associated factors have been identified. The link between radiation and sarcoma development has been recognized since the 1930s[17]. The incidence of sarcoma is increased eight fold to 50-fold in patients treated with radiation therapy for cancer of the breast, cervix, ovary, teates, or lymphatic system[18, 19]. However, the risk of sarcoma appears to be related to the dose of radiation. The median latency period is approximately 10 years, but ranges between 4 and 50 years after therapy.

Chronic lymphoedema following axillary dissection is another major risk factor, the subsequent lymphangio-sarcoma is known as Steward-Treves Syndrome. Lymphangio-sarcoma has also been seen after filarial infections and in the setting of congenital or heritable lymphoedema, in which case the lower extremities are usually the site of the tumour[20].

Chemical herbicides and dioxin have been claimed to cause increased sarcomas in forestry workers and Vietnam veterans, but the data are conflicting[21, 22].
Specific inherited genetic alterations are associated with an increased risk of both bone and soft tissue sarcoma. The oncogenes that have been implicated in the development of soft tissue sarcomas include MDM2; N-myc, c-erbB2, and members of the ras family. Amplification of these genes in several subtypes of Soft Tissue Sarcomas has been shown to correlate with an adverse outcome[23]. Cytogenetic analysis of soft tissue tumours has also identified distinct chromosomal translocations that code for oncoproteins associated with certain histologic subtypes. The best characterized gene re-arrangements have been found in alveolar rhabdomyosarcoma (PAX3-FHKR fusion), Clear-cell Sarcoma (EWS-ATFI fusion), and Synovial Sarcoma (SSX-SYT fusion)[24]. Alterations in the important cell regulatory genes, p.53 and Rb, are common, and thus, it is not surprising that inherited mutations of these genes in hereditary retinoblastoma and Li-Fraumeni Syndrome confer a substantial risk for sarcoma[25]. Neurofibromatosis and familial adenomatous polyposis (Gardner's syndrome) also carry increase risk of STS[26].

PATHOLOGY

The overwhelming majority of soft tissue tumours are benign. Malignant soft tissue tumours are unusual in that there is almost no evidence of malignant transformation of benign tumours (the exception being malignant degeneration of peripheral nerve tumours in neurofibromatosis) Pathological assessment of STS involves assessment of the direction of differentiation, and the tumour grade. A distinction is made between the direction of differentiation and the tissue of origin, as sarcomas may be found in areas in which the corresponding normal tissue is absent. Assessment of the tissue type may be difficult and may require immunohistochemistry and even electron microscopy being needed in many cases[27, 28]. The difficulty of histological typing increases as the degree of differentiation lessens. From a clinical point of view, however, the grade rather than the precise tissue histiogenesis is critical for tumour behaviour and prognosis[29].

There are approximately 70 different histologic types of STS. Most sarcomas are classified according to the normal cell type they mimic, based on the system proposed by Enzinger and Weiss[30]. The relative frequency of the various types of sarcomas differs according to a patient's age. In children, for example, the most common sarcoma is rhabdomyosacroma while malignant fibrous histiocytoma (MFH), liposarcoma and leiomyosarcoma constitute the majority of adult STS. In the extremities MFH and liposarcoma are common, while in the retroperitoneum MFH is uncommon, but leiomyosarcoma and liposarcoma predominate.

Malignant fibrous histiocytoma (MFH), a type of sarcoma, is a malignant neoplasm of uncertain origin that arises both in soft tissue and bone. It was first introduced in 1961 by Kauffman and Stout[31] and controversy has plagued it since. They described MFH as a tumour rich in histiocytes with a storiform growth pattern. By 1977, MFH was considered the most common soft tissue sarcoma of adults. In 2002, the World Health Organization (WHO) declassified MFH as a formal diagnostic entity and renamed it as an undifferentiated pleomorphic sarcoma not otherwise

specified, NOS[32]. This new terminology has been supported by a compelling body of evidence to suggest that MFH represents a final common pathway in tumours that undergo progression towards indifferentiation[33-36]. While it remains unclear how to most accurately organize these tumours, the term malignant fibrous histiocytoma represents the diagnosis for thousands of patients and is still commonly used by both patients and physicians.

CLINICAL PRESENTATION

Soft Tissue Sarcomas can occur in any anatomic region of the body because of the ubiquitous nature of connective tissue, but most sarcomas (60%) develop in the extremities. Three times as many sarcomas develop in the legs as in the arms. Other sites include the trunk (31%) and head and neck region (9%). They commonly present as an asymptomatic mass. Pain if present is usually mild and occurs later in the course of the disease. Thus, a patient might delay seeking medical attention, and a definitive diagnosis also might be delayed[37]. Trauma may call the tumour to attention but it is not aetiological. The common differential diagnoses of benign soft tissue tumour such as lipomas lymphangiomas, leiomyomas and neuromas, haematoma or muscle injury frequently result in diagnostic delays, the delay being attributed to the patient and doctor at the same rate. Intra-abdominal tumours also tend to be painless, and often reach a very large size before coming to clinical attention. The usual symptoms are vague fullness and early satiety. Non-specific abdominal pain is common and about 25% of patients report sensory neurological symptoms[38,39]. Patients with pelvic sarcomas might present with swelling of the leg that simulates primary iliofemoral thrombosis or with pain in the distribution of the femoral or sciatic nerve. Hypoglycemia is rare and may be associated with large retroperitoneal sarcomas.

DIAGNOSIS

Diagnostic tools employed in tissue diagnosis include light microscopy, immunohistochemistry, electron microscopy and molecular studies.

In addition to making a diagnosis, the pathologist also provides an important information by grading the disease. Any mass >5 cm in diameter, or any new mass that persists for longer than 4 weeks, should be considered for biopsy[40]. It is critical that the biopsy technique does not compromise subsequent therapeutic options. Fine-needle aspiration biopsy is the preferred method because it is less invasive, less expensive and easy to perform; however, it requires an expertise in cytopathology for interpretation. The diagnostic accuracy in patients with primary tumours ranges from 60% to 96%[41]. Tru-cut biopsy is a safe, accurate, and economical procedure for diagnosing STS. In addition, enough tissue is usually obtained for use in several diagnostic tests, such as election microscopy, cytogenetic analysis, and flow cytometry. The diagnostic accuracy of tru-cut needle biopsy-based findings is reported to be 93%[42]. Open biopsy is a reliable diagnostic method that obtains adequate tissue. Incisional biopsy ideally should be performed in a designated treatment centre by the same surgeon who will perform the definitive surgery. The biopsy incision should be oriented longitudinally along the extremity to allow a subsequent wide local excision that encompasses the biopsy site, scar, and tumour en bloc. Adequate haemotasis must be achieved at the time of biopsy to prevent the dissemination of tumour cells resulting from the formation of haematoma in adjacent tissue planes. An excisional biopsy of easily accessible (superficial) extremity or truncal lesions smaller than 3 cm can often be performed.

For intra-abdominal masses, a pre-operative biopsy is usually unnecessary. The exception to this is where a diagnosis of lymphoma is considered likely. In this case, percutaneous or laparoscopic biopsy is appropriate[43]. As with any rare and complex lesion, quality control of pathological assessment is important, biopsies should be assessed by experienced pathologists.

INVESTIGATIONS

Pre-treatment radiologic imaging is critical in 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 and in detecting recurrences after surgical resection. Each imaging modality, however, has a particular place in patients with STS. Plain radiography of the affected part will exclude osseous nature of the lesion. Chest radiography should be performed in patients with primary sarcoma to look for lung metastasis. Computed Tomography (CT) of the chest should be considered for patients with high-grade lesions or tumours larger than 5 cm (T2). Contrast enhanced CT can assess the extent of the soft tissue burden and the proximity of the tumour to vital structures. CT is also the preferred imaging technique for evaluating retroperitoneal sarcomas[44].

Magnetic Resonance Imaging (MRI) is the preferred imaging modality for extremity sarcomas[45, 46]. It can accurately delineate muscle groups and distinguish among bone, vascular structures, and tumour. Special techniques, including magnetic resonance angiography, can be performed if adjacent vascular structures must be delineated. Intravenous Urography (IVU), Barium enema or Barium meal may be needed in visceral sarcoma. Nerve conduction studies may be done where a particular nerve is involved.

STAGING & PROGNOSTIC FACTORS

The current American Joint Committee on Cancer (AJCC) staging criteria for STS rely on the histologic grade; the tumour size and depth, and the presence of distant or nodal metastases[47] as shown in table I. These criteria do not apply to visceral sarcomas, Kaposi sarcoma, dermatofibrosarcoma or desmoid tumours.

Table I: AJCC TNM Staging

TNM Classification	Description	Stage Grouping
G_1	Well differentiated	Stage IA $G_{1,2}$ T_1 N_o M_o
G_2	Moderately differentiated	Stage IB $G_{1,2}$ T_{2a} N_o M_o
G_3	Poorly differentiated	Stage IIA $G_{1,2}$ T_{2b} N_o M_o
G_4	Undifferentiated	Stage IIB $G_{3,4}$ T_1 N_o M_o
T_1	Tumour ≤5 cm in greatest diameter	Stage IIC $G_{3,4}$ T_{2a} N_o M_o
T_{1a}	Superficial	Stage III $G_{3,4}$ T_{2b} N_o M_o
T_{1b}	Deep	Stage IV Any G, Any TN_1 and/or M_1
T_2	Tumour >5 cm in greatest diameter	
T_{2a}	Superficial	
T_{2b}	Deep	
N_o	No regional nodal metastasis	
N_1	Regional Nodal metastasis	
M_o	No distant metastasis	
M_1	Distant metastasis	

The histologic grade of a STS remains the most important prognostic factor. To accurately determine the tumour grade, an adequate tissue sample must be appropriately fixed, stained and examined by an experienced pathologist. The features that define the grade are the degree of cellularity, differentiation, pleomorphism, and necrosis as well as the number of mitoses. The metastatic potentials for STS by grade are as follows: 5% to 10% for low grade lesions, 25% to 30% for intermediate-grade lesions, and 50%-60% for high-grade tumours[48]. In the 2002 AJCC Staging System, Grades 1 and 2 are considered low grade and Grade 3 and 4 considered high-grade.

The size of a soft tissue sarcoma is an important prognostic variable. Sarcomas have been classified into two groups on the basis of size. T_1 lesions are ≤5 cm and T_2 lesions are >5 cm. Lesions <5 cm even of high grade have limited risk of local or distant recurrence, and should not be grouped with large high-grade lesions for treatment purposes. Lymph node metastasis of STS is rare, less than >5% show nodal

spread. These are most often in patients with epitheloid or synovial cell sarcomas and they have the same prognostic significance as distant metastases[16]. Nodal disease is designated stage IV disease. The lung is the major site of metastasis for extremity STS, while the liver is the main site for visceral tumours. Retroperitoneal lesions spread to both lung and liver[49, 50]. The prognostic significance of grade and size varies over time. Grade is the prime determinant of distant recurrence and death for the first 2 years. For later metastases, however, size is more important than grade[51].

TREATMENT OF PRIMARY DISEASE

Accurate preoperative histologic diagnosis is of critical importance in choosing the appropriate primary treatment strategy for patient with STS. The overall five-year survival rate in patients with STS of all stages remains only 50% to 60%[52]. Most patients die of metastatic disease, which becomes evident within two to three years of the initial diagnosis in 80% of cases.

Surgery:

Surgery remains the main potentially curative therapy for STS. The type of surgical resection is determined by several factors including tumour location, tumour size and the depth of invasion, the involvement of nearby structures, the need for skin grafting or autogenous tissue reconstruction, and patient's performance status. Over the last two decades, the role of adjuvant radiotherapy has gradually been defined, allowing evolution of treatment from a situation where amputation was the standard treatment to the present time where limb-sparring surgery is appropriate in more than 90% of patients with extremity STS[53]. 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 should be included en block with the resected specimen. Major neurovascular structures can usually be preserved if they are involved and need to be resected for curative reasons it is a relative indication for amputation. However, because neither a positive surgical margin nor local recurrence has been shown to clearly adversely affect overall survival[54], this should be taken into consideration if achieving clear surgical margins would require amputation or substantial functional compromise of an extremity.

Radiotherapy

In the 1970s, 50% of patients with extremity sarcomas underwent amputation for local control of their tumours[55]. However, large numbers of patients died of metastatic disease despite a local recurrence rate of less than 10% after radical surgery. This realization prompted the development of local therapy involving conservative surgical excision in combination with postoperative radiation therapy, which yielded improved local control rates of 78% to 91%[56, 57]. For lesions $\leq$5 cm in diameter, the prognosis is good after surgery alone, regardless of the histological grade, so adjuvant radiotherapy is unnecessary[58]. External beam radiotherapy has been used for both low and high grade lesions >5 cm, and brachytherapy (interstitial radiotherapy, delivered via temporary catheters placed during primary surgery) has been used successfully for high-grade lesions >5 cm[59, 60]. Various combinations of pre-operative radiotherapy and chemotherapy have been studied in attempt to define the optimal method to minimize local recurrence. Presently available data suggest that local control rates are similar for pre-operative chemoradiation, pre-operative radiation alone, and post-operative radiation[61-63]. Complication and re-operation rates tend to be higher for those having neoadjuvant therapy, suggesting that post-operative adjuvant radiation is the most effective and convenient approach. The long-term effects of radiation therapy (those occurring more than one year after the completion of therapy) are generally related to fibrosis, necrosis, oedema, fracture and contractures all of which can substantially impairs function.

Chemotherapy:

From the standpoint of response to chemotherapy, sarcomas vary from histologic subtypes that are very responsive to cytotoxic chemotherapy to subtypes that are universally resistant to current agents. Three drugs have been associated with response rates of 20% or more in patients with advanced STS, these are doxorubicin, dacarbazine and ifosfamide[55]. Meta-analysis of the published reports suggested that postoperative adjuvant chemotherapy significantly improves the overall and disease free survival for those with large (>5cm) high grade sarcoma[64]. These analyses were based on published results, leaving room for criticism. A major deterrent to the use of adjuvant chemotherapy has been the risk of its causing adverse toxic effects in patients who do not otherwise respond to therapy. With the advent of growth factors such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, the morbidity related to neutropenia has been minimized; however, dose-limiting thrombocytopenia continues to pose a challenge in the treatment of patients with chemotherapy[55].

Intra-abdominal Sarcomas

Retroperitoneal sarcomas frequently present a surgical challenge due to involvement of surrounding organs. They typically do not produce symptoms until they grow large enough to compress or invade contiguous structures. As complete excision with negative margins offer the only chance of cure, en block excision of any involved organ should be anticipated. Excision of kidney, pancreas, colon or spleen is required in 50-80% of cases[38, 65, 66].

Within the group of patients who had complete resection of their tumour, the grade of the tumour is the dominant factor in determining outcome[38]. Debulking does not improve survival, and so should be reserved for specific palliation and relief of obstruction[38]. The overall prognosis for patient with retroperitoneal tumours is worse than that for patients with extremity sarcomas. Survival rates at five years range from 40% to 50%. The best chance for long term survival for patients with retroperitoneal sarcoma is achieved with a margin-negative resection[55]. The role of adjuvant radiotherapy is less clear for retroperitoneal sarcomas than for those of the extremities. There are suggestions that it improves local control, but the cost, in the form of gastrointestinal morbidity, is high[67, 68]. It is not usually recommended for routine use[69].

Gastrointestinal sarcomas present with symptoms similar to those of carcinoma from the same organ, and the diagnosis is often made at laparotomy. Lymph node metastasis occurs in only 0% to 16% of cases[70, 71]. Consequently, lymphadenectomy is not routinely performed as part of resection. Surgical strategy is directed at removing the tumour with negative margins. Despite achieving negative margins, recurrence rates are high, usually in the form of hepatic metastases[72].

RECURRENT DISEASE

Most STS that recur do so within two to three years of the completion of treatment.

Local recurrence

Local recurrence in the extremity presents as a nodule or nodules along the scar, while patients with intra-abdominal or retroperitoneal recurrence have non-specific symptoms related to mass effect, usually after the disease has reached considerable size[73]. If the recurrence is isolated, re-resection is indicated followed by adjuvant radiation[69]. The preferred treatment for locally recurrent retroperitoneal tumours is also surgical resection, if possible. In the largest series of patients with retroperitoneal sarcoma, investigators were able to adequately resect recurrent tumour in 57% of the patients. However, adequate resection was possible in only 20% after a second recurrence and in 10% after a third[39].

Distant recurrence

Pulmonary metastases are the common in patients with extremity sarcomas, with disease recurring in up to 20% of these patients[54]. Extra-pulmonary metastases are uncommon, and are usually seen in the setting of wide spread disease. Metastases from visceral sarcomas are mostly found in the liver[74], whereas retroperitoneal sarcomas spread to the liver and lung with approximately equal frequency. The patient with lung metastasis should have thoracotomy if the local disease is controlled or controllable, and the pulmonary disease is potentially completely resectable[49]. Wedge resection with negative margins is the procedure of choice. The same consideration applies for isolated liver recurrence[74]. Unresectable recurrence has a poor prognosis and these patients should be considered for systemic chemotherapy. Agents mostly used are similar to those used in adjuvant chemotherapy which includes doxorubicin, decarbazine, DTIC and ifosfamide. Unfortunately, historically, the response rates to chemotherapy in patients with Stage IV STS have been low. Several prognostic factors have been identified that can predict the response to chemotherapy; these include previous response to chemotherapy, age, presence or absence of hepatic metastases, tumour grade and direction of the disease-free interval[75].

Conclusion

Soft Tissue Sarcomas are heterogeneous group of rare tumours. Optimal results of treatment require multidisciplinary interaction between the referring practitioner, the treating surgeon, the pathologist, the radiotherapist and the chemotherapist. Treatment of STS is primarily surgical resection with a margin of normal tissue; post-operative radiotherapy provides improved local control, with little impact on survival and adjuvant chemotherapy provide similar local benefit but at the cost of a higher incidence of complications. A lot of research has been done in the developed countries in the understanding of the molecular characteristic of these tumours, but more still have to be done that can translate into molecularly based therapies that may be incorporated into the current standard treatment, this might be of increase benefit to all patients with soft tissue sarcoma. As for practitioners in developing countries, despite the unavailability and/or unaffordability of both radiotherapy and chemotherapy

in most centres, we should still strive to offer our patients close to the standard treatment that is currently recommended.

REFERENCES

1. Wingo PA, Tong T, Bolden S: CA Cancer J Clin 1995; 44: 8-30.
2. Jemal A, Tiwari RC, Murray T, et al. Cancer Statistics, 2004. CA Cancer J Clin 2004; 54: 8-29.
3. Ani AN, Attah EB, Ajayi OO. Dermatofibrosacoma protubrans. Ana analysis of 8 cases an African population. Am Surg 1976; 934-940.
4. Out AA. Kaposi's Sarcoma. Niger Med Pract 1990; 19: 87-92.
5. Banjo AAF, Elesha SO, Abudu OO. Hemangiopericytoma of the uterus. Niger Med Pract 1997; 33: 65-67.
6. Rafindadi AH, Malami GA. Vascular tumours in Zaria A ten year pathological review. Niger Postg Med J 1999; 6: 157-160.
7. Seleye-Fubara D, Nwosa S.O., Bob-Yellowe E. Soft tissue sarcoma in the Niger Delta Region of Nigeria (A referral Hospital's study). Nig. J. Med. 2005; 14: 188-194.
8. Adeniji KA. Histopathological and histochemical pattern of soft tissue sarcoma in Ilorin, Nigeria. Afr J Med Med Sci 2003; 32:269-273
9. Adigun IA, Rahman GA, Buhari MO, Ogundipe KO, Omotayo JA. Soft tissue sarcoma in black Africans: Pattern, distribution and management dilemma. J. Natl. Med. Ass. 2006; 99: 88-93.
10. Ezeoma E. R. Soft Tissue Sarcomas. DOKITA. 1998; 25(1): 128-132.
11. Arlen M, Marcore RC: Surgical management of soft tissue sarcomas. Philadelphia. W. D. Saunders 1987: 334.
12. Devita VT Jr. Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2000: 1841-1891.
13. Coindre JM, Terrier P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 2001; 91: 1914-1926.
14. Hicks BA, Hensle TW, Burbige KA, Oeter Almer R, Bladder man agement in children with genital sarcoma. J Paediat Surg 1993; 28: 1019-1022.
15. Seleye-Fubara D. Histological study of soft tissue tumours in University of Port Harcourt Teaching Hospital, Port Harcourt (a ten year retrospective stydy. National Postgraduate Medical College of Nigeria dissertation. November 2001.
16. Fong Y, Coit DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg 1993; 217: 72-77.
17. Martland HS. The occurrence of malignancy in radioactive persons. A general review of data gathered in the study of radium dial painters, with special reference to the occurrence of osteogenic sarcoma and the interrelationship of certain blood diseases. Am. J. Cancer 1931; 15: 2435-516.
18. Brady MS, Gaynor JJ, Brennan MF. Radiation-associated sarcoma of bone and soft tissue. Arch Surg 1992; 127: 1379.
19. Zahm SH, Fraumeni JF Jr. The epidemiology of soft tissue sarcoma. Semin Oncol 1997; 24: 504-514.
20. Muller R, Hadju SI, Brennan MF. Lymphangiosarcoma associated with chronic filarial lymphoedema. Cancer 1987; 59: 179.
21. Fingerhut MA, Halperin WE, Marlow DA et al. Cancer mortality in workers exposed to 2, 3, 7, 8 tetrachlorodibenzo-p-dioxin. N. Engl J. Med. 1991; 324: 212-16.
22. Hardell L, Sandstrom A. Case-control study: Soft tissue sarcomas and exposure to Phenoxyacetic acids or Chlorophenols. Br. J. Cancer 1979; 39: 711-17.
23. Levins EA. Prognostic factors in soft tissue sarcoma. Semin Surg Oncol 1999; 17.
24. Vorburger SA, Hunt KK. Experimental Approaches in Pollock RE (ed). Soft Tissue Sarcomas. Hamilton, Ontario, BC Decker, Inc., 2002: 89-109.
25. Li FP, Fraumeni JF Jr. Soft tissue sarcomas, breast cancer and other neoplasms: A familial syndrome? Ann. Intern. Med. 1969; 71: 747-52.
26. Sorensen SA, Mulvihill JJ, Neilsen A. A long-term follow-up of Von Recklinghausen neurofibromatosis: survival and malignant neoplasms. N. Engl. J. Med. 1986; 314: 1010-15.
27. Van Haelst UJGM. Electron microscopy in the study of soft tissue tumours: Diagnosis/differential diagnosis and histogenesis. In: Van Oostero AT, Van Unnik JAM (eds) Management of Soft Tissue and Bone Sarcomas, New York: Raven, 1986: 77-91.
28. Hibshoosh H, Lattes R. Immunohistochemical and molecular genetic approaches to soft tissue tumour diagnosis: A primer. Semin. Oncol, 1997; 24: 515-25.
29. Preasant CA, Russell WO, Alexander RW, Fu YS. Soft-tissue and bone sarcoma histopathology peer review: The frequency of disagreement in diagnosis and the need for second pathology opinions: The Southeastern Cancer Study Group experience. J. Clin. Oncl. 1986; 4: 1658-61.
30. Enzinger FM, Weiss SW: Soft Tissue Tumours. 2nd ed. St. Louis, MO, CV Mosby Co, 1988.
31. Kauffman SL, Stout AP. Histiocytic tumour (fibrous xanthoma and histiocytoma) in children cancer 1961; 14: 469-482.
32. World Health Organization classification of tumours: Pathology and Genetics of Tumour of Soft tissue and Bone. Edited by Fletcher CDM, UK; Mertens F, Lyon, France, IARC. Press, 2002
33. Akerman, M.: Malignant fibrous histiocytoma--the commonest soft tissue sarcoma or a nonexistent entity? Acta Orthop Scand Suppl, 273: 41-6, 1997.
34. Dehner, L. P.: Malignant fibrous histiocytoma. Nonspecific morphologic pattern, specific pathologic entity, or both? Arch Pathol Lab Med, 112(3): 236-7, 1988.
35. Fletcher, C. D.: Pleomorphic malignant fibrous histiocytoma: fact or fiction? A critical reappraisal based on 159 tumors diagnosed as pleomorphic sarcoma. Am J Surg Pathol, 16(3): 213-28, 1992.
36. Hollowood, K., and Fletcher, C. D.: Malignant fibrous histiocytoma: morphologic pattern or pathologic entity? Semin Diagn Pathol, 12(3): 210-20, 1995
37. Lawrence W Jr, Donegan WL, Natarajan N, et al: Adult Soft Tissue Sarcomas: A pattern of Care Survey of the American College of Surgeons. Ann Surg 1987; 205: 349-359.
38. Jaques DP, Coit DG, Hadju SI, Brennan MF. Management of Primary and recurrent soft-tissue sarcoma of the retroperitoneum. Ann Surg. 1990; 212: 51-9.
39. Lewis JJ, Leung Dit, Woodruff J, Brennan MF. Retroperitoneal soft tissue sarcoma: Analysis of 500 patients treated and followed at a single institution. Ann Surg. 1998; 228: 355-65.

40. Brennan MF. Management of extremity soft-tissue sarcoma. Ann. J. Surg. 1989; 158: 71-8.
41. De Saint Aubain Somerhausen N, Fletcher CD. Soft-tissue sarcomas: an update. Eur J Surg Oncol. 1999; 25: 215-220.
42. Dupuy DE, Rosenberg AE, Punyaratabandhu T, et al. Accuracy of CT-guided needle biopsy of musculoskeletal neoplasm. AJR Am J Roentgenol 1998; 171: 759-762.
43. Mann GB, Conlon KC, La Quaglia M, Dougherty E, Moskowitz CH, Zelenetz AD. Emerging role of laparoscopy in the diagnosis of lymphoma. J. Clin. Oncol. 1998; 16: 1909-15.
44. Heslin MJ, Smith JK. Imaging of soft tissue sarcomas. Surg Oncol Clin N Am 1999; 8: 91-107.
45. Hanna SL, Fletcher BD. MR imaging of malignant soft-tissue tumours. Magn Reson Imaging Clin N Am. 1995; 3: 629-650.
46. Demas BE, Heelan RT, Lane J, et al. Soft-tissue sarcomas of the extremities: Comparison of MR and CT in determining the extent of disease. AJR Am J Roentgenol. 1988; 150: 615-520.
47. Greene FL, Page DL, Fleming FD et al. (eds). American Joint Committee on Cancer: Cancer Staging Manual 6th ed. New York, NY: Springer; 2002: 221-226.
48. Coindre JM, Terrier P, Bui NB, et al. Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol 1996; 14: 869-877.
49. Gadd MA, Casper ES, Woodruff J, McCormack PM, Brennan MF. Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. Ann Surg. 1993; 218: 705-12.
50. Jaques DP, Coit DG, Casper ES, Brennan MF. Hepatic metastases from soft tissue sarcoma. Ann Surg. 1995; 221: 392-7.
51. Lewis JJ. Leung DH, Casper ES, Wordruff J, Hadju SI, Brennan MF. Multifactorial analysis of long-term follow-up (more than 5 years) of primary extremity sarcoma. Arch. Surg. 1999; 134: 190-4.
52. Pisters P. Staging and Prognosis, in Pollock RE (ed). American Cancer Society Atlas of Clinical Oncology: Soft Tissue Sarcomas. Hamiliton, Ontario: BC Decker, Inc,; 2002: 80-88.
53. Lewis JJ, Brennan MF. Soft tissue sarcomas. In: Sabiston (ed). The Biological Basis of Modern Surgical Practice, 15th edn. New York: Saunders, 1996; 528-34.
54. Tanabe KK, Pollock RE, Ellis M, et al. Influence of surgical margins on outcome in patients with preoperative by irradiated extremity soft tissue sarcomas. Cancer 1994, 73: 1652-1659.
55. Cormier JN, Pollock RE. Soft tissue sarcomas CA Cancer J Clin 2004; 54: 94-109.
56. Lindberg RD, Martin RG, Romsdahl MM, Barkley HT Jr. Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. Cancer 1981; 47: 2391-2397.
57. Suit HD, Rassell WO. Radiation therapy of soft tissue sarcomas. Cancer 1975; 36: 759-764.
58. Fleming ID, Cooper JS, Henson DE et al. AJCC Cancer Staging Manual, 5th edn. Philadelphia: Lippincott-Raveu, 1997.
59. Brennan MF, Hilaris B, Shin MH et al. Local recurrence in adult soft-tissue sarcoma: A randomized trial of brachtherapy. Arch Surg. 1987; 122: 1289-93.
60. Harrison LB, Franzese F, Gaynor JJ, Brennan MF. Long term results of a prospective trial of adjuvant brachytherapy in the management of completely resected soft tissue sarcomas of the extremity and superficial trunk. Int. J. Radiat. Oncol Biol Phys. 1993; 27: 259-65.
61. Suit HD, Mankin HJ, Schiller AL. Results of treatment of sarcoma of soft tissue by radiation and surgery of Massachusetts General Hospital. Cancer Treat. Symp. 1985; 3: 33-47.
62. Denton JW, Dunham WK; Salter M et al. Preoperative regional chemotherapy and rapid-fraction irradiation for sarcomas of the soft tissue and bone. Surg. Gynaecol. Obstet. 1984; 158: 545-51.
63. Cheng EY. Dusenbery KE. Winters MR. Thompson RC. Soft tissue sarcomas: Preoperative versus postoperative radiotherapy. J. Surg. Oncol. 1996; 61: 90-9.
64. Tierney JF, Mosseri V, Stewart LA, Souhami RL, Parmar MKB. Adjuvant Chemotherapy for soft-tissue sarcoma: Review and meta-analysis of the published results of randomized clinical trials. Br. J. Cancer 1995: 72: 469-75.
65. Alavarenga JC, Ball AB, Fisher C et al. Limitation of surgery in the treatment of retroperitoneal sarcoma. Br. J. Surg. 1991; 78: 912-16.
66. Dalton RR, Donohue JH. Management of retroperitoneal sarcomas. Surgery 1989; 106: 725-33.
67. Harason LB, Gutierrez E, Fischer JJ. Retroperitoneal sarcomas. The Yale experience and a review of the Literature. J. Surg. Oncol. 1986; 32: 159-66.
68. McGrath PC, Neifeld JP, Lawrence W Jr et al. Improved survival following complete excision of retroperitoneal sarcomas. Ann. Surg. 1984; 200: 200-204.
69. Lewis JJ, Brennan MF. Soft tissue sarcomas. Curr. Robl. Surg. 1996; 33: 817-80.
70. Shiu MH, Farr GH, Egeli RA, et al. Myosarcomas of the small and large intestine: a clinicopathologic study. J Surg. Oncol 1983; 24: 67-72.
71. Lindsay PC, Ordonez N, Raaf JH. Gastric leiomyosarcoma: Clinical and pathological review of fifty patients. J Surg Oncol 1981; 18: 399-421.
72. McGrath PC, Neifeld JP, Lawrence W Jr et al. Gastrointestinal Sarcomas: Analysis of prognostic factors. Ann. Surg. 1987; 206: 706-10.
73. Mann GB, Lewis JJ, Brennan MF. Adult soft tissue sarcoma. Aust. N.Z.J. Surg. 1999; 69: 336-343.
74. Ng EH, Pollack RE, Romsdahl MM. Prognostic implications of patterns of failure for gastrointestinal leiomyosarcomas. Cancer. 1992; 69: 1334-41.
75. Van Glabbeke M, van Oosterom AT, Oosterhuis JW et al. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with authracycline - containing first line regimens a European Organization for Research and Treatment of Cancer Soft tissue and Bone Sarcoma Group Study. J Clin Oncol. 1999; 17: 150-157.