A Review Of Soft Tissue Sarcoma

I. A. ADIGUN, G. A. RAHMAN

Division of Plastic and Reconstructive Surgery
Division of General Surgery
Department of Surgery,
University of Ilorin Teaching Hospital, Ilorin.

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

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. 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. In Nigeria, there is paucity of information on STS, with a few reports from Ibadan, Calabar, Lagos, Zaria, Port Harcourt and Ilorin. 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.

The peak incidence is in childhood while a second peak occurs in adult 40-50 years of age. 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%). Currently, more than 50 histologic types of STS have been identified, but the most common are malignant fibrous histiocytoma (28%),...
leiomyosarcoma (12%), liposarcoma (15%), synovial sarcoma (10%) and malignant peripheral nerve sheath tumour (6%)\textsuperscript{15}. Rhabdomyosarcoma is the most common STS of childhood worldwide\textsuperscript{16} while malignant fibrous histiocytoma (MFH) is the commonest soft tissue sarcoma in adults\textsuperscript{15}. The dominant pattern of metastasis is haematogenous. Lymph node metastasis is rare (less than 5%), except for a few histologic subtypes such as epitheloid sarcoma, synovial sarcoma, rhabdomyosarcoma and angiosarcoma\textsuperscript{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\textsuperscript{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\textsuperscript{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 lymphangiosarcoma 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\textsuperscript{20}.

Chemical herbicides and dioxin have been claimed to cause increased sarcomas in forestry workers and Vietnam veterans, but the data are conflicting\textsuperscript{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\textsuperscript{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)\textsuperscript{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\textsuperscript{25}. Neurofibromatosis and familial adenomatous polyposis (Gardner’s syndrome) also carry increase risk of STS\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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. 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 indiffentiation. 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. 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. 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. 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%. 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 electron microscopy, cytogenetic analysis, and flow cytometry. The diagnostic accuracy of tru-cut needle biopsy-based findings is reported to be 93%. 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. 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.
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

<table>
<thead>
<tr>
<th>TNM Classification</th>
<th>Description</th>
<th>Stage Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>G(_1)</td>
<td>Well differentiated</td>
<td>Stage I A G(_{1,2}) T(_1) N(_0) M(_0)</td>
</tr>
<tr>
<td>G(_2)</td>
<td>Moderately differentiated</td>
<td>Stage I B G(<em>{1,2}) T(</em>{2a}) N(_0) M(_0)</td>
</tr>
<tr>
<td>G(_3)</td>
<td>Poorly differentiated</td>
<td>Stage II A G(<em>{1,2}) T(</em>{2b}) N(_0) M(_0)</td>
</tr>
<tr>
<td>G(_4)</td>
<td>Undifferentiated</td>
<td>Stage II B G(_{3,4}) T(_1) N(_0) M(_0)</td>
</tr>
<tr>
<td>T(_1)</td>
<td>Tumour (\leq 5) cm in greatest diameter</td>
<td>Stage II C G(<em>{3,4}) T(</em>{2a}) N(_0) M(_0)</td>
</tr>
<tr>
<td>T(_{1a})</td>
<td>Superficial</td>
<td>Stage III G(<em>{3,4}) T(</em>{2b}) N(_0) M(_0)</td>
</tr>
<tr>
<td>T(_{1b})</td>
<td>Deep</td>
<td>Stage IV Any G, Any TN(_1) and/or M(_1)</td>
</tr>
<tr>
<td>T(_2)</td>
<td>Tumour (&gt;5) cm in greatest diameter</td>
<td></td>
</tr>
<tr>
<td>T(_{2a})</td>
<td>Superficial</td>
<td></td>
</tr>
<tr>
<td>T(_{2b})</td>
<td>Deep</td>
<td></td>
</tr>
<tr>
<td>N(_0)</td>
<td>No regional nodal metastasis</td>
<td></td>
</tr>
<tr>
<td>N(_1)</td>
<td>Regional Nodal metastasis</td>
<td></td>
</tr>
<tr>
<td>M(_0)</td>
<td>No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M(_1)</td>
<td>Distant metastasis</td>
<td></td>
</tr>
</tbody>
</table>

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 \(\leq 5\) 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 epithelioid or synovial cell sarcomas and they have the same prognostic significance as distant metastases. 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. 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.

**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%. 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-sparing surgery is appropriate in more than 90% of patients with extremity STS. 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, 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. 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%. For lesions ≤5 cm in diameter, the prognosis is good after surgery alone, regardless of the histological grade, so adjuvant radiotherapy is unnecessary. 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. Various combinations of pre-operative radiotherapy and chemotherapy have been studied in an 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. 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 impair 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. 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. 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.
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 bloc excision of any involved organ should be anticipated. Excision of kidney, pancreas, colon or spleen is required in 50-80% of cases.

Within the group of patients who had complete resection of their tumour, the grade of the tumour is the dominant factor in determining outcome. Debulking does not improve survival, and so should be reserved for specific palliation and relief of obstruction. 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. 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. It is not usually recommended for routine use.

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. 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.

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 nonspecific symptoms related to mass effect, usually after the disease has reached considerable size. If the recurrence is isolated, re-resection is indicated followed by adjuvant radiation. 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.

Distant recurrence
Pulmonary metastases are the common in patients with extremity sarcomas, with disease recurring in up to 20% of these patients. 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, 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. Wedge resection with negative margins is the procedure of choice. The same consideration applies for isolated liver recurrence. 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.

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

A Review Of Soft Tissue Sarcoma: 1 A. Adigun, 2 G. A. Rahman