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Musculoskeletal tumours throughout history and beyond: Clinical features, imaging, staging and biopsy

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SYSTEMATIC REVIEW

Musculoskeletal tumours throughout history and beyond: Clinical features, imaging, staging and biopsy

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Abstract

Background: Over the last century, there has been a remarkable development in the study of bone and soft tissue sarcomas. This is primarily due to the improved knowledge of the nature of these lesions and the improved imaging technology. In literature there are many protocols that are being used and all of them have reported various advantages and disadvantages of each technique used. However, there is no set guideline and whatever has been proposed has been developed on the basis of the experience of different centres and different surgeons.

Objective: The current systematic review was planned to thoroughly evaluate the levels of evidence on which we base decisions for surgical management of lower extremity bone tumours.

Methods: The review included descriptive studies published in the English language. Studies included case reports, case series and experiences of different centres for the surgical management of lower extremity bone tumours. Articles reporting all levels of evidence – Level I to V – were included. PubMed, ERIC, MEDLINE, EMBASE and Cochrane Reviews databases from 2002 to 2012 were searched.

Results: Information was gathered and thoroughly studied from 63 articles. There were no Level I studies, 2(3.2%) Level II studies, 47(74.6%) Level III, and the remaining 14(22.2%) studies were Level IV and Level V.

Conclusion: Sarcomas are rarely occurring neoplastic conditions which are present in all age groups but commonly affect young age population. Most are asymptomatic but can present with pain or pathological fracture. These lesions are commonly diagnosed with plain radiographs. CT scan and MRI may be used to delineate anatomy and to quantify the extent of soft tissue involvement. Various advantages and disadvantages associated with each aspect in the management of patients starting from the basic history-taking, physical examination, imaging, biopsy principles, peri-operative laboratory work-up and staging of the cancer were studied. Treatment ranges from conservative to en-block resection including extended curettage. Aggressive tumours should be closely followed up for recurrence and metastasis.

Keywords: Musculoskeletal, Orthopaedic, Tumour, History, Staging.

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Introduction

Sarcomas have been found in literature since the time of the ancient Egyptians in 1500 BC.[1] Galen was the first to use the term "sarcoma" which comes from Sarx (flesh), and he distinguished them from cancers, that these arise in the flesh.[2,3] Till the 1800s there was no progress and the mainstay of treatment was amputation.

The first case series of bone tumours was published by Samuel Gross in 1879 after the advent of X-rays and microscope. He published 165 cases comrising of giant cell tumours, osteosarcoma and Ewing's and he gave both clinical and pathological views.[4] In 1900s James Ewing and Ernest Codman were the ones who formed the first orthopaedic tumour registry. Ernest Codman is known for what he called the Codman's triangle.[5,6] Ewing was a pathologist who suffered from chronic osteomyelitis, which was never cured.[7] William Coley was a physician and is considered the pioneer of using radiation, immunotherapy and chemotherapy for cancers.[8] He used Coley's reagent, which was a bacterial solution, which he injected and found that the sarcoma regressed with that. His daughter formed an institute after that and the research of immunotherapy developed from there.[8]

Over the last century, there has been a remarkable development in the study of bone and soft tissue sarcomas. This is primarily due to the improved knowledge of the nature of these lesions, improved imaging technology – previously it was just X-rays that were used to base the findings upon and skipped lesions as well as neurovascular status could not be identified. Hence a wide margin was not a plausible option. But now with improved imaging technology, such as magnetic resonance imaging (MRI), accurate knowledge of the extent of the tumour is possible.[9,10] Biopsy techniques have also improved and there is better pathological recognition before starting the treatment.[11] The most impact that has been made in survival has been the advent of chemotherapy because previously when there was only surgery available for bone

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sarcomas, more than 80% patients used to die. The 5-year survival rate was <20%. But with the advent of chemotherapy, it has gone up to 78-80% and it has led to the increased survival in these patients and has helped in limb sparing surgery.[12] The modern modular endoprosthesis has allowed the surgeons to salvage the limb even in large tumour resections. Allograft banks have also helped in reconstruction and limb-saving surgeries.[13]

The current systematic review included studies from 2002 to 2012 about the levels of evidence on which health professionals base decisions for surgical management of lower extremity bone tumours. PubMed, Education Resources Information Centre (ERIC), MEDLINE, EMBASE and Cochrane Review databases were searched and resulted in 63 articles that were thoroughly scanned. There were no Level I studies, 2(3.2%) Level II studies, 47(74.6%) Level III, and the remaining 14(22.2%) studies were Level IV and Level V. These included case reports, case series and experiences of different centres. It was evident that there are many protocols being used and all of them have been reported to have lots of advantages and disadvantages.[14] However, there is no set guideline and whatever has been developed has been on the basis of the experience of different centres and different surgeons.

Soft Tissue Sarcoma: Soft tissue and bone sarcomas are very rare and heterogeneous group of tumours. They are <1% of all adult malignancies and <15% of all paediatric malignancies.[15]

Risk factors include radiation therapy, especially in childhood, exposure to chemicals such as vinyl chloride which is used in the plastic industry and arsenic, immunodeficiency, prior injury and chronic tissue irritation such as burns and scars, Paget's disease, bone infarcts, neurofibromatosis itself and various cancer syndromes like the hereditary retinoblastoma, Li Fraumeni syndrome and Gardner's syndrome.[16]

Sarcomas originate from mesoderm and are classified according to the adult tissue that they resemble. If they come from the muscle, they are rahbdomyo-sarcoma etc. and if they are bone sarcoma, they are classified according to the type of matrix they produce, like osteoid-producing ones are osteosarcomas and chondroid-producing are chondrosarcomas. With regard to grading, it is low, intermediate and high based on tumour morphology, extent of pleomorphism, atypia, mitosis and necrosis. Some use a 4-tier system as GI, II, III, IV but what needs to be understood is that the grade presents biological aggressiveness and correlates with the likelihood of metastasis. So a high-grade lesion has a higher chance of metastasising and it also has a high chance of being locally aggressive and progressing quickly with respect to time.[17]

Usually sarcomas grow centrifugally and the periphery is usually the least mature and they are enclosed by a reactive zone, which is the pseudocapsule, and this consists of compressed tumour cells, fibro-vascular zone of reactive tissue and a variable inflammatory component. Sometimes there is local invasion of this capsule and there are "skip metastases" found locally. Sarcomas usually respect anatomical borders and they take the path of least resistance and grow within the anatomical compartment in which they arise. But later if the tumour is very aggressive, it can violate the walls. Yet joint involvement usually is rare.[16,18]

Metastatic pattern usually involves dissemination almost exclusively through the blood. Lymphatic metastasis is negligible. Metastasis to lungs is the most common site.[16,18,19]

Assessment of Patient: Age of the patient can be an extremely important determinant in some lesions in which the age range of occurrence may be quite narrow. For example, malignant osseous lesions in patients under one year of age are usually metastatic neuroblastoma.[20] Malignant osseous lesions in those aged 1-30 years are usually osteosarcoma or Ewing's sarcoma.[16] Malignant osseous lesions in the 30-60-year range most commonly will be either chondrosarcoma, primary lymphoma or malignant fibrous histiocytoma, while malignant lesions in those aged >50 years most commonly will be due to metastatic disease or multiple myeloma.[21,22]

Pain in bone sarcoma is initially activity-related and usually it becomes progressive and at rest or at night. Soft tissue sarcomas are usually painless and the patient presents with mass, except for nerve sheath tumours, which may come with pain and neurological signs.

Physical examination should include general health, and, for the mass itself, the size, location, shape, consistency, mobility, tenderness, local temperature, change with position should be noted, and the same should be the case with atrophy of surrounding musculature, any neurological or vascular deficits, and systemic signs of other diseases like cafe-au-lait spots for neurofibromatosis. Also of importance is the examination of regional lymph nodes.[17,23]

Radiological Assessment

Plain X-ray: Initially, a musculoskeletal tumour should be simply imaged with a plain film that remains the most reliable imaging method for the assessment of both biological activity and probable histological diagnosis of an osseous lesion.10 Points to remember when assessing an X-ray include solitary/multiple lesions; location of the

bone involved; margins of the lesion well or ill-defined; the cortex eroded or destroyed; any peri-osteal new-bone formation; and the possibility of the tumour extending into the soft tissues.

According to location and age, differential diagnosis for epiphyseal lesions usually within the age range 10-15 years are generally chondroblastoma,[24] while in age range 30-40, they are usually giant cell tumours.[25] Similarly, for diaphyseal lesions in the younger age group, it is Ewing's sarcoma or fibrous dysplasia, and in the adults, it is usually lymphomas.[21] For spine lesions in patients >40 years, metastasis and multiple myeloma are at the top of the list.[26] In young patients there are more benign tumours like histocytosis and haemangioma.[27]

Patterns of bone destruction usually range from geographical to moth-eaten to permeative with increasing trend towards more aggressive tumours. Geographical lesions are probably locally invading tumours. Moth-eaten bone is found in myeloma and metastatic disease and signifies an increased disease burden.[26] Permeative is locally aggressive and malignant tumour like Ewing's and osteosarcoma.[16]

Peri-osteal reactions are graded from solid in benign tumours with thicker peri-osteum to onion peel appearance representing aggressive lesion.[27] Quickly growing tumour stretches the Sharpey's fibres, those that attach the peri-osteum to the bone. They stretch to such a degree that they become perpendicular to the bone, and then, when ossification takes place, lead to sunburst time of appearance or speculated appearance. More malignant and aggressive tumours don't have time for ossification, and results in a Codman's triangle formation.[5] This happens so quickly that the entire peri-osteum lifts up and it does not get time to ossify, and what one sees is a rim of the thing. So it is not a complete triangle.

Then the matrix that the bone lays down, usually the cartilaginous tumours, results in a chrondroid matrix, which usually appears fluffy like popcorn. The osteoid matrix is more dense and the tumour usually remains inside the bone.[28,29]

Computed Tomography (CT) Scan
It is used for assessing ossification and integrity of cortex; pathological fractures; localising the nidus of osteoid osteoma; detecting whether a thin rim of reactive bone is around an ABC; evaluating calcification in a suspected cartilaginous lesion and endosteal cortical erosion in a suspected chondrosarcoma; surgical planning and custom-made implant manufacturing; and pulmonary metastasis.

A CT scan is the only tool if the MRI is prohibited.
MRI: It has revolutionised bone sarcoma treatment. Benefits include calculation of the size and extent, intramedullary and extra-medullary spread and neurovascular structures, and it helps in a diagnosis, lipoma and haemangioma, without biopsy. Any soft tissue neoplasm deep to the fascia or >5cm is malignant until proven otherwise.[10,30]

Bone Scan: A bone scan is helpful in determining multiple lesions or skeletal metastases with limited sensitivity and specificity. It would miss intramedullary small skip lesions and it may be false negative (FN) in multiple myeloma and some cases of renal cell carcinoma.

Positron emission tomography (PET) Scan: The PET scan is the latest talk of the town.[31] It checks the distribution of positron-emitting radioisotopes, which are linked to biologically active molecules. The fluorodeoxyglucose (FDG) used is an analogue of glucose that becomes trapped in malignant cells and in proportion to their respective rate of glycolysis/activity. This results in providing a non-invasive three-dimensional (3D) visualisation of anatomy, if combined with CT/MRI, as well as a quantitative assessment of the physiology of the tumour. Another area of help is to differentiate between post-surgical or post-radiation changes and recurrence of tumour, which the MRI cannot. Viable tumour cells will actively light up in a PET scan.

Blood Tests: Albumin and total lymphocyte count (TLC) are used for assessing nutritional status of the patient which is directly associated with wound healing and wound dehiscence risk. Complete blood count (CBC) is the baseline to rule out infection and to check if leukaemia is suspected. Erythrocyte sedimentation rate (ESR) is elevated in infections, metastatic carcinoma and other tumours as well. If multiple myeloma is suspected, then the options are serum protein electrophoresis, prostate-specific antigen (PSA) for prostate carcinoma, calcium, alkaline phosphatase and parathyroid hormone (PTH) for metastatic or metabolic bone disease, and blood urea nitrogen (BUN) and creatinine if renal tumours are suspected. All the investigations should be completed before a biopsy. The differential diagnosis, extent of the lesion and potential resectability can affect the type of biopsy.[32]

Biopsy: Fine needle aspiration cytology (FNAC) is very cost-effective and can be done using a simple 10cc needle. It is up to 90% accurate at determining malignancy. It has fewer complications and may be good for obese patients or for tumours near neurovascular structure – if it is done radiologically-guided. The disadvantages are that it has very small sample size and requires a very expert and

dedicated pathologist, and one can only do cytology. It is good for metastatic lesions and sampling lymph nodes because you just need to identify if the lesion is malignant.

Core needle biopsy gets a little tissue and is also cost-effective. Core needle biopsy has a yield of up to 84-98% and accuracy of 81%. Accuracy further improves if it is done with image guidance.[33]

Incisional biopsy is the gold standard. It can employ frozen section to confirm that adequate tissue is sent. Even for some tumours one can plan surgery in one go. If clinically a giant cell tumour is suspected, a frozen section is sent to get confirmation and to do the surgery at the same stage. Contamination can occur which can compromise definite resection, especially if done by an inexperienced surgeon in the field of orthopaedic oncology. Cost is another issue. To overcome that, studies reported that out-patient clinic-based biopsy is safe, with diagnostic accuracy of 95.5% with low morbidity.[34,35]

Excisional biopsy is for small subcutaneous masses <3cm which are unlikely to be malignant upon radiological examination. For larger deeper lesions, excisional biopsy is safe if the MRI appearance is diagnostic and confirmatory of lipomas.[36]

Biopsy principles: The smallest of longitudinal incisions is needed. When doing a deep incision, like piercing the fascia, it should go through a single muscle compartment and should not contaminate an inter-muscular plane.[37] Demarcation lines and the principle of biopsy can be seen on the figure (figure).

A knife or curette is used while ensuring it is sharp. If going for bone holes, they should be oblong so that one can increase the length of the bone hole, but should not increase its diameter, as diameter affects stability. The corners are kept round to avoid stress points.

One should always obtain enough tissue and frozen section should be sent. If a tourniquet is used, it should not exsanguinate the limb. Any haematoma should be drained and haemostasis secured because the haematoma will be considered contaminated. Drains are used only when necessary. Drain tract is treated just like biopsy tract and has to be excised with it, and, as such, it should be in line with the incision.[38,39] It is critical that biopsy should preferably be done by the primary oncology surgeon who will do the definite procedure, otherwise limb-saving results will be suboptimal. Just getting the diagnosis is not the key.

Staging of Musculoskeletal Tumour: The Enneking staging system is the one that is accepted by the Musculoskeletal Tumour Society.[40] This defines benign tumours into latent, active and aggressive. Latent tumours are the ones that remain static or heal spontaneously such as lipomas or non-ossifying fibromas. Active tumours are those that progress with growth, but are limited by natural barriers as they don't grow out of the bone. Examples are angiolipoma and aneurysmal bone cyst. The aggressive tumours are the one ones that are progressive by growth,

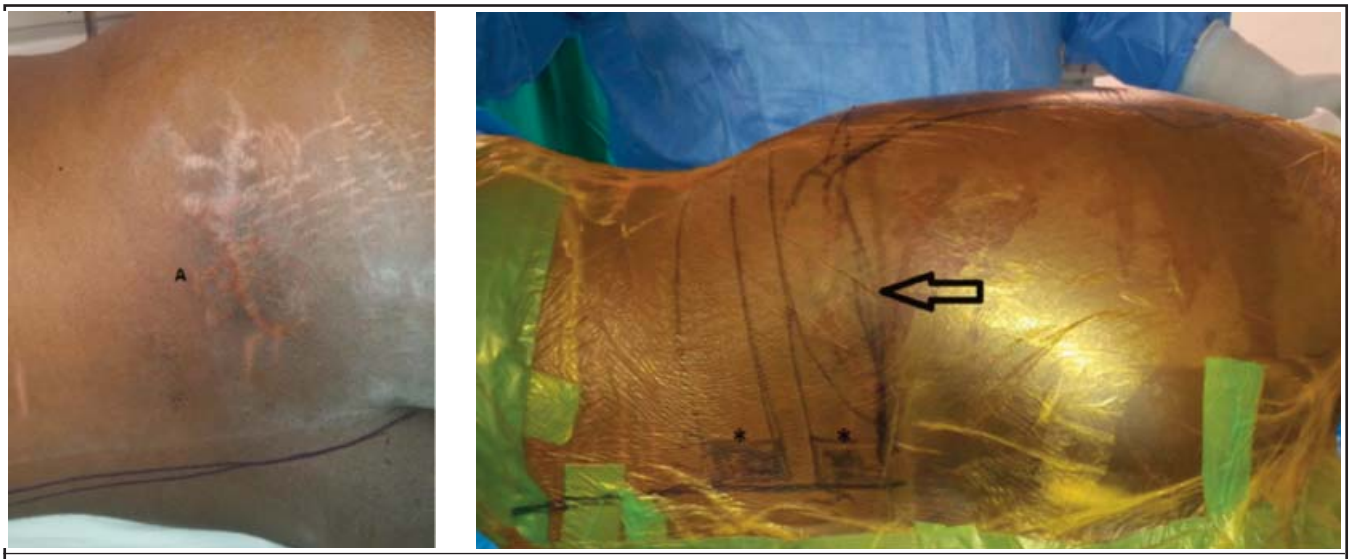

Figure: 14-year-old boy with osteosarcoma over right buttock region, biopsied with large transverse incision. Clinical photograph with the patient in left lateral position, showing a large transverse incision (14 cm) just above the right buttock region done for an incisional biopsy for a suspected sarcoma (A). Right photograph showing the large incision (arrow) we were forced to do to include the previous large scar as well, which compromised the blood supply to the skin flap leading to marginal necrosis and second debridement and excision of necrotic skin.
Asterisks showing L4 & L5 vertebrae levels..

invasive and not limited by natural barriers, like the giant cell tumour or aggressive fibromatosis.

Enneking staging of malignant tumours is based on histological grade, low or high, location, intra-compartmental or extra-compartmental, and whether metastasis is present. It includes stage-I tumours, intra and extra-compartmental with no metastasis.[40]

Similarly, the American Joint Committee on Cancer Staging system is the standard tumour, node and metastases (TNM) classification that covers all types of tumours. For soft tissue sarcomas, the T1 and T2 are according to the cut-off of 5cm. For the bone tumours, the T1 and T2 cut-off is 8cm.[38,41]

Conclusion

Bone and soft tissue sarcomas are frequently occurring neoplastic conditions which are present in all age groups, but commonly affect young population. Most are asymptomatic, but can present with pain or pathological fracture. These lesions are commonly diagnosed with plain radiographs. CT scan and MRI may be used to delineate anatomy and the extent of soft tissue involvement. Following the clinical, laboratory and radiological work-up, biopsy is the major mode of assessment to identify and lead to a definitive diagnosis. Based on the results, a directed approach is followed by a treatment plan which is surgery in most cases, and the decision is made with regard to the type of surgery to be planned.

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