Classification, imaging, biopsy and staging of osteosarcoma

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Abstract

Osteosarcoma is the most common primary osseous malignancy excluding malignant neoplasms of marrow origin (myeloma, lymphoma and leukemia) and accounts for approximately 20% of bone cancers. It predominantly affects patients younger than 20 years and mainly occurs in the long bones of the extremities, the most common being the metaphyseal area around the knee. These are classified as primary (central or surface) and secondary osteosarcomas arising in preexisting conditions. The conventional plain radiograph is the best for probable diagnosis as it describes features like sun burst appearance, Codman's triangle, new bone formation in soft tissues along with permeative pattern of destruction of the bone and other characteristics for specific subtypes of osteosarcomas. X-ray chest can detect metastasis in the lungs, but computerized tomography (CT) scan of the thorax is more helpful. Magnetic resonance imaging (MRI) of the lesion delineates its extent into the soft tissues, the medullary canal, the joint, skip lesions and the proximity of the tumor to the neurovascular structures. Tc99 bone scan detects the osseous metastases. Positron Emission Tomography (PET) is used for metastatic workup and/or local recurrence after resection. The role of biochemical markers like alkaline phosphatase and lactate dehydrogenase is pertinent for prognosis and treatment response. The biopsy confirms the diagnosis and reveals the grade of the tumor. Enneking system for staging malignant musculoskeletal tumors and American Joint Committee on Cancer (AJCC) staging systems are most commonly used for extremity sarcomas.

Keywords: Osteosarcoma, imaging, biopsy, Enneking staging

Introduction

Osteosarcoma is defined as the primary malignant mesenchymal bone tumor where the malignant tumor cells directly form the osteoid or bone or both.[1-12] Demonstration of osteoid directly formed by the malignant cells in histopathology is essential for making the diagnosis of osteosarcoma.[2,3]

Although the exact cause of osteosarcoma is still unknown, defects in RB and p53 genes play an important role in the process. Patients with germline mutations in RB have approximately 1000-fold increased risk of osteosarcoma and similarly patients with Li-Fraumeni syndrome (germline p53 mutation) also have greatly elevated incidence of this tumor. Abnormalities in INK4a, which encodes p16 (a cell cycle regulator) and p14 (which aids and abets p53 function) are also seen. It is noteworthy that osteosarcoma occurs more commonly at sites of bone growth, presumably because proliferation makes osteoblastic cells to acquire mutations that could lead to transformation.[1] Radiation too has been implicated in causation.[1,2] The risk of developing postradiation osteosarcoma correlates with radiation dose and use of electrophilic chemotherapeutic agents.[13-15] An etiological relationship has not been proven in prosthesis and metal hardware associated osteosarcomas.[16]

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Classification

Osteosarcomas are classified as primary and secondary. Primary are further sub-typed as intramedullry/central and surface osteosarcomas as per World Health Organization classification[2] [Box 1].

Radiological Investigations

Common sites of involvement of osteosarcoma are the metaphyseal areas (91%) of long bones of the extremities with its occurrence in (descending order) lower end of femur, upper end of tibia, upper end of humerus and upper end of femur. It can uncommonly occur in the diaphysis (9%) [Figure 1a]. Almost 50% of osteosarcomas occur around the

knee. Involvement of nonlong bones like jaw (gnathic), pelvis, scapula, spine, and skull increases with age. Involvement beyond the wrist and ankle (acral sites) is extremely rare.[2]

Plain X-ray

The characteristic radiological features are sun-burst appearance, periosteal lifting with formation of Codman's triangle [Figure 2], new bone formation in the soft tissues along with permeative pattern of destruction of bone and other features for specific types of osteosarcoma.[2,8,17,18] Osteolysis and expansion in the telangiectatic variety [Figure 3] of bone is observed while more of osteoblastic appearance is seen in the sclerosing type of osteosarcoma [Figure 1b]. The physis (growth plate) may, but not always, act as a barrier to tumor growth. Surface osteosarcomas have typical appearances [Figure 4]. After chemotherapy the tumor becomes well defined, capsulated, and more mineralized [Figure 5]. X-ray chest can detect metastasis in form of cannon ball appearance or nodules in the lungs [Figure 6a], but it is less sensitive than computerized tomography (CT) scan of the thorax [Figure 6b] for early detection of small sub-centimal nodules.[19]

Box 1: Classification of osteosarcoma

Primary osteosarcomas

Conventional-intramedullary/central high grade (most common) further sub-typed as:

- Osteoblastic (50%)
- Chondroblastic (25%)
- Fibroblastic (25%)

Small cell

Telangiectatic

Low grade central

Surface osteosarcomas:

- Parosteal
- Periosteal
- High grade surface

Secondary osteosracomas can occur in Paget's disease and after radiation exposure.[1,2]

Unusual forms of osteosarcoma given below are viewed as subtypes of conventional osteosarcoma because their biological behavior is similar.[2]

- Osteoblastic osteosarcoma-sclerosing type
- Osteosarcoma resembling osteoblastoma
- Chondromyxoid fibroma-like osteosarcoma
- Chondroblastoma-like osteosarcoma
- Clear-cell osteosarcoma
- Malignant fibrous histiocytoma-like osteosarcoma
- Giant cell rich osteosarcoma
- Epithelioid osteosarcoma

Computerized tomography scan

CT scan delineates the bony anatomy/architecture like cortical integrity more clearly and picks up pathological fracture and is helpful in assessing ossification and calcification (chondroid component) more accurately.[20,21] However, the soft tissue component and medullary extent is best defined by an MRI.[22-24]

Magnetic resonance imaging

MRI is the most accurate tool for determining the limits of tumor within and outside the bone.[7,22-24] MRI should include the whole of the involved bone with one joint above and below so that skip lesions are not missed in the same bone and across the joint. MRI accurately and precisely delineates (1) extent of the tumor into the soft tissues and the medullary canal, (2) involvement of joint, (3) crossing of the lesion through and/or around the growth plate, (4) any skip lesion in the same bone and across the joint in other bone, (5) proximity and/or encasement of the neurovascular bundle by the tumor [Figure 7]. Recently, even the

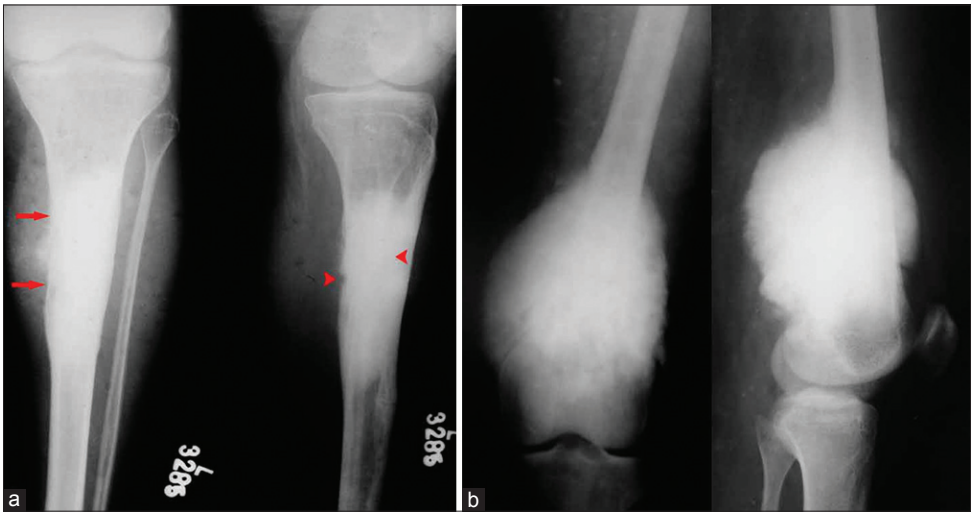

Figure 1: (a) X-ray anteroposterior and lateral views of proximal tibia and knee joint showing diaphyseal osteosarcoma of tibia with sclerosis (arrow), cortical destruction on posteromedial side (arrow heads) and new bone formation in the soft tissues (b) x-ray distal end of femur (anteroposterior and lateral views) showing sclerosis/radio-opacity in sclerosing osteosarcoma

response of chemotherapy is being judged by MRI as the neo-angiogenesis decreases with chemotherapy, necrosis occurs, and the tumor shrinks with better capsulation. This is done by performing a contrast enhancement and diffusion MRI.[25,26] MRI is also being coupled with Positron Emission Tomography for detection of the systemic involvement by the tumor, local recurrence, and metastasis after treatment. In view of the nonspecific findings of an MRI, it should always be correlated with the patient's x-ray.

Radionuclide bone scan

Tc99 methylenediphosphonate (Tc99 MDP) bone scan is the most commonly used investigation for detecting osseous metastasis [Figure 6c]. It is performed by injecting 20 mCi of isotope intravenously and taking images at different intervals, in three phases: (1) the flow phase, (2) the immediate or equilibrium phase, and (3) the delayed phase. The flow phase demonstrates blood flow just like radionuclide angiogram; the equilibrium phase shows the reactive vascular flow and the distribution in the intercellular spaces, and the delayed phase is after 2-4 hours when the radionuclide is excreted in the urine except in the areas of the osteoblastic activities. This radio-isotope has special predilection to the sites of increased osteoblastic activity and highly vascular areas like the sites of metastasis in sarcomas. It is most easily available and cost-effective investigation for detecting bony metastasis in osteosarcoma.[27]

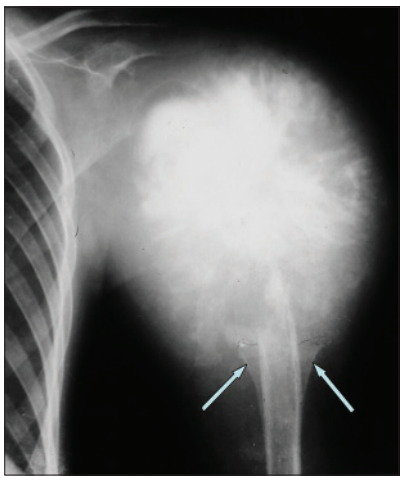

Figure 2: X-ray of humerus anteroposterior view showing osteosarcoma of the proximal humerus- typical sun burst or sun ray appearance, new bone formation in soft tissues, and Codman's triangles (arrows)

Positron emission tomography

Positron Emission Tomography (PET), which picks up metabolic activity is evolving with tremendous potential in oncology.[28-34] Further combining the images of 'form' i.e. the anatomical structure provided by CT and MRI and those of 'function' i.e. metabolic or biochemical activity, provided by PET can be precisely aligned or correlated. MRI combined with PET facility reduces radiation exposure when compared to a CT.

PET is utilized in: (1) selecting the region of a tumor most likely to yield diagnostic information for biopsy, (2) staging known malignancies, (3) monitoring the effect of therapy, (4) to establish the cause of suspected recurrence seen on other imaging modalities. It differentiates between fibrosis and recurrent tumor (5) detecting tumor recurrence, especially in the presence of elevated levels of tumor markers, (6) differentiating benign from malignant lesions, (7) searching for an unknown primary tumor with metastasis of unknown origin, (8) guiding radiation therapy planning.[33]

The main drawback is the difficulty and cost of producing and transporting the radiopharmaceuticals used for PET imaging, which are usually extremely short-lived. The half life of radioactive fluorine[18] used to trace glucose metabolism (using fluorodeoxyglucose, FDG) is 2 hours only. Its production requires a very expensive cyclotron as well as a production line for the radiopharmaceuticals. It can

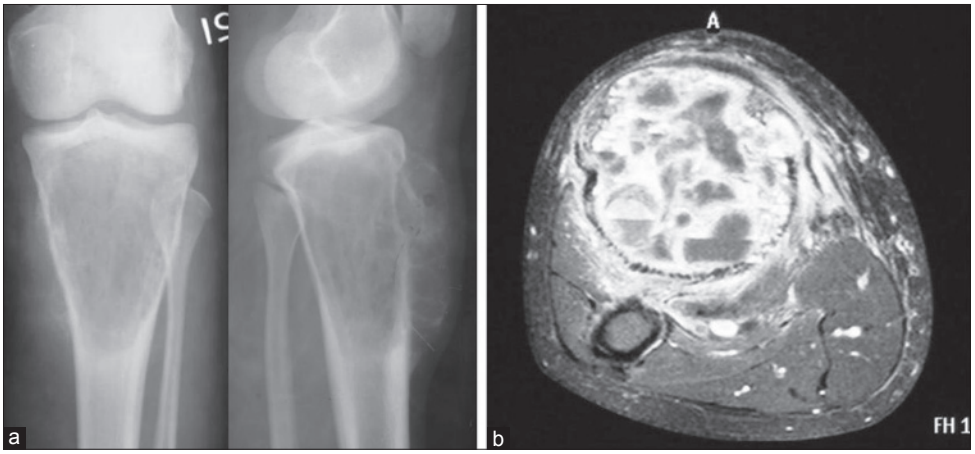

Figure 3: Telangiectatic type of osteosarcoma of the proximal tibia: (a) X-ray anteroposterior and lateral views showing lysis and expansion (b) MRI showing fluid levels

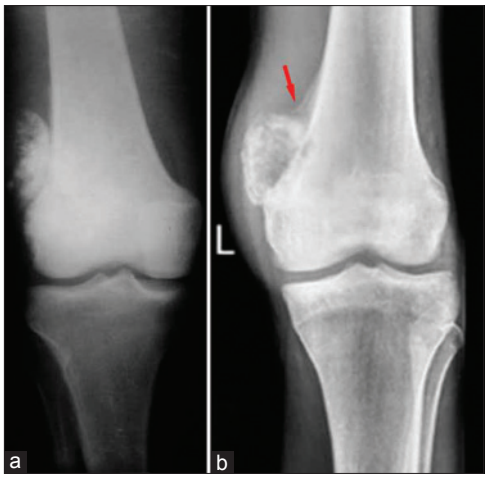

Figure 4: X-ray of knee joint anteroposterior views showing surface osteosarcoma: (a) parosteal (b) periosteal. See the under lying cortex is visibly intact in 'a' and lifting of periosteum in 'b' (red arrow). However, both are on the surface of the bone

give false negative and positive results and is still considered the investigation under continuing research.[33,34]

Biochemical markers

The role of biochemical markers like serum alkaline phosphatase (ALP) and lactate dehydrogenases (LDH) for diagnosis, prognosis and response to treatment is pertinent to mention. Levels of alkaline phosphatase are elevated in osteosarcoma due to increased osteoblastic activity. Higher levels are associated with heavy tumor burden and poor prognosis. The response of therapy can be monitored with the levels of these enzymes. High levels after treatment may persist with residual disease or recurrence and in the presence of metastasis.[8]

Biopsy

Biopsy should be performed after complete history, clinical examination and imaging. It confirms the diagnosis,

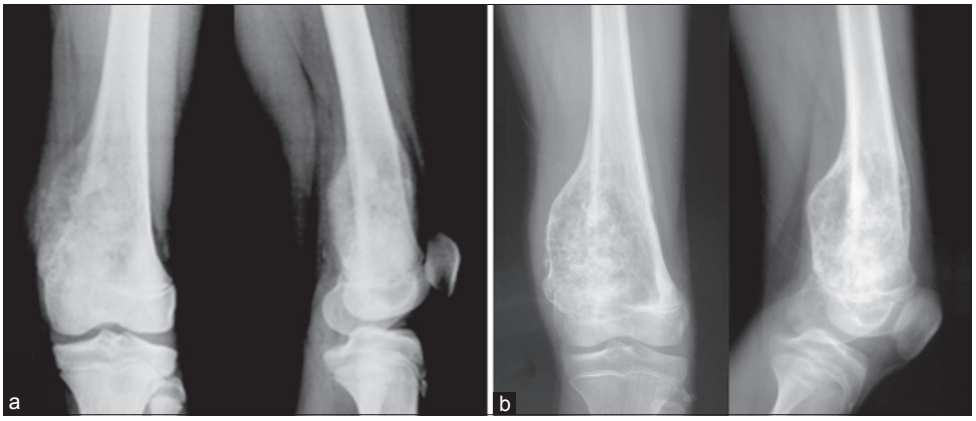

Figure 5: X-ray anteroposterior and lateral views showing that after chemotherapy the tumor becomes well defined with better capsulation: (a) before chemotherapy and (b) after chemotherapy

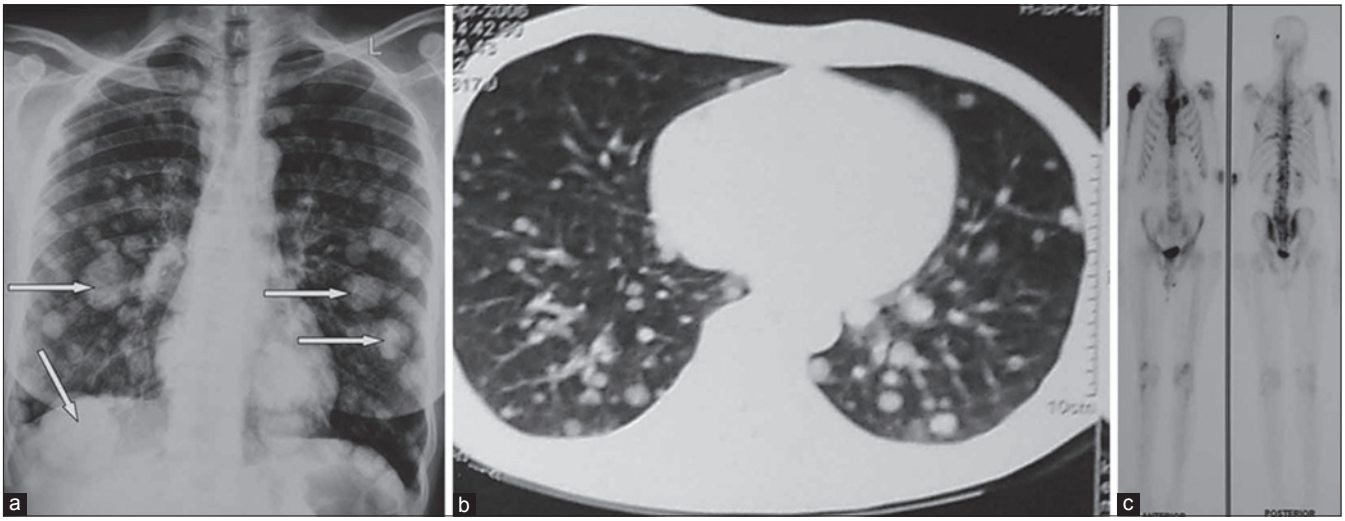

Figure 6: (a) Plain X-ray chest of a patient of osteosarcoma showing multiple metastatic lung nodules (b) CT scan (axial section) demonstrating multiple metastases in both lungs (c) Tc-99m bone scan of osteosarcoma in the proximal humerus with hot spot at this site and in spine, ribs and a focus in the skull bone

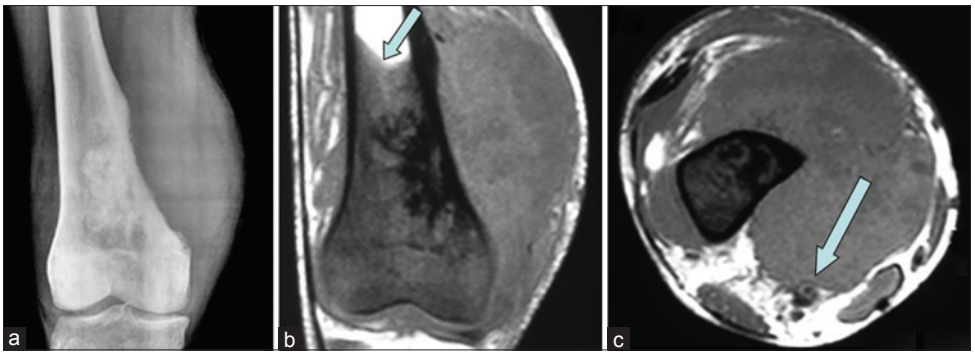

Figure 7: Osteosarcoma in the distal end of femur: (a) X-ray thigh with knee anteroposterior view showing big soft tissue component on the medial side; (b) MRI-coronal section showing the medullary extent (arrow); (c) MRI-axial section showing the proximity of the popliteal vessels

reveals specific type and furnishes the grade of the tumor. It is performed by either an open (incisional) or a closed method. Closed biopsy is performed as fine needle aspiration cytology (FNAC) and core needle biopsy.[7] Open or incisional biopsy is performed through a small incision [Figure 8] and has the major advantage of obtaining adequate amount of sample for histopathology as well as for ancillary studies like immunohistocytochemistry (IHC) and genetic studies. But it takes more time and requires operation theatre set-up with instruments. There are more chances of contamination of normal soft tissue by tumor cells through an impending hematoma and also other complications like infection and wound problems posing greater morbidity. Further, there is more cost to the patient as it may require short stay in the hospital. However, if performed meticulously and properly, the complications can be reduced markedly almost comparable to those of a core needle biopsy.[7] Percutaneous core needle biopsy has now evolved as a better, safe and accurate method for diagnosing of bone tumors. It is performed through a small stab using the Jamshidi needle and taking multiple cores from the representative part of the tumor [Figure 9]. It is less extensive and less time consuming outpatient procedure performed safely and quickly under local anesthesia and is cost effective. There is minimal soft tissue trauma with less contamination of normal tissue by the tumor cells around the tract of the needle which is easily excisable during the limb salvage surgery. It is very suitable for deep and difficult areas like the pelvis and spine.[5,6] The efficacy and accuracy can be further increased by performing this under image guidance i.e. under CT scan, MRI or ultrasonography. The recent literature advocates core needle biopsy as it provides adequate amount of sample for the diagnosis and the ancillary studies, and has less number of complications.[35-48]

FNAC does not have much role in majority of bone and soft tissue sarcomas as only few cells are inadequate for making a specific diagnosis and conducting ancillary studies. Ideally one should not start oncological treatment on the basis of a cytological diagnosis.[7]

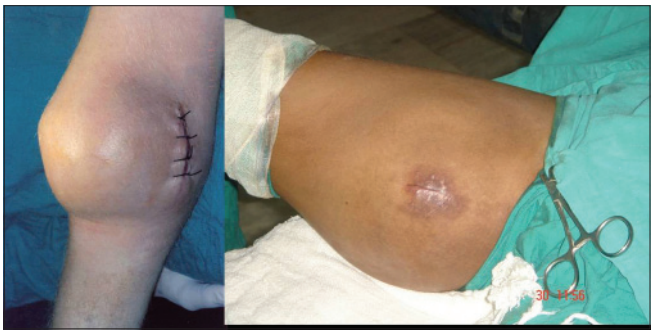

Figure 8: Open biopsies taken through small two cm incisions without making different planes. The incisions were placed such that these can be well resected with definitive resection of the tumor

Whether performed open or close, there are set principles for biopsy of musculoskeletal tumors which holds true for osteosarcoma too. Where, who, and how the biopsy should be performed are important issues. The biopsy is such an instrumental step that if not performed properly, the end result of definitive treatment can be affected significantly. We have noticed poorly performed biopsies in patients referred from periphery by nonspecialized general orthopedic surgeons and by un-experienced junior surgeons even at our institute. The incisions for biopsy were wrongly placed [Figure 10], patients had infection at the biopsy site due to big hematoma, and there were nondiagnostic samples due to inadequate material taken from nonrepresentative areas of the tumor. Due to these improper biopsies, the optimal treatment plan required alteration. The importance of biopsy has been well emphasized in literature by Mankin *et al*. who observed that because of wrong biopsies unnecessary amputations were performed in 4.5% of patients and the prognosis and outcome was altered in 8.5% of their patients. They found 18.2% major errors in diagnosis and 10.3% of biopsies being nonrepresentative. It has been emphasized that ideally the biopsy should be performed at the center where the definitive treatment of the tumor is to be performed under the guidance of a welltrained oncologist, taking all precautions, and following the basic principles.[46-50] If the principles are followed properly the final

outcome will obviously be better with lesser complications. This will prevent the repetition of biopsy and the treatment delay with reduction of overall cost[42] [Box 2].

Staging

The common staging systems for malignant bone tumors are: Enneking system for staging malignant musculoskeletal tumors and the American Joint Committee on Cancer (AJCC) System for staging bone sarcomas.[6] The former is based on the histological grade of the tumor, its local extent and the presence or absence of metastasis [Table 1]. Low grade lesions are stage-I, are well differentiated, have few mitoses and exhibit only moderate cytological atypia with low risk of metastasis (less than 25%). High grade lesions are stage-II are poorly differentiated, have high mitotic rate, and high cell to matrix ratio. On the basis of the involvement of the anatomical compartment (as determined by the natural anatomical barriers to tumor growth like cortical bone, articular cartilage, fascial septa, or joint capsules) these are further sub-divided as A and B. Stage–IA and IIA are contained in well defined compartment (intracompartmental) and stage–IB and IIB lesions extend beyond the compartment of origin (extracompartmental). Stage –III are lesions with metastasis (lymph node or distant) regardless of the size and grade.[2,7]

The AJCC system for bone sarcomas is based on tumor grade, size, presence, and location of metastases [Table 2]. Stage-I tumors are low grade and stage-II are high grade, which are subdivided based on tumor size. Stages I-A and II-A are 8 cm or less in their greatest linear measurement; stage I-B and II-B are larger than 8 cm. Stage III tumors have "skip metastases", which are defined as discontinuous lesions within the same bone. Stage IV-A involves pulmonary metastases, whereas Stage IV-B involves nonpulmonary metastases. The stage IV is subdivided because patients with nonpulmonary metastases from osteosarcoma have worse prognosis than those with only pulmonary metastases.[7,51-53]

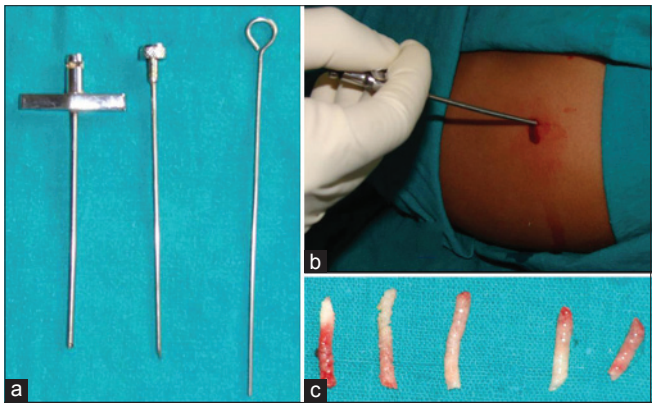

Figure 9: Core needle biopsy: (a) Jamshidi needle with trochar and stylet. (b) Biopsy being taken through stab incision. (c) Five good cores taken

Conclusion

The plain radiograph provides the best clue to the diagnosis and MRI the local extent. Thorax CT scan and Tc99 bone scan are used for the detection of lung and bony

Table 1: Enneking system for staging malignant musculoskeletal tumors

Stage	Grade	Site	Metastasis
IA	Low	Intracompartmental	None
IB	Low	Extracompartmental	None
IA	High	Intracompartmental	None
IIB	High	Extracompartmental	None
III	Any	Any	Regional or distant metastasis

Table 2: American joint committee on cancer system for staging bone sarcomas

Stage	Grade	Size	Metastasis
I-A	Low	<8 cm	None
I-B	Low	>8 cm	None
II-A	High	<8 cm	None
II-B	High	>8 cm	None
III	Any	Any	Skip metastasis
IV-A	Any	Any	Pulmonary metastasis
IV-B	Any	Any	Nonpulmonary metastasis

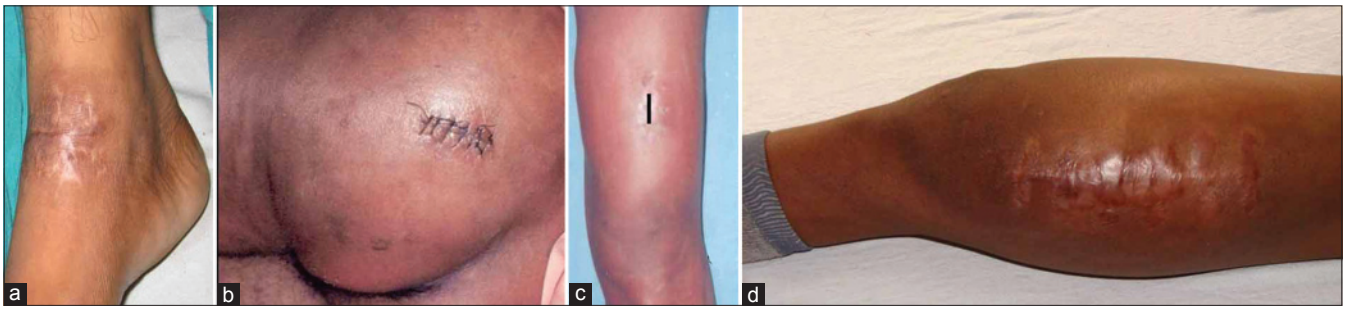

Figure 10: Poorly performed biopsies: (a) Avoid transverse incision in the extremity because this is difficult to excise with definitive resection. (b) Never biopsy through buttock as this is the flap for the coverage in the hind quarter amputation if required. (c) Never biopsy through rectus femoris; very important for knee extension (d) Poor biopsy: Long incision and widely placed sutures marks will require excision of wide area of skin and under lying tissues if salvage surgery is contemplated and the wound closure may be compromised

Box 2: Principles of biopsy

Perform all the relevant imaging investigations before biopsy.

Biopsy should be performed at the treating center by the member of the treating team or at least under his/her guidance. Refer the patient before biopsy if treatment is not feasible at the peripheral center.

If tourniquet is used, elevate the limb but do not exsanguinate with compression.

No transverse incision in the extremities. Avoid major neurovascular structures.

Place the incision such that it can be easily excised with the definitive resection and should not jeopardize the future plan of surgery and function of the limb. The needle biopsy tract should be tattooed in order to excise it easily. The surgeon should be familiar with incisions of limb salvage and those for the standard and nonstandard amputation flaps.

Make no different planes during open biopsy rather reach the tumor with a single deep stab/incision until the depth of the tumor to avoid seepage of tumor cells under these planes. Do not reach the lesion in between the muscle planes rather go through a single muscle plane to avoid contamination of more muscle groups.

Sample the soft tissue component in the bone sarcomas. Material should be taken from the viable peripheral area of the tumor and not from the central necrotic area and the Codman's triangle having just reactive bone. Do not squeeze the tumor during biopsy.

If required, make circular/oval window in the bone to decrease the chances of pathological fracture; avoid quadrangular widow. Protect the limb if the chances of fractures are likely which alters the prognosis.

Achieve complete hemostasis to avoid contamination of the tissues with seepage of blood under tissue planes. In the bone, the hole can be plugged with small amount of bone cement. The wound should be sutured tightly and avoid widely placed suture. If required, the drain should be in the line of incision, not on the side.

If frozen section facility exists the diagnostic tissue can be confirmed intraoperatively. Take adequate material and do not divide the tissue for different pathologists rather furnish them the slides/block if the review is required.

Tissue should be adequately immersed in formalin/preservation fluid in a ratio of 1:20 (tissue: fluid) and do not allow it to dry on the table. The sample could be sent immediately as a fresh specimen for potential frozen section and immunohistocytochemistry studies.

Fill up the biopsy form properly with all relevant clinical, radiological, and the previous FNAC/biopsy details if available. Assist the pathologist in making diagnosis rather than testing or confusing them.

There should be always a multidisciplinary team (MDT) to discuss oncological cases. The MDT should include the surgeon, radiologist, pathologist, chemotherapist, and the radiation oncologist.

"Always culture a biopsy and biopsy a culture" as we are in the endemic area of infections (including tuberculosis) which can mimic tumors.

MDT: Multidisciplinary team, FNAC: Fine needle aspiration cytology

metastasis respectively. The biopsy confirms the diagnosis and reveals the grade of the lesion. The basic principles of biopsy should be followed precisely and meticulously. After clinical, radiological and the histopathological examinations the tumor can be staged adequately [Box 3]. It is pertinent to mention that the patient should be immediately referred to the treating specialist centre for early diagnosis and treatment as this can make limb salvage possible in large number of patients. The urgent need of the MDT (multidisciplinay team) for the better out come in all musculoskeletal sarcomas can not be over-emphasised. However, the biological behavior of osteosarcoma is yet to be fully understood.

Box 3: Algorithm for staging osteosarcoma in distal femur

Clinical examination: Painful, ill-defined diffuse mass lesion in the metaphyseal area of the distal femur- suspect osteosarcoma

Plain X-ray of the lower thigh with knee (for probable diagnosis) and X-ray chest (may detect lung nodules i.e. metastasis)

MRI of the distal thigh with inclusion of hip and knee joint

(for tumor size, local extent and skip lesion, if any)

CT scan thorax (for lung metastasis),

Tc-99 bone scan (for osseous metastasis)

Biopsy (for confirmation of diagnosis and grade of the lesion)

Stage the lesion as per local extent including the size, grade and metastasis in view of the above mentioned investigations

Example-if MRI shows the lesion extending all around the femur into the soft tissues with no metastasis on CT scan thorax and bone scan; and is high grade on biopsy it is stage-II-B lesion (Enneking staging) as are the majority of the osteosarcomas at presentation, MRI: Magnetic resonance imaging, CT: Computerized tomography

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