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Magnetic Resonance Imaging (Mri), The Preferred Evaluation Tool In Soft Tissue Sarcoma: Literature Review, Demonstrated With A Case Report

Uduma Felix U (Department of Radiology, Faculty of Clinical Sciences, University of Uyo, Nigeria- Polyclinic Bonanjo, Douala)

Fokam Pius G (Orthopaedic unit, Department of Surgery, Hopital General, Douala, Cameroon- Polyclinic Bonanjo, Douala)

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Magnetic Resonance Imaging (Mri), The Preferred Evaluation Tool In Soft Tissue Sarcoma: Literature Review, Demonstrated With A Case Report

Abstract

Author (s)

Uduma Felix U

Department of Radiology, Faculty of Clinical Sciences, University of Uyo, Nigeria.
E-mail: felixuduma@yahoo.com

Fokam Pius G

Orthopaedic unit, Department of Surgery, Hopital General, Douala, Cameroon

Soft tissue sarcoma is a heterogeneous group of mesenchymal malignant tumours. They are rare tumours constituting only 1% of all malignancies. Our index patient who has right thigh soft tissue sarcoma with distant metastasis belongs to the tumour age range but has no risk factor. Magnetic resonance imaging (MRI) helped us to adequately characterise the primary tumour and stage the tumour as American Joint Cancer Committee stage IVB. Histology confirmed it as Fibro sarcoma. MRI has superior soft tissue contrast and multi-planar imaging capabilities. These are advantageous to tumour localization and depth assessment which are integral part of the modified staging system. This invariably qualified MRI as the current preferred imaging tool for soft tissue sarcomas.

Key words: Soft tissue, Sarcoma, Magnetic Resonance Imaging, Staging

Introduction

Soft tissue in this context are heterogeneous group of extra-skeletal tissues of the body that share a mesenchymal origin.[Sengupta et al,2009,Clark et al,2005,Barai et al, 2004,John Wayne,2007,Verweji,2009, Kransdorf and Murphy,2000, Robinson et al, 1994, Lietman, 2010,Borden et al,2003,Yagnik et al,2009] They are predominantly supportive structures and they include fat, fibrous tissues, blood vessels, deep skin tissues, peripheral nerves, voluntary and involuntary muscles.[Memorial Sloan,2011,Rau and Avabratha,2010]

Soft tissue sarcoma (STS) consist of a group of diverse malignant tumours which are relatively rare, accounting for less than 1% of all adult cancers.[Spunt et al,2002,Billingsley et al,1999,Demetri et al.2010, Ioamidis and Lau,2003].

STS are classified on basis of the adult mesenchymal tissue they resemble. For example, the designate of liposarcoma does not mean a lesion arose from fat but rather it is a malignant neoplasm that differentiate into a tissue that microscopically simulate normal

adult fat.[Kransdorf and Murphy, 2000] Whilst the preferred method of imaging is MRI, other ancillary tools are also available.[Grimer and Judson et al,2010]. Pre-treatment diagnosis and staging is critical before planning a good treatment protocol. The new staging method incorporates tumour size and depth as strong prognostic factors. This mandates the utility of a cross-sectional imaging tool with superior soft tissue contrast resolution and pluridirectional imaging capabilities. Magnetic resonance imaging (MRI) aptly fits into the above requirement, thus becoming the primary imaging method for soft-tissue sarcomas.[Lietman,2010]. It is used for lesion detection, dimensional assessment and local staging of soft tissue sarcomas.[Borden et al,2003]. For STS, the main prognostic factors are grade, size, depth, diagnosis and the age of the patient.[Grimer and Mottard et al,2010]. Of these factor, the only one which can be altered, and thus improve prognosis, is the size of the tumour at diagnosis. [Grimer and Mottard et al,2010]. Tumour size is related to survival and correlates strongly with the incidence of detectable metastases at diagnosis. [Grimer and Mottard et al, 2010]. For every 1 cm increase in the size of a STS at diagnosis

there is a 3% to 5% decrease in the chance of cure. [Grimer and Mottard et al,2010].

The location and depth of the mass can be assessed on physical Examination.[Lietman,2010]. But evaluation of the extent of disease and proximity of vital structures (such as neurovascular bundles), can only be facilitated by a modality with exquisite soft tissue contrast resolution like MRI in comparison to CT.[Costelloe et al,2007]. MRI may assist to exclude some soft tissue neoplasia hitherto considered as malignant to be benign. Benign Soft tissue tumours especially lipomas are 100 times as common as STS.[Kransdorf and Murphy,2000]. Lesions that can be deemed determinate and usually diagnosed as benign based on MRI findings include lipomas, hemangiomas, granuloma annulare, and ganglion cysts. [Lietman,2010]. Such determinate lesions usually do not require a biopsy. [Lietman,2010]. However, most other soft-tissue lesions are indeterminate on MRI and require a biopsy to determine what they are and how they should be treated.[Lietman,2010, Grimer and Judson et al,2010]. Still MRI helps to plan the biopsy in these indeterminate cases. [Lietman,2010]..

The goal of surgery is to resect tumour with wide margin (2-3cm) when possible removing at least one un-involved tissue plane circumferentially.[Clark et al,2005]. The resection surgery involves careful preoperative planning, almost always with an MRI.[Perry,2002] MRI is routinely used to monitor the response to radiotherapy, local recurrence and complications of treatment .[Saundry et al,1999]. In fact, MRI can be used as the primary imaging modality in the evaluation for recurrent tumor and better delineation of an early postoperative site than ultrasound.[Barai et al,2004, Costelloe et al,2007] .

However, correct histological diagnosis can only be made in 25–40% of soft tissue masses when using MRI. This is because considerable overlap in morphological and signal features of most masses (long T1 and long T2) limits the ability of MRI to identify types and subtypes of soft tissue sarcoma and to discriminate benign from malignant

masses.[Kransdorf and Murphy,2000,Borden et al,2003]

Case Study.

MJ, a 33 year old Para-6 Cameroonian widow was referred to Radiological Department of Polyclinic, Bonanjo with history of recurrent progressive, painful right thigh swelling. She had excision of similar swelling about a year ago. Histiological report of the surgical excision was Fibrosarcoma.

We commenced evaluation of the presenting swelling with right thigh radiography which showed no osseous lesion nor cortical defect. Thigh echogram showed a voluminous mass in the lateral right thigh measuring 88 x70mm (FIG 1). The mass is hypoechoic with fairly defined margins. Abdomino-pelvic echogram was not contributory.

MRI of the right thigh was subsequently done . MRI showed 27.4 x 20.6 x 12.34 cm superficial mass in the lateral compartment of the right thigh with extension into the anterior compartment. Coronal T1W (FIG 2) and sagittal T2W (FIG 3) images showed a lobulated solid mass extending from proximal 1/3 to distal 1/3 of the thigh . This mass is T1W hypointense to nearby subcutaneous fat and isointense to skeletal muscles. It harbours multiple T1W hypointense necrotic areas and internal septations. The mass is completely delineated by a hypointense pseudocapsule. On T2W and FLAIR sequences the mass has prolonged T1 and T2 relaxation times. Axial enhanced image (FIG 4) showed total enhancement of lobules and septae as well as mural enhancement of the necrotic centres and pseudocapsule . Chest radiograph showed bilateral multiple canon ball lesions (FIG .5) . Based on the above , a diagnosis of soft tissue sarcoma stage IVb was made.



Fig 1

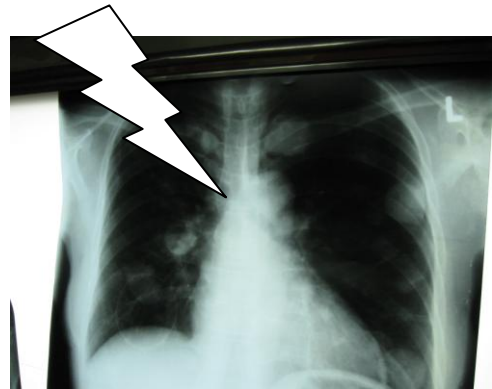


Fig 4

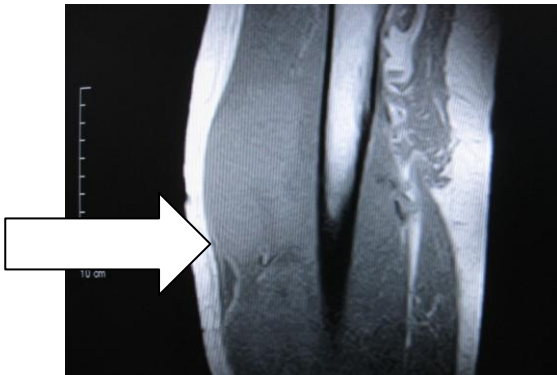


Fig-2

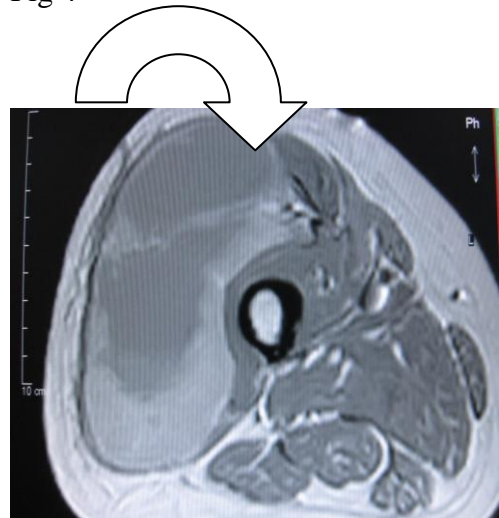


Fig-5



Fig 3

Discussion

The word Sarcoma has its origin from Greek word meaning flesh.[Rau and Avabratha,2010]. Soft tissue Sarcomas constitute a heterogeneous group of rare solid tumors of mesenchymal cell origin with distinct clinical and pathological features.[Memorial Sloan,2011,Rau and Avabratha,2010, Grimer and Judison et al,2010,Delaney and Kirsch,2011,Stojadinovic et al,2002,Eriksson,2010,O'Connor et al,2004]. Collectively, sarcomas account for approximately 1% of all adult and 7–15% of pediatric malignancies[Sengupta et al,2009,Clark et al,2005,Yagnik et

al,2009, Demetri et al,2010, Grimer and Judson et al,2010, Grimer and Mottard et al,2010 Eriksson,2010]. The incidence varies by age and site of location eg during childhood Rhabdosarcoma is the commonest whereas Liposarcoma is the most common in adult.[Rau and Avabratha,2010, Demetri et al,2010]. STS may occur at any age, but most common in middle aged and older adults[Grimer and Judson et al,2010]. STS occur primarily in adults, and incidence rates rise gradually with age.[Lietman,2010]. The commonest age range is 41-60years[Clark et al,2005]. STS can even been seen at birth. For example an infantile form, also known as congenital fibrosarcoma, is a malignant proliferation of fibroblasts often seen in the first 5 years of life, with about one-third present at birth[Laffan et al, 2009]. Males have more STS than females[Clark et al,2005] and Rhabdomyosarcoma is higher for boys than girls and in white children than blacks [Clark et al,2005]. The incidence peaks at 5years for boys and age 3 for girls[Clark et al,2005]. Historically, because of the heterogeneity of STS, the true incidence has generally been under-reported[Eriksson,2010] STS are rare neoplasms with approximately 8,000-10 000 new cases per year in the United States and a mortality rate of 50% [Clark et al,2005, Yagnik et al,2009, Stojodinovic et al,2002]. Recent estimates from the cancer networks suggested that about 1500- 3000 patients (all sarcomas) are diagnosed per annum in the UK, including sarcomas of the head and neck, gynaecological sarcomas and GIST that were either not accurately diagnosed in the past, or not captured by cancer registries[Clark et al,2005, Grimer and Judson et al,2010]. Gastrointestinal stromal tumors (GIST) may not have been counted in tumor registry databases before 2001[Demetri et al,2010]. GIST is expected to have an incidence of at least 5000 new cases per year in the United States [Demetri et al,2010]. Overall incidence of STS seems to be increasing, perhaps as a result of improved recognition with modern imaging tool and increase in kaposis sarcoma associated with AIDS and human herpesvirus [Clark et al,2005, Delaney and Kirsch,2010]] Most STS are sporadic, few have identifiable cause.

STS constitute a heterogeneous group of tumours , often with a distinct age distribution,

site of presentation, natural biological behaviour, histiology and prognosis.[Grimer and Judson et al,2010]. WHO has defined approximately 50 different histological subtypes based on adult tissue they mimic[Clark et al,2005, Memorial Sloan,2011, Eriksson,2010 Grimer and Judson et al,2010]. Their nosology reflect this simulations eg leiomyosarcoma, fibrosarcoma, liposarcoma, alveolar soft part sarcoma, rhabdomyosarcoma, synovial sarcoma, malignant peripheral nerve tumour, angiosarcoma, gastrointestinal stromal tumours(GIST), pleomorphic sarcoma (*malignant fibrous histiocytoma(MFH)*), etcetra. Six of the more common histopathologies are fibrosarcoma, leiomyosarcoma, liposarcoma, MFH, malignant peripheral nerve sheath tumors, and synovial sarcoma[Borden et al,2003]. Knowledge of the biological differences between subtypes, such as their unique genetic "fingerprints, natural history and the sensitivity to treatment of different subtypes, has gradually increased over the years[Memorial Sloan,2011, Eriksson,2010]. The improved classification and characterisations of STS evolved with immuno-histochemistry. [Clark et al,2005]

There is no clearly defined etiology in most cases of STS, but a number of associated or predisposing factors have been identified[Delaney and Kirsch,2010]] These include a genetic predisposition, gene mutations, certain viral infections especially EBV, radiation therapy, chemotherapy, chemical carcinogens, chronic irritation, and lymphedema [Clark et al,2005, Yagnik et al,2009, Demetri et al,2010, Grimer and Judson et al,2010]. Occupational hazards like exposure to phenoxyacetic acid in herbicides and chlorophenols in wood preservatives, thorotrast, vinyl chloride have risk of sarcomas[Yagnik et al,2009 Grimer and Judson et al,2010].] STS may also develop 3-15 yrs after therapeutic irradiation of lymphoma, cancer of cervix and testis. Stewart-Treve's syndrome is chronic lymphoedema associated lymphangiosarcoma which occurs as a rare complication of treatment for breast cancer [Clark et al,2005 Grimer and Judson et al,2010]. There are also some genetic risk factors with up to 10% of

STS being attributable to inherited syndromes [Barai et al, 2004]. Neurofibromatosis 1 carries 10% lifetime risk of malignant tumours of peripheral nerve sheath caused by mutations in the *NF1* gene or p53 gene [Lietman, 2010, Billingsley et al, 1999, Grimer and Judson et al, 2010]. Retinoblastoma owing to a gene line mutation in RB1 tumour suppressor gene face an exceptionally high risk of osteosarcoma and STS which is further elevated by the receipt of radiotherapy [Grimer and Judson et al, 2010, Perry, 2002]. Also, patients with Li-Fraumeni's syndrome and Von Recklinghausens disease also have increased risk of sarcoma. As many as 7 percent of children with STS may have Li-Fraumeni syndrome (LFS) [Delaney and Kirsch, 2010].

LFS is an autosomal dominant cancer predisposition syndrome caused by germline mutations (ie, in every cell) in the *TP53* tumour suppressor gene [Lietman, 2010, Borden et al, 2003, Delaney and Kirsch, 2010, Grimer and Judson et al, 2010]. LFS is primarily characterized by soft tissue and bone sarcomas, breast cancer; brain tumor, leukemia, and adrenocortical cancer occurring before the age of 45 [Grimer and Judson et al, 2010, Delaney and Kirsch, 2010].

STS may arise virtually anywhere [Gordon et al, 1991]. 40% of STS occur in the lower limb/ girdle, 20% in the upper limb/ girdle and 20% in the retro-peritoneum/ intra-peritoneum, 10% in the trunk and 10% in the head/ neck [Clark et al, 2005, Lietman, 2010, Yagnik et al, 2009, Billingsley et al, 1999, Demetri et al, 2010]. Non-orthopaedic sites are uterus, retroperitoneum, thorax or head and neck [Eriksson, 2010]. Retroperitoneal sarcomas are generally liposarcomas or leiomyosarcomas [Borden et al, 2003]. Congenital fibrosarcomas are also most often seen in the extremities (74%), followed by the head and neck (15%) [Laffan et al, 2009].

The classical presentation of STS is a painless, gradually enlarging mass [Lietman, 2010, Yagnik et al, 2009]. Unlike bone sarcomas, soft-tissue sarcomas frequently are not associated with pain, so lack of pain does not make a mass more likely to be benign. [Lietman, 2010] The

size of tumour at time of diagnosis varies according to site. Tumours at distal limbs, head and neck are usually smaller because they are noticed early whereas thigh and retroperitoneal tumours may become huge before they are detected. Any soft tissue lump exhibiting any of the following four clinical features should be considered to be malignant until proved otherwise [(i) increasing in size, (ii) size >5 cm, (iii) deep to the deep fascia, (iv) painful. The presence or absence of pain is not typically predictive of malignancy [Lietman, 2010] Grimer and Judson et al, 2010]. Bleeding from soft-tissue sarcoma is a very rare presentation for extremity sarcoma. [Yagnik et al, 2009]

Recurrence after previous excision also suggest malignancy. [Grimer and Mottard et al]

The more of these clinical features present, the greater the risk of malignancy with increasing size being the best individual indicator [Grimer and Judson et al, 2010]. In general, the deeper the mass, the more likely it is to be a sarcoma. [Perry, 2002]. When sarcoma are superficial, they generally have a less aggressive biological behaviour than deep lesion [Kransdorf and Murphy, 2000]. Although there are exceptions, most malignant STS grow as a deep space-occupying lesion enlarging in the centripetal fashion, pushing rather than infiltrating adjacent structures. Our index patient had superficial tumour localization. As they tumour grow they compress adjacent tissue with formation of a pseudocapsule of fibrous tissue, seen in our patient. In general, the only way to be sure that a mass is not malignant is to biopsy it [Lietman, 2010]. The majority of retroperitoneal sarcomas are insidious in terms of growth and lack of early symptoms. But involvement of contiguous structures such as major blood vessels, nerves, and viscera lead to mass effects like paraesthesia, bladder compression, hydronephrosis. [Borden et al, 2003]. While STS is not a common tumor, accounting for only 1% of cancer diagnoses in the United States, it carries a high mortality rate, and tumor grade is a strong predictor of outcome [Fernebro et al, 2006]. Accurate imaging studies that can provide additional information on grading and staging may be useful in the management of the

disease[Ioannidis and Lau,2003]. Diagnosis is based on radiology, cyto-histopathology and immunochemistry

Fine needle aspiration cytology(FNAC) is restricted to assessing metastasis and recurrence. This is because it may obtain specimen from reactive zones instead of tumour core[Sengupta et al,2009]. STS are graded on basis of histopathology and cytology into a) high grade consisting of pleomorphic cells or round cells and b) low grade consisting of spindle cells or myxoid cells. This cytological grading is based on cellular architecture of aspirate, predominant cell type, necrosis, mitotic rate, cellular pleomorphism, irregularity, nucleolar prominence and lobulation[Ioannidis and Lau,2003]. Thus the anatomic location, tumour size, histological grading, lymph node involvement and distant metastasis became the basis of tumour staging. The staging system now is based on the modified 1997 American joint committee on cancer(AJCC) shown below[Yagnik et al,2009,Cheng and Thompson,1999].

The introduction of new parameters in staging like anatomical location, depth with reference to investing muscle fascia makes MRI the modality of choice due to its inherent multi-planar potentials and better anatomical definitions[Cheng and Thompson,1999]. MRI have become part of the standard procedure for the preoperative evaluation of STS because of high-resolution mapping of the anatomical extension of the tumour [Fernebro et al, 2006]. Also, MRI can define vascular involvement or displacement thereby diluting the usefulness of contrast angiography. It also serves as operative road map or anatomic atlas. Dynamic, contrast-enhanced MRI is used to differentiate viable from nonviable (necrotic or avascular) tumour areas, and could therefore potentially be valuable for preoperative prognostication [Fernebro et al, 2006] Conventional MRI is the modality of choice for depicting morphological changes in the tumor and surrounding tissue after neoadjuvant therapy but is limited in its ability to determine tumor necrosis [Borden et al,2003] Dynamic enhanced MRI techniques can reliably predict degree of tumor necrosis, differentiates tumour core and capsule from the surrounding oedema

and identify tumor recurrence after surgery [Kransdorf and Murphy,2000,Borden et al,2003] The fast STIR sequence is excellent for evaluation of soft-tissue tumors, and contrast-enhancement is not always needed. [Tokuda,2009] . The most promising and important sequences for evaluation of soft-tissue tumors are those that entail fat suppression[Tokuda,2009]. Suppression of the relatively high signal intensity of fat leads to more efficient use of the dynamic range for display of tissue contrast on MR images and reduction of the severity of artifacts since fat is a major contributor to many motion artifacts, [Tokuda,2009]. Use of T1-weighted fat-suppressed contrast-enhanced imaging can improve lesion detection, tissue characterization, and determination of tumor extent [Tokuda,2009] .

But MRI has a lower resolution than microscopic examination, hence histology is still required [Fernebro et al, 2006] MRI is non-specific in the diagnosis of benign or malignant tumours. Cystic lesions may still be differentiated from solid lesions using ultrasound (USS) if masses are accessible to sonography and Doppler study is able to detect tumour thrombus in vessels[Fornage,2000]. USS in combination with physical examination andUS-guided needle biopsy can provide a cost-effective shortcut to a final diagnosis. USS should be used as the first-line examination technique, with MRI being reserved for use as a problem-solving tool when US is inconclusive[Fornage,2000]. Ultrasound may be useful for following patients for postoperative recurrence in the extremities[Borden et al,2003].

Evaluation of soft-tissue sarcoma includes evaluation of the primary site as well as of the potential sites for metastases [Ioannidis and Lau,2003]. The regional nature of MRI precludes identification of lymph nodes outside of the imaging plane and of pulmonary metastases[Borden et al,2003] High resolution Computed tomography is the current mainstay for staging of disease in the lungs given the risk for hematogenous spread from a high-grade sarcoma.[Borden et al,2003, Demetri et al,2010, Grimer and Judson et al,2010]. CT also is advantageous in separating

intra-abdominal STS especially liposarcoma from bowel loops [Clark et al,2005] But MRI is better to separate psoas muscles from retroperitoneal STS. ¹⁸F-fluoro-deoxyglucose Positron emission tomography (PET) can overcome limitations in MRI in quantifying biological activity and for whole body staging [Borden et al,2003]. In addition, PET allows detection of abnormal lymph nodes away from the site of the tumor as well as lung metastases [Borden et al,2003]. PET scan may be useful for prognostication and grading, and to assess response to chemotherapy. [Demetri et al,2010]. Positron emission tomography (PET) scanning may be helpful in specific circumstances (e.g., prior to radical amputation following recurrent disease), but cannot at the present time be recommended as a routine staging investigation in patients with STS [Grimer and Judson et al,2010]. ¹⁸F-FDG PET is considered as a potentially major advance in clinical practice, because it may offer information about not only the anatomic extent but also the behavior of tumors, thus helping to guide therapeutic choices [Ioannidis and Lau,2003]. MRI is preferred for extremity sarcomas, whereas CT is preferred for retroperitoneal sarcomas [Demetri et al,2010]. Radiological evaluations especially in Africa usually begin with conventional radiography despite being frequently un-rewarding. It may rule out exostosis masquerading as STS. Also, non-specific dystrophic calcifications in slowly growing lower extremity mass in young adult radiographs suggest synovial sarcoma as a diagnosis of exclusion [Kransdorf and Murphy,2000]

Abdominal/pelvic CT should be considered for myxoid round cell liposarcoma, leiomyosarcoma, epithelioid sarcoma, or angiosarcoma, and MRI of the total spine should be considered for myxoid round cell liposarcomas because of the higher risk for metastasis to spine compared with other STS. [Demetri et al,2010]. Central nervous system imaging should be considered for patients with alveolar soft part sarcomas and angiosarcomas because alveolar soft part sarcomas have a relatively increased propensity to metastasize to the brain, especially in patients with stage IV disease in the presence of pulmonary metastases [Demetri et al,2010].

Biopsy is the cornerstone of the investigation [Yagnik et al,2009] Lesions <5cm are best diagnosed by excisional biopsy. Lesions >5cm are candidates for Tru-Cut or incisional biopsy. [Ioannidis and Lau,2003]. Incisional biopsy is more specific and sensitive as compared to Tru-Cut biopsy [Ioannidis and Lau,2003]. Another reason that contrast enhancement may be helpful in the evaluation of a soft-tissue mass is to help the radiologist plan the biopsy route, especially in evaluation of a cystic or necrotic mass. [Tokuda,2009] The area of enhancement representing more viable tumor tissue typically has higher diagnostic yield than the unenhanced necrotic areas of the mass [Tokuda,2009]. STS with a microscopically infiltrative growth pattern, as determined on whole-tumour sections, have a considerably higher risk for both local recurrence and metastasis compared to STS with a pushing growth pattern [Fernebro et al, 2006]. Tumours with infiltrative growth have an increased risk for local recurrences as well as for metastases [Fernebro et al, 2006] Tumours with diffuse infiltrative growth on MRI had a worse prognosis, both with regards to local recurrence and metastasis, whereas tumours with a pushing or focally infiltrative growth pattern on MRI had a better prognosis [Fernebro et al, 2006]. Pushing growth pattern was considered when the tumour was well defined without peripheral extension to the surrounding tissue, whereas classified as infiltrative if the tumour had an irregular surface with spicula-like extensions into the surrounding tissue. [Fernebro et al, 2006] Infiltrative growth was classified as focal (< 25% of the tumour circumference) or diffuse (> 25% of the circumference) [Fernebro et al, 2006]. Scintigraphy using ⁶⁷Ga are to detect metastasis, local bone invasion and staging [Barai et al,2004]. Barai et al,2004, substantiated the use of bone scan with 76.1% positive values in skeletal metastasis in symptomatic bone pain patients.

The main cause of death in sarcoma is distant metastases [Yagnik et al,2009]. The most common site of metastases for soft-tissue sarcoma of extremities is the lung as in our patient [Robinson et al,1994, Borden et al,2003, Yagnik et al,2009,Billingsley et al,1999, Demetri et al,2010, Ioannidis and Lau,2003]. Of patients with extremity

sarcoma, approximately 20% will have isolated pulmonary metastatic disease at some point in the course of their disease [Billingsley et al,1999]. Although pulmonary metastases most commonly arise from primary tumors in the extremities, they may arise from almost any histologic variant or primary site [Billingsley et al,1999]. Metastases, mainly pulmonary, are seen in 5%–10% of infantile or congenital fibrosarcoma cases, with local recurrence reported to be between 17% and 43% [Cheng and Thompson,1999]. Most metastases from soft-tissue sarcomas are to the lung and, less commonly the lymph nodes. [Perry,2002]. Less than 3% of adult sarcoma patients will have metastases to lymph nodes [Borden et al,2003]. STS arising in the abdominal cavity commonly metastasize to the liver and peritoneum [Delaney and Kirsch,2010]: Abdominal metastasis of STS is rare and survival is dismal [Behran wala et al,2004]

The major therapeutic goals are long-term survival, avoidance of local recurrence, maximising function and minimising morbidity [Grimer and Judson et al,2010]. Surgical excision remains the treatment of choice for metastases of soft tissue sarcoma to the lung [Billingsley et al,1999]. The ability to resect metastatic disease completely is consistently the most significant factor in determining postmetastasis survival [Billingsley et al,1999].

STS are very heterogeneous tumors, both pathologically and clinically, making standardization of therapy very difficult. [Ramaa musthy et al,2009] Delineation and greater understanding of these genetic abnormalities may lead to more effective medical therapy [Lietman,2010]. The anatomic site of the primary disease is an important variable influencing treatment and outcome [Demetri et al,2010]. Nowadays' mainstay of therapy is surgery [Yagnik et al,2009, Eriksson,2010] The principle of management is complete excision of tumor with negative surgical margin [Yagnik et al,2009]. The most important treatment for all localized STS is radical surgery whenever possible. Resection with appropriately negative margins is recommended, although negative but closer margins may be effective in patients undergoing

radiotherapy. [Demetri et al,2010]. Function preserving Limb conservation is the goal of treatment of STS of the limbs, although 5-10% will ultimately require amputation [Clark et al,2005 Yagnik et al,2009,Goel et al,2007, Ramaa musthy et al,2009]. Amputation is reserved only for patients with vascular, neurologic or bone involvement [Yagnik et al,2009,Ramaa musthy et al,2009]. The skin is rarely involved in STS and helpful for wound closure. Vascular reconstruction with saphenous vein harvested from opposite leg are practised in vessel compromised [Cheng and Thompson,1999]. If neurovascular structures are not encased (ie, not more than 50% surrounded in the case of arteries or motor nerves), then these structures are spared [Lietman,2010]. If arteries are encased, the vessels are bypassed and the encased structure is left with the resection specimen [Lietman,2010]. Because of their large size and locally advanced presentation (60% high grade), retroperitoneal sarcomas are often difficult to manage [Borden et al,2003].

Standard therapy for retroperitoneal sarcoma is surgical resection including en-bloc resection with surrounding viscera, [Borden et al,2003] Unlike extremity sarcoma, the majority of deaths from retroperitoneal sarcoma result from local disease progression [Borden et al,2003].

Combination therapy is superior to that of surgery alone. Patients with low risk for local recurrence do not require radiotherapy [Yagnik et al,2009].

STS have traditionally been managed by wide excisional biopsy and radiotherapy [Yagnik et al,2009] Radiotherapy is also considered for high grade tumours of limb and when patient declines surgery. For orthopaedic sites, pre- or postoperative radiotherapy decreases local recurrence [Eriksson,2010]. Radiotherapy is delivered by external beam or brachytherapy. Neoadjuvant radiation therapy and chemotherapy are frequently used as adjuncts [Lietman,2010]

The role of chemotherapy in soft-tissue sarcoma still needs to be defined and reserved for advanced disease [Clark et al,2005 Yagnik et al,2009, Ioannidis and Lau,2003]. Chemotherapy has been widely used for

decades in different situations in STS: (i) as palliative treatment in advanced cases; (ii) for down-staging, i.e. decreasing size and eradicate micro-metastases to facilitate radical surgery of the primary tumour, lung metastases or, occasionally, metastases in other sites; and (iii) as adjuvant or neoadjuvant treatment in high-grade localized disease in combination with the local treatment of the primary tumour[Eriksson,2010]. The response to chemotherapy in metastasis depends on tissue sub-type. Rhabdomyosarcoma response to chemotherapy is better in children than adults. Doxorubicin and ifosfamide are the two drugs with the best established response rates in soft-tissue sarcoma, and a combination of these drugs has been a 'gold standard' for several years[Eriksson,2010]. The most effective drugs, especially doxorubicin, have shown an ability to produce overall response (complete or partial) in advanced cases in the range of 20–30% , even if additional patients benefit minor responses or stable disease for a shorter or longer time. With the addition of more drugs, e.g. ifosfamide, in combinations, the overall response seems to be somewhat improved , but the effect on overall survival is uncertain. [Eriksson,2010] However, there is an emerging knowledge of the biology and sensitivity to treatment for different histological subtypes. New drugs such as gemcitabine, taxanes and trabectedin have been explored in several studies, showing promising results[Eriksson,2010] Specific treatment for different subtypes is emerging. Examples are trabectedin in liposacoma and leiomyosarcoma, and taxanes in angiosarcoma[Eriksson,2010]. .

Anthracyclines and ifosfamide have been established as the most active chemotherapeutic agents for metastatic adult soft tissue sarcomas with single-agent response rates of 16–36% [Borden et al,2003]. Other agents have had response rates of 10–20%, but only dacarbazine has been used extensively in combination chemotherapy studies[Borden et al,2003] .

Combination regimens have response rates of 35–60% but have increased toxicity compared with single agents[Billingsley et al,1999]. In general, combinations not containing an anthracycline had poor activity[Borden et al,2003] knowledge related to specific treatment

for different subtypes is emerging[Eriksson,2010]

Resolution of the histopathological complexity is being aided by data from molecular and chromosomal characterization. Improvements in imaging, definition of prognostic factors, and surgical and radiotherapeutic treatment have resulted in improved local control [Borden et al,2003]

Some histiotypes seem to be totally resistant, at least to the chemotherapeutic drugs available today[Eriksson,2010]. Immunoactive drugs such as interferon or modern targeted drugs may have an effect in some cases. There is no evidence for the use of chemotherapy in, for example, gastrointestinal stromal tumours (GISTs) , extraskeletal myxoid chondrosarcoma , clear cell sarcoma or alveolar soft part sarcoma [Eriksson,2010]

Rather low sensitivity for chemotherapy is reported for example, epithelioid cell sarcoma, adult fibrosarcoma, haemangiopericytoma, and malignant peripheral nerve sheet tumour (MPNST), but some patients with these variants may show response[Eriksson,2010]

Intermediate sensitivity for chemotherapy seems to be present for most of the more common types of STS, such as liposarcoma, leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma and angiosarcoma [Eriksson,2010] .

Some sarcomas more common in childhood and adolescence are in most cases clearly sensitive to multiagent combinations of drugs. This is true for extraskeletal Ewing sarcoma, rhabdomyosarcoma of embryonal and alveolar types, and desmoplastic small round cell tumour; the latter has a very poor prognosis[Eriksson,2010]

Despite multidisciplinary and multimodality treatment, 10–20% of the tumours recur locally and distant metastases develop in about 30% of the patients[Fernebro et al,2006]. Resections with wide margins are generally associated with a low (< 10%) risk of recurrence[Perry,2002]. Microscopically positive surgical margins are associated with a higher rate of local recurrence and lower rate of disease-free survival in

patients with extremity sarcomas [Demetri et al,2010]. Patients who have a recurrence are at increased risk for metastatic disease, and it is often very hard to achieve local control, as these patients frequently have had tumor contamination of the wound [Lietman,2010]. Approximately half of all STS patients with intermediate or high-grade tumours develop metastatic disease requiring systemic treatment the overall survival is approximately 50% at 5 years [Grimer and Judson et al,2010]. Recurrent tumor usually presents as a mass that exhibits increased signal intensity on T2 – weighted MRI images and demonstrates internal enhancement after administration of intravenous contrast. These imaging characteristics can help differentiate tumor from post-therapeutic soft tissue alterations [Costelloe et al,2007]. Nodular granulation tissue/scar may enhance internally but is expected to remain stable or decrease in size on follow-up examinations [Costelloe et al,2007].

Little benefit after amputation, pulmonary metastectomy and aggressive chemotherapy has been achieved in advanced disease [Clark et al,2005]. Surgical simple removal of visible tumour leaves microscopic disease in situ at a recurrence rate of 90% [Clark et al,2005]. 5-10% of recurrence rate might be expected after optimal treatment of STS of the limbs. Whilst most events will arise in the first five years following diagnosis, low grade tumours in particular may relapse late. [Grimer and Judson et al,2010]. Since 2/3 of recurrence rate occur within 2 years, follow-up should be most intense during this period. Follow up protocol is clinical examination every month for 2 years, one in 3 months for next year, six monthly up to 5 years and thereafter yearly [Lietman,2010,Cheng and Thompson,1999]. Follow up should be continued for a minimum of 8 years for high grade tumours and longer for low grade tumours [Grimer and Judson et

al,2010]. MRI and chest x-ray are done in follow-up. 3-5 years survival rates for stages I, II, III, and IV are approximately 90, 70, 50 and 10 -20% respectively

Patient's prognosis or local recurrence is dependent on the patient's age, histologic grade, size, resection margin, vascular invasion and location of the tumor [Lietman,2010], Grimer and Judson et al,2010, Stojodinovic et al,2002,Perry,2002, Cheng and Thompson,1999,Fernebro et al, 2006]. Resection margins of 1 cm or greater or resections with a fascial boundary are adequate and will leave patients with a much lower than 10% risk of recurrence. [Lietman,2010]. Despite progress in multimodality treatment, more than 4000 Americans will die each year of soft tissue sarcoma [Billingsley et al,1999].

Future research challenges include homogenizing and improvement of STS histo-subtyping, possibly with genetic markers, as well as molecular prognostication will better determine the most accurate treatment modality for each of these heterogeneous group of mesenchymal malignancies.

Differential diagnosis of soft tissue-sarcoma includes lipoma, sebaceous cyst, neurofibroma, myositis ossificans, squamous cell cancer, melanoma et cetra [Yagnik et al,2009]

Conclusion

Soft tissue sarcoma is a heterogenous group of malignant tumours that are mesodermal in origin. Tumor's site, size and depth are important integral components of staging and prognosis. Magnetic resonance imaging is the gold standard and preferred imaging tool that can substantially resolved these staging prerequisites by virtue of its good soft tissue contrast resolution.

Stage	Grade.	Tissue size	localization	Node	Metastasis.
1A	Low	≤ 5cm	Superficial.	-	-
1B	Low	>5cm	Superficial.	-	-
IIA	Low	>5cm	Deep.	-	-
IIB	High.	>5cm	Superficial.	-	-
III	High.	>5cm	Deep.		
IVA	Any.	Any.	Any	+	-
IVB	Any.	Any.	Any	-	+

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